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**A PRAGMATIC APPROACH TO MOBILE ATTENTION BIAS
MODIFICATION IN A CLINICAL SETTING**

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LEE KONG CHIAN SCHOOL OF MEDICINE

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LEE KONG CHIAN SCHOOL OF MEDICINE

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Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research, is free of plagiarised materials, and has not been submitted for a higher degree to any other University or Institution.

05/04/2023

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Supervisor Declaration Statement

I have reviewed the content and presentation style of this thesis and declare it is free of plagiarism and of sufficient grammatical clarity to be examined. To the best of my knowledge, the research and writing are those of the candidate except as acknowledged in the Author Attribution Statement. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

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Professor Helen Elizabeth Smith

Authorship Attribution Statement

This thesis contains material from (a) paper(s) published in a/the following peer-reviewed journal(s) where I was the first and/or corresponding author.

Chapter 1 is published as Zhang MW, Ying JB, Song G, Fung DSS, Smith HE. Recent Advances in Attention Bias Modification for Substance Addictions. *Int J Environ Res Public Health*, 2018 Apr 23;15(4). DOI: 10.3390/ijerph15040832.

The contributions of the co-authors are as follows:

- I formulated the plan for the perspective article, under the joint supervision of my supervisors, Professor Helen Smith and A/Prof Daniel Fung.
- I prepared the initial manuscript drafts.
- Dr Ying Jiangbo assisted in the verification of the results extracted from the papers included in this perspective article.
- Dr Song Guo provided inputs relating to clinical implications.
- The original draft of the manuscript I prepared was jointly revised with Professor Helen Smith and A/Prof Daniel Fung.

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The contributions of the co-authors are as follows:

- I formulated the plan for the protocol, under the joint supervision of my supervisors, Professor Helen Smith and A/Prof Daniel Fung.
- I prepared the initial manuscript drafts.
- A/Prof Roger Ho Chun Man provided inputs pertaining to the meta-analytical approach for data synthesis.
- The rest of the co-authors provided critical comments and inputs to the manuscript prior to submission and publication.

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The contributions of the co-authors are as follows:

- I formulated the plan for the review, under the joint supervision of my supervisors, Smith HE and Fung DSS.
- I prepared the initial manuscript drafts, which were revised by all co-authors.
- Dr Ying Jiangbo assisted in the screening of the articles and verification of the extracted data from the articles.
- Dr Guo Song helped to resolve any disagreements amongst the authors in the data extracted.
- I performed the qualitative synthesis of the articles and prepared the initial manuscript drafts.
- Professor Helen Smith provided guidance in addressing some of the peer reviewers' comments.
- The manuscript was subsequently revised by the rest of the co-authors prior to publication.

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- I formulated the plan for the review (which includes all study designs), to address the limitation of the prior review I published.
- Dr Ying Jiangbo assisted in the verification of the articles identified by the search strategy and the verification of the extracted data from the articles.
- Dr Guo Song helped to resolve any disagreements amongst the authors in the data extracted.
- I performed the qualitative synthesis of the articles and prepared the initial manuscript drafts.
- Professor Helen Smith provided critical inputs in addressing the peer reviewers' comments.
- The rest of the co-authors provided critical comments to better the manuscript prior to publication.

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- The manuscript was subsequently revised by the rest of the co-authors prior to publication.

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- I formulated and conceptualized the plan for this review of previous content analyses.
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- Dr Ying Jiangbo and Dr Roger Ho provided critical inputs pertaining to the methods.
- I prepared the initial manuscript drafts, which were revised by all co-authors.

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- Dr Guo Song helped to resolve any disagreements amongst the authors in the data extracted.
- I performed the qualitative synthesis and prepared the initial manuscript.
- The manuscript was subsequently revised by Professor Helen Smith and then by the rest of the co-authors prior to publication.

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- I conceptualized the plan for the review.
- I reviewed the literature and extracted the data from the relevant articles.
- I wrote up the initial draft of the manuscript.
- Professor Helen Smith provided guidance with regards to the presentation of the results and provided critical inputs to better the initial draft of the manuscript.
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The contributions of the co-authors are as follows:

- I conceptualized the plan for the application and research platform, with further inputs from all the co-authors in refining the design of the platform.
- I worked with an independent developer in conceptualizing them.
- I wrote the initial draft of the manuscript, which was then revised by the rest of the co-authors.

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The contributions of the co-authors are as follows:

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- All the authors jointly conceptualized the study.
- I was involved in data collation along with Ms Amron and Ms Mahreen.
- I code and analysed the initial data, which was verified by Dr Ying Jiangbo.
- All authors reviewed the final dataset.
- I wrote up the first draft of the manuscript. Professor Helen Smith provided critical inputs to the first draft of the manuscript.
- All authors provided further inputs to the final manuscript.

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The contributions of the co-authors are as follows:

- I conceptualized the plan for the feasibility and acceptability study.
- I collated the data from the participants. Ms Amron and Ms Mahreen also assisted in the collation of data from some of the participants.

- Dr Ying Jiangbo assisted in the verification of the coding of the data.
- I performed the statistical analysis of the collated data.
- I wrote up the initial draft of the manuscript. All the co-authors provided critical comments to the manuscript.

-

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- I wrote up the manuscript and submitted it for consideration.

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The contributions of the co-authors are as follows:

- I conceptualized the plan for the codesign workshops.

- Professor Helen Smith provided critical inputs to the conceptualization of the workshops.
- I ran the workshops with the assistance of Dr Sandor Heng, who assisted in taking field notes during the conduct of the workshop.
- I transcribed and performed the initial coding of all the audio recordings. Dr Sandor Heng independently coded the transcribed audio recordings.
- I performed the thematic analysis of the data that was coded.
- I wrote the initial version of the manuscript, which Professor Helen Smith provided further critical comments.
- All co-authors provided critical comments for the final manuscript, which I independently revised.

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- Professor Helen Smith & A/Prof Daniel Fung provided critical inputs to the protocol.
- I wrote the first draft of the manuscript.
- All authors provided critical comments to the manuscript prior to submission.

..05/04/2023.

Date



Zhang Weibin, Melvyn

Summary

Substance use & alcohol use disorders are highly prevalent globally, and Singapore is no exception. In Singapore, pharmacological approaches are available for the treatment of alcohol use disorders and the maintenance of abstinence, but for other substance use disorders (opioid use, cannabis use and stimulant use), the pharmacological options available are limited. Psychological approaches are paramount in the maintenance of abstinence. Despite the effectiveness of conventional psychological approaches, such as cognitive behavioural therapy for relapse prevention, a significant proportion of individuals still lapse or even relapse. The advances in experimental psychology and increased recognition of cognitive deficits among individuals with addictive disorders, have in turn led to a better understanding of unconscious, automatic biases, that of attention and approach biases that might result in individuals relapsing. Attentional biases are the most fundamental of these unconscious processes, as they refer to how attentional processes are preferentially being allocated to the substance-related stimulus. Despite advances in experimental psychology, there remains several research gaps. These include a lack of synthesized evidence demonstrating that attentional biases are consistently present amongst individuals with substance use disorders and reviews synthesizing the evidence for bias modification in these highly prevalent substance disorders. Whilst the advances in technologies have led to the delivery of these bias modification interventions using web or mobile technologies, there has not been any prior reviews of the published literature, or content analyses of commercial applications. More recently, gamification technologies have been applied to bias modification interventions, but there remains limited understanding of the rationale for gamification, and the gamification strategies that render interventions effective. Most importantly, there have not been any exploration of such interventions amongst an Asian cohort of treatment-seeking individuals with addictive disorders. Also, the interventions that have been used to date for bias modification often are developed by academics and developers but rarely have addressed the needs of patient participants.

In consideration of the research gaps, the aim of my doctoral work was to develop a mobile attention bias modification intervention that could be used as an adjunct to conventional pharmaceutical and psychological therapies for treatment-seeking Asian individuals with addictive disorders. There was a total of nine objectives. In addressing the research gap pertaining to attentional biases amongst individuals with highly

prevalent addictive disorders (objective 1), two systematic reviews were undertaken. Both demonstrated that attentional biases are consistently present amongst individuals with opioid, cannabis, and stimulant use disorders. Unfortunately, evidence synthesis for bias modification cannot be undertaken in view of the heterogeneity of the outcomes used. For objective 2 (Review of Mobile Interventions), my systematic review of mobile bias interventions found that 7 out of the 8 identified published studies have reported the effectiveness of mobile bias modification. My content analyses of commercial applications found 5 out of 17 commercial applications targeted bias modification for addictive disorders. Only one has been scientifically evaluated, indicating a large disconnect between academics and developers.

To better understand gamification as applied to bias modification interventions (objective 3), I undertook a literature review, and found two out of four studies reporting gamified bias intervention to be effective. The review also highlighted some of the gamification strategies applied that render interventions to be effective. Another content analysis of commercially available gamified application was conducted, to identify common gamification strategies adopted. A review of the task paradigms was undertaken (objective 4), to conceptualise the mobile attention bias intervention that will be further tested. The feasibility and acceptability study (objective 5) I undertook demonstrated the feasibility of recruitment and the administration of the intervention; and the acceptability of the intervention, judged by the ease of use, interactivity, and the change in confidence following intervention. To accommodate patients' perspective (objective 6), I undertook a series of codesign workshops involving healthcare professional and patient participants. The codesign workshops identified limitations of the conventional mobile attention bias modification interventions; the participants also suggested ways to improve the existing application, such as the lengthening the stimulus presentation intervals and the consideration of gamification strategies. I undertook a pilot study to examine if the intended processes of the definitive study (such as the recruitment of participants, the process of randomization, the administration of intervention) (Objective 7) would work. Whilst the pilot study could not be taken to completion in view of COVID-19, it enabled the conduct of a risk assessment that identified all issues that might affect the definitive randomized trial. I undertook another study (Objective 8) to determine if a new method of computing attentional biases (trial-level bias score) could identify more baseline biases; and

another study examining the feasibility of a single-session approach in modifying attentional biases. These were planned for in order to mitigate against the risk of recruitment and attrition, and they helped to revise the methods for the definitive trial. The work undertaken to date has enabled the conceptualization of a protocol for a definitive randomized trial (Objective 9), which on completion of this PhD I will seek extramural funding and time to conduct.

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Abbreviations

AB	Attention Bias
ABM	Attention Bias Modification
APPS	Applications
ACHESS	Alcohol-Comprehensive Health Enhancement Support System
ASI-LITE	Addiction Severity Index-Lite
ALIVE	Games for Health Serious Games Grant
ANOVA	Analysis of Variance
CBT	Cognitive Behavioural Therapy
CNB	Central Narcotics Bureau
CAMP	Community Addictions Management Program
COVID-19	Coronavirus pandemic
CONSORT	Consolidated Standards of Reporting Trials
CRT	Cognitive remediation therapy
DEA	United States Drug Enforcement Agency
DSRB	Domain Specific Research Board
E-Health	Electronic Health
FDA	Food and Drug Administration
GABA	γ -aminobutyric acid
HIV/AIDS	Acquired Immunodeficiency Syndrome
HBRA	Human Biomedical Research Act
IMH	Institute of Mental Health
LBMI-A	Location-Based Monitoring and Intervention System for Alcohol Use Disorders
M-Health	Mobile Health
MUST	Danish Acronym for Theories and Methods of Initial Analysis and Design Activities
MRC	Medical Research Council
MS	Milliseconds
NAMS	National Addictions Management Services
NMDA	N-Nitrosodimethylamine
NIHR	National Institute for Health Research
NHG	National Healthcare Group
OTS	Off the shelf

OST	Opioid Substitution Therapy
PDR	Participatory Research Design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
REVMAN5	Review Manager 5
RE-AIM	Reach, Effectiveness, Adoption, Implementation and Maintenance
SOA	Stimulus Onset Asynchrony
SDS	Severity of Drug Dependence Scale
TLBS	Trial Level Bias Score
UNDOC	United Nations Office on Drugs and Crime
VAS	Visual Analogue Scale
WHO	World Health Organization

Chapter 1 Introduction

Introduction

Chapter 1 provides an overview of the background information that is pertinent for this PhD body of work. Section 1.1 through to 1.3 provide an overview of the substance use problem globally and in Singapore. Section 1.2 describes both the pharmacological and psychological treatments that are used. Section 1.4 present the rationale and reasons for undertaking this work. Section 1.5 discusses the theoretical basis for cognitive biases (attentional and approach biases), the methods in which biases are assessed and modified. This section also presents published research findings regarding the existence of cognitive biases in substance disorders and the effectiveness of different bias modification interventions. Section 1.6 presents the research gaps identified based on the available evidence in 2017 and describes how these research gaps informed my research plans. The aims and objectives of this PhD are presented in Section 1.7 and 1.8. The chapter concludes with an outline of this dissertation's structure and the justification of the originality and novelty of this work.

1.1 Epidemiology of Substance Use Disorders: A Global Perspective

Statistics released by the United Nations Office on Drugs and Crime (UNDOC) reported that 269 million individuals consumed illicit drugs in 2018, a 30% increase in number when compared to the figures from 2009 (1). Cannabis was the most abused illicit drug, with 192 million individuals using it globally (1). The use of illicit drugs such as opioids has increased by 71% (1). Underlying the increase in opioids use is the abuse of synthetic opioids, such as fentanyl. In 2018, an estimated total of 58 million individuals used opioids in the past year, whilst 27 million individuals have used amphetamine or another prescription stimulant (1). Drug use has been associated with many medical and psychiatric comorbidities and can also result in death due to overdose (2). Of the 11.3 million individuals who inject drugs globally, many are at an increased risk of an overdose, with higher chances of acquiring infections like Hepatitis B, C and Human Immunodeficiency Virus (HIV). This predisposition towards HIV infection is usually through shared needles or engagement in high-risk sexual activities (2). Cannabis alone accounts for 66% of the estimated 167,000 deaths related to drug use

disorders in 2017; and 50% of the 42 million years lost due to disability or early death, were due to drug use (1).

In addition to the rising use of illicit substances, there is increasing use of legal substances, like alcohol, are also a concern. The World Health Organization, in their 2018 report, highlighted that the harmful use of alcohol accounts for 3 million deaths across the world (3). An estimated 2.3 billion individuals globally are using alcohol, with more than half of the population of the Americas, Europe, and the Western Pacific consuming alcohol (3). Alcohol use accounts for significant morbidities, accounting for 5.1% of the global burden of disease and injury (3).

1.2 Treatment Approaches for Substance Use Disorders

Given the growing prevalence of substance use disorders, it is pertinent to understand the available treatment approaches. They can be classified into that of pharmacological and psychological interventions. Pharmacological agents can be considered for individuals in acute intoxication or withdrawal states; and can be used to reduce the reinforcing effects of substances; or to maintain abstinence (4). Medications are also prescribed to treat other comorbid psychiatric conditions (4).

Regarding pharmacological treatment of alcohol use disorders, medications like Naltrexone (an opioid antagonist) can reduce the reinforcing effects of alcohol (5). Others like Acamprosate (a γ -aminobutyric acid, GABA analog) can reduce cravings, and those like Disulfiram can serve as aversive agents and help maintain abstinence among motivated individuals (6). For illicit drugs like cannabis and stimulants like methamphetamine, there exist no pharmacological options approved by the Food and Drug Administration (FDA) (4). Symptomatic medications, like benzodiazepines and antipsychotics can help treat the acute intoxication symptoms (4). For opioid use disorders, medications like naloxone are prescribed to individuals who present with symptoms suggestive of an opioid overdose, while medications like methadone (a full opioid agonist) or buprenorphine (partial opioid agonist) are considered as part of an opioid-substitution program (4). Opioid substitution therapy (OST) refers to the medical administration of a prescribed psychoactive substance that is pharmacologically related to that producing dependence (7). This kind of therapy helps in the prevention of withdrawal and in the reduction of cravings while minimizing the

harms and risk of infections associated with the injection of illicit opioids (7). Such therapies have been proven to be cost-effective (7).

Psychological approaches are crucial for treating substance use disorders. These therapies can help identify if an individual has a substance problem, engage with them in treatment, and facilitate their reintegration into the community (8). Commonly used psychological interventions include contingency management, behavioural couples therapy for drug-related problems, cognitive behavioural therapy, and motivational interviewing (8, 9). In contingency management, positive behaviours, such as the submission of a drug-negative urine sample, allows individuals to be rewarded with an incentive (9, 10). Contingency management is based on operant conditioning, and the reinforcer value can increase depending on the duration of abstinence (9, 10). The focus in behavioural-couple therapy is on improving an individuals' ability to cope with substance use and the relationship with their partner (11). The underlying assumption is that there is a reciprocal relationship between substance use and dysfunctional relationships; since substance use can impact relationship; relationship distress in turn contributes to further substance use (11). Cognitive behavioural therapy (CBT) involves cognitive reappraisal, skills training, and behavioural strategies to avoid triggers, as well as skills related to drug refusal and coping (9). Cognitive behavioural therapy is also appropriate for individuals with comorbid psychiatric disorders (9). In motivational interviewing, the therapy targets individuals' ambivalence toward change.

To date, there have been several reviews that have investigated the effectiveness of these psychological interventions. Smedslund et al. in their synthesis of 59 studies involving motivational interviewing, reported that motivational interviewing effectively reduced substance use (12). Magill et al. in their meta-analysis of cognitive behavioural therapy for alcohol and drug disorders, reported a moderate to large effect size when CBT was compared against none (i.e., waitlist) or minimal treatment (i.e., brief psychoeducation) (13).

1.3 Substance Use in Singapore

In Singapore, there is a paucity of large-scale epidemiological studies on illicit drug use. The only available study was conducted by the World Health Organization in 2004, which reported the prevalence of drug use disorders among men and women to be

0.28% and 0.07%, respectively; and that of alcohol use disorders were 1.40% and 0.19%, respectively (14).

Apart from the report by the WHO, the annual reports published by the Singaporean drug enforcement authority (Central Narcotics Bureau (CNB)) have offered key insights into local illicit drug situation. In 2017, the CNB reported that the three drugs used most amongst those they arrested were methamphetamine (stimulant), heroin (opioid), and cannabis, and these remained the same in 2018 (15, 16). In 2019, there was a change and heroin featured less frequently, with methamphetamine, cannabis, novel psychoactive substances becoming the top three (17). Novel psychoactive substances are synthetic derivatives of traditionally abused substances, such as cannabinoids and stimulants (18). It is important to note that the statistics provided by CNB are not prevalence rates of use for Singapore, but rather the number of individuals using illicit drug and arrested. Nevertheless, these statistics can provide insights into the changing trend of illicit drugs used.

As highlighted in Section 1.1, there have been an increasing trend of alcohol use globally. In Singapore, regarding alcohol disorder, the prevalence of alcohol use disorders and alcohol dependence in 2016 was that of 1.7% for males and 0.5% for females, according to the World Health Organization Report in 2018 (19). The overall prevalence for alcohol use disorder in Singapore is 1.1%, a sharp contrast against the prevalence of 4.7% across the Western Pacific region (19).

To address drug use disorders, the Singaporean government has developed healthcare services, including a national centre (National Addictions Management Service, NAMS) to address substance and behavioural addictions locally. At NAMS, psychological and pharmacological treatment approaches are available. In contrast to many other countries, Singapore does not offer OST for individuals abusing illicit opioids because when it was available some users mixed it with other illicit drugs and injected the mixture (20, 21). Therefore, opioid substitutes are available only for elderly individuals previously abusing opium (20, 21). In this context, treatment-seeking individuals with opioid use disorders typically undergo detoxification with symptomatic medications, followed by rehabilitation using psychological interventions (20, 21).

NAMS data on patient case mix demonstrates an increasing number of individuals seeking treatment for alcohol and other substance-related addiction disorders. In 2016, based on a study that monitored patients' treatment outcomes across a 6-month period, 223 and 315 patients with alcohol and substance use disorders received treatment and were followed up. In 2017, these numbers increased to 337 and 473, respectively (alcohol and substance use). The total number of individuals seen for alcohol problems increased from 316 in 2008 to 574 in 2017; whereas the total number seen for substance addiction increased from 449 in 2008 to 738 in 2017. These figures indicate that there is an upwards trend in the number of individuals seeking help for addiction-related issues.

To date, no published studies have reported on the relapse rates after treatment amongst local individuals with substance disorders. In the clinical setting, we have seen individuals who were previously admitted for inpatient detoxification and rehabilitation treatment at NAMS, who have relapsed despite treatment. Perhaps, closest approximation of relapse rates in Singapore are the statistics from the CNB. As per the CNB report, a total of 1917 individuals were apprehended in 2017, who were engaged in repeated drug use (15). Considering the relapse rates globally, Smyth et al. reported a relapse rate of 59% among their sample of opioid-dependent Irish individuals following residential addiction treatment (22). Other studies have reported relapse rates for addictive disorders of 72-88% on follow-up, after 12-36 months (23).

1.4 Rationale for this Body of Work

As discussed, in Section 1.2, therapies like cognitive behavioural therapy have been widely used to help individuals achieve abstinence, as prior research has demonstrated its effectiveness. McHugh, Hearon, and Otto had reported that cognitive behavioural therapy was moderately effective in promoting abstinence (effect size: Cohen's $d = 0.45$) (9). According to them, the intervention's effect size ranged from 0.24 to large Cohen d , depending on the type of illicit drug targeted; larger effect sizes were seen when treating cannabis use disorders, followed by cocaine and opioids. The smallest effect sizes were for polysubstance disorders (9). Whilst CBT has been previously demonstrated to be effective, factors such as the co-existing medical problems,

cognitive impairment, and social stressors can complicate the delivery of such interventions, thus limiting the overall effectiveness (9).

An attempt to overcome limitations pertaining to access has been the consideration of the use of technologies in widespread implementation of these therapies, but there remain several issues (24). With therapies like CBT, the gains are very much dependent on adherence and the completion of extra-sessions assignments (also known as homework) (25). Kazantzis et al. have reported a relationship between homework completion and eventual treatment outcomes (25). Also, whilst technology has enabled the dissemination and implementation of CBT, there have been studies that reported low uptake rates for a web-based intervention for individuals with stimulant use disorders (26); and those with cocaine use disorders (27). A recent meta-analytical study by Fleury et al. of treatment outcomes reported in studies conducted between 2000 and 2015 found that less than 10% of individuals were maintained in remission (28). All the factors discussed highlighted the shortcomings of existing psychological interventions. The fact that only 10% of individuals are maintained in remission indicates a need to consider other therapies addressing factors leading to relapse.

In recent years, there has also been evidence highlighting cognitive deficits amongst individuals living with substance use disorders, which might contribute to relapse (29). These findings revealed that individuals with alcohol, stimulant or opioid use disorders tend to have deficits in executive functioning and decision-making (29). Besides, individuals using cannabis tend to have deficits in their episodic memory and attentional processes (29). Cognitive training programs, such as cognitive remediation, working memory training, inhibitory control, and cognitive bias modification (attention and approach bias modification), have been investigated, to address these cognitive deficits (30-32).

Cognitive remediation therapy (CRT) has shown to help improve working and verbal memory, verbal learning, attention, and processing speed (30-32). Working memory training helps individuals expand their working memory capacity to manipulate better and prioritize information (33). By doing so, individuals can make more appropriate decision relating to substance use (33). Inhibitory control training helps in remediating the deficits associated with inhibitory control, which are linked with increased

substance use (34). Cognitive bias modification aids in modifying automatic processes that occur in response to substance cues (35). Of all the different methods of cognitive remediation, cognitive bias modification (attention and approach bias modification) has been purported as the most promising method of cognitive remediation, as it does not involve a high cognitive load, and has shown promising results (29). More importantly, cognitive bias modification (attention and approach bias modification) could help mediate aspects of cognitive functioning that traditional psychotherapies do not target, that of the unconscious, automatic processes (35).

Recent studies have highlighted the issues associated with conventional psychotherapies like CBT and the challenges associated with therapies like CBT and its computerized version. With evidence of cognitive deficits amongst individuals with addictive disorders, it is important that future training programs remediate these deficits. The trends highlighted by CNB and the statistics available from NAMS suggest that with time, more individuals will be presenting for treatment in Singapore and that these individuals will be using drugs (such as cannabis, stimulants like methamphetamine, and opioids). Given the potential of cognitive bias modification in cognitive remediation and its initial promising results, in the next section, the theoretical concepts underlying cognitive bias modification will be discussed, as well as the methods for bias assessment and retraining and the evidence for cognitive bias modification.

1.5 Cognitive Biases in Substance Use Disorders

1.5.1 Theoretical Basis & Limitations of Existing Theories

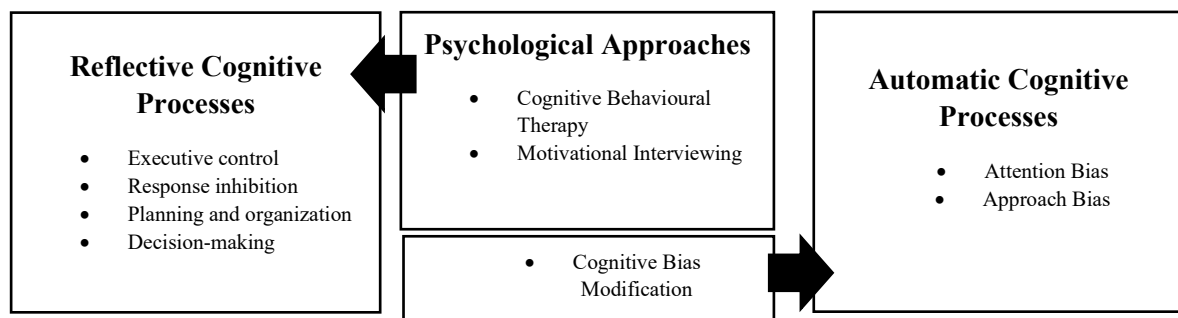
The cognitive biases present in individuals with substance-use disorders include attention and approach biases. Attention bias refers to how individuals preferentially orient their attention to substance-related stimuli in their normal environments (36). Approach biases refer to how individuals have automated tendencies that draw them towards substance-related stimuli (37). Several theoretical models have been proposed for these biases. One of the earliest theories proposed that these biases develop because of classical conditioning (38). The repetitive associations of drug-related stimuli with the rewarding effects of substance use result in a conditioned response (i.e., attentional biases and rapid orientation) towards substance cues (38).

On the other hand, the incentive-sensitisation theory postulates that the repetitive usage of a substance leads, in turn, to an increased dopaminergic response, which results in increased salience and motivation in seeking out substance-related cues, or the substance itself (39). Other theories, such as the elaborated intrusion theory, postulate that once an individual has a craving, they will further ‘elaborate’ on it, either by ruminating on the craving itself or by maintaining attentional focus on the external cues that triggered it (40). In contrast, the negative withdrawal theory states that biases develop, as individuals tend to seek out substances to minimize experiencing the negative withdrawal symptoms associated with not using the substance (41). The theory of current concerns states that if a patient is motivated in seeking out their drug of choice, their motivational state is likely to bias their cognitive processing (42).

The advancements in neurobiology have provided justifications for how substance use results in the sensitisation of the dopaminergic functions in the subcortical structures (43). These structures are typically involved in reward and associative learning. This, in turn, results in cravings and increased salience towards substance-related cues (43). The increased activation in the subcortical areas is associated with concomitant hypoactivity in the prefrontal cortex, thereby resulting in the loss of executive control over one’s behaviours (44). As aforementioned, executive functioning comprises functions like that of working memory, response inhibition, sustained attention and all of these are relevant to addiction (45). Such an understanding has resulted in a paradigm shift. While executive functioning is of importance in the initiation and maintenance of addictive behaviours, some individuals might experience persistent difficulties with inhibiting their substance use, especially if they have used substances chronically. This is mainly because the chronic use of addictive drugs results in neuroadaptations in the limbic systems that tend to sensitize unconscious, automatic behavioural reactions (43). The dual-process theory accommodates these observations and overcomes the limitations of previous theories. It justifies why some individuals have persistent difficulties (46). The theory postulates that the repetitive use of a substance leads to an increase in the automatic processing of substance cues (attention and approach biases), with a corresponding inhibition of the normal cognitive control process (i.e., the executive functioning processes) (46). Thus, the automatic processing of substance cues is an implicit (or impulsive, automatic) process and is not subjected and targeted upon by conventional psychotherapies such as CBT or contingency management (46). It is

possible that the failure to remediate these implicit processes accounts for the relapse observed amongst individuals who have received interventions like cognitive behavioural therapies. Figure 1.1 provides an overview of the differences in cognitive targets for conventional and cognitive bias modification therapies.

Figure 1.1 Overview of reflective and automatic cognitive processes and psychological treatment options.



The recognition that these automatic processes exist, and the limitations of conventional interventions have led to the development of a bias retraining intervention, known as attention or approach bias modification intervention. Attention bias modification modifies the preferential allocation of attentional resources to drugs cues by shifting the attention to neutral (non-drug cues) (47). In addictive disorders, attentional biases were the first to be examined, following the work of MacLeod on attentional biases in anxiety disorders (48). Several early studies, including the work of Field & Eastwood, Field et al., and Schoenmakers et al. have provided evidence for these biases (49-51). Approach bias modification involves training individuals to have an avoidance response to drug cues, and an approach response to non-drug cues (52). Attention bias in addictive disorders is the primary focus of this body of work.

Whilst the above-mentioned theories have provided justifications for the existence of attentional or approach biases, there is criticism of some of the proposed theories. Theories such as classical conditioning theory, negative withdrawal theory and the incentive-sensitization theories have been criticized to be too unitary in nature (53). The way these theories account for automatic biases, makes motivation, salience, and conditioned responses mutually exclusive (53). Also, it seems that some of these theories better account for biases in certain substance disorders more than others. For

example, the negative withdrawal theory helps account for opioid use disorder, given that this disorder is associated with severe physical and psychological withdrawal (53). The incentive-sensitization theory accounts best for stimulant use disorders since such disorders are associated with intense cravings and strong responsiveness to drug cues (53). These theories highlight the neuroadaptations that occur in individuals with chronic drug use, thus making it appear that individuals do not have any control over their decisions to use substances (53). These theories fail to consider the other processes of executive control and how it regulates automatic processes (53).

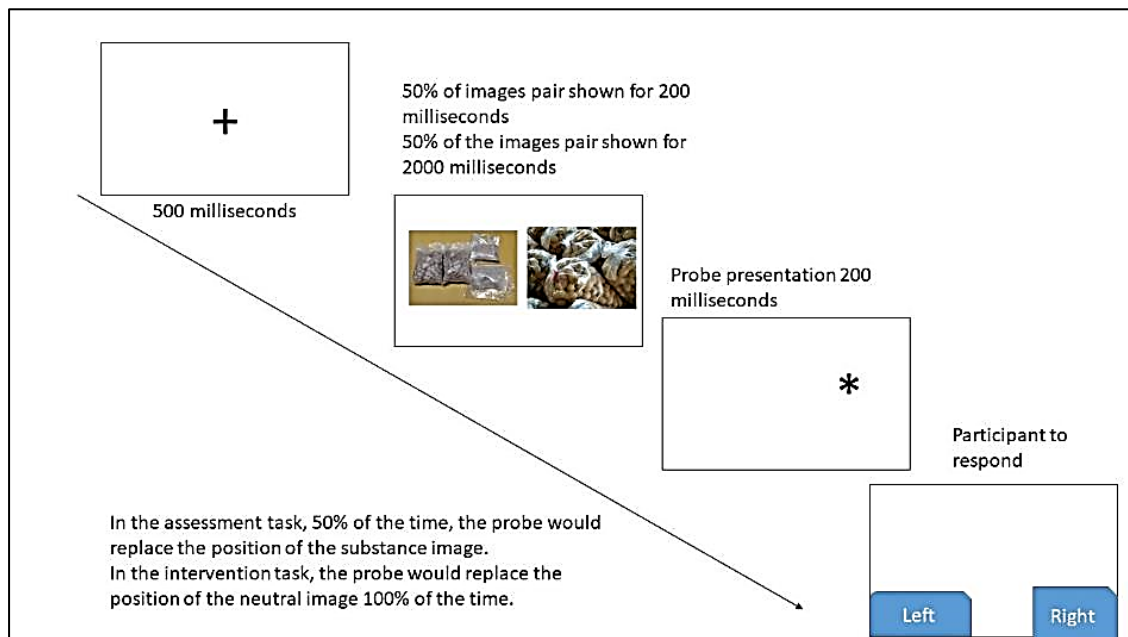
While the dual process theory addresses the limitations of previous unitary theories, it is not without criticism. Whilst the dual-process theory was revolutionary in introducing the concept of two separate cognitive processes, that of the reflective control and automatic processes, its weakness is the presentation of these two processes functioning independently. In reality, there is likely to be an interaction between these two systems, as automatic processes might be reliant on reflective processes, in order to be efficient and multiple other processes also mediate the interaction between the systems (54). Also, the dual-process theory does not state when the reflective control process occurs, and why they occur (54). Researchers like Wiers et al. have recommended that both these processes be considered as states, in a system of overlapping functional components. Cunningham & Zelazo, as cited in Wiers et al., have introduced the concept of iterative reprocessing, to account for these states, and to explain how the reflective and automatic systems interact (55). Iterative reprocessing states that when evaluations are based on a few iterations of the evaluative cycle, they tend to be automatic, and these could occur outside of cognitive monitoring (55). Evaluations that are based on greater iterations are relatively more reflective (55). Despite these criticisms relating to the previous theories and the dual-process theory, it remains clear that automatic biases might account for why individuals relapse.

1.5.2 Methods for Assessment and Modification of Attentional Biases

In the assessment of attention bias, indirect measures such as the Stroop or the Visual probe task are traditionally used (56). In the Stroop task, participants are presented with both drug-related and neutral words on a computer screen. Participants are required to name the colour of each word presented whilst ignoring the word's semantic meaning (57). Attention biases are present in participants who are slower in naming the colours

of the drug-related word. The drug-related words take up more attention processes (57). The visual probe task could be used for both attentional bias assessment and modification (58). In both the assessment and modification tasks, participants are presented with a set of pictorial stimuli, with one being a substance cue, and the other a neutral cue (58). Both the images disappear simultaneously, and a probe would appear (58). For bias assessment, in 50% of the trials, the probe would appear in the drug stimulus position, and in the other 50% of the trials, together with the neutral stimulus (58). Attention bias is present if individuals are quicker to respond to the probe, which replaces the drug-stimuli compared to probes replacing the neutral stimuli (58).

In the attention bias modification task, the probe always replaces that of the neutral stimulus, thereby effecting a change and retraining of the attentional processes away from the substance of interest and the neutral stimuli (58). This shift is accomplished through extensive multiple repetitive trials helping to weaken and change the biased, automatic, impulsive reactions. Doing so creates more time for the individual to rely on their executive functioning capabilities to make decisions regarding drug use (58). These tasks are often referred to as indirect measures of attentional biases since they use reaction times as a surrogate measure of underlying biases. Attention bias assessment and modification tasks are highly repetitive in nature and involves both effort and concentration. Undertaking these tasks is not easy, as individuals are presented with multiple repeats of the same trial paradigm (presentation of the set of pictorial stimuli, a probe, and having to respond rapidly to indicate the probe's position). Such tasks typically include multiple trials as described by Charles et al., wherein the participants undertook a total of 64 trials in the assessment phase, followed by 512 trials in the intervention phase (59). Figure 1.2 provides an illustrative example of an attention bias assessment task.

Figure 1.2 Example of an Attention Bias Assessment Task

Prior research has highlighted the poor reliabilities of these tasks' psychometrics properties (60). For the visual probe task, reliability is poor when stimulus presentation intervals are around 150 milliseconds (60). For the Stroop task, reliability is affected if unblocked (mix of substance and neutral words, instead of presenting substance and neutral words by blocks) stimulus are used (60). In contrast, the presentation of pictorial stimuli increases the reliability when compared to the use of word stimuli. Field et al. furthered the work by highlighting that the nature of the stimulus could result in poor reliabilities and proposed for personalization of the images (61). Ataya et al. reported the superior reliability of the Stroop task over the visual probe task (60). However, Field et al. highlighted the drawbacks of the Stroop task, given that it measures not only attentional processes, but also inhibitory control (61). The visual probe task is preferred over the Stroop task for several reasons. The visual probe task is better in assessing for visuospatial attention and it also helps to minimize any response bias due to the participants' underlying motivational state (61). It may also more accurately depict the real-life situation that individuals face, in that they must split their attention between different competing stimuli (63).

Traditionally, reaction time-based tasks have been used, but advances in experimental psychology have resulted in new modalities for bias assessment, facilitating direct measurement of attention biases. This is achieved by measuring eye movements and

their corresponding fixation times (64, 65). Attentional biases are present if individuals with substance use disorders managed to hold their gaze on substance-related cues for longer periods (as measured by eye movement and fixation times) when shown the visual probe task (64). The distinct advantages of measuring eye movements and their fixation times are that they can measure the total time that attention was directed towards the stimulus, as compared to the visual probe which typically only provide information regarding where the participants' attention was allocated when the stimulus disappeared (66). Previous studies have demonstrated that the fixation time measure is more sensitive a measure of attentional bias as compared to reaction time (60,61).

While this is an advantage in terms of assessment, there remains a need to balance the need for accuracy and the complexity of the procedure, and practicalities such as whether the procedure could be performed outside the confines of a laboratory environment. Measurement of eye movements and fixation time could only be done in the laboratory environment, given the need for participants to be seated at a fixed position from the monitor/ tracking device, and with their head resting on a bracket (66). Participants are allowed some head movements, and the amount they could move their head depends on the distance they are from the screen. As an example, for the eye tracking device (Tobii EyeX controller), if participants are seated 700mm from the screen, their head movements are limited to 240mm leftwards and 195mm upwards or downwards (67). For the purposes of this Ph.D. dissertation, indirect measures of assessment for attentional biases will be considered, as they are less expensive and less complex for patients to use.

1.5.3 Overview of Current Findings on Attentional Biases in Addictive Disorders

For Opioid use disorders, previous research has found differences in the magnitude of attentional biases amongst users and non-users, and amongst those with different severity of opioid addiction. Fadardi et al. examined a cohort of 53 individuals on methadone maintenance therapy and 71 individuals who were not misusing (68). They reported that substance users had had higher biases for drug-related stimulus, even after controlling for effects such as age and education (68). Similar findings were reported in the studies of Constantinou et al. and Bearre et al. (69-70). Constantinou et al. examined attentional biases and cravings amongst current users of opioids, ex-users of opioids and non-users (69). The authors' definitions were as follows: current users

consisted of individuals undergoing methadone maintenance treatment; ex-users consisted of abstinent participants attending programs and non-users who have never used opioids (69). They found that those who were currently abusing had a greater magnitude of attentional biases (69). They found that ex-users exhibited a bias away from the drug-related stimulus, which was related to their total duration of abstinence (69). Bearre et al. study reported a relationship between dependence severity (based on the monthly frequency of heroin used, via inhalation or injection) and the overall attentional biases (70). Characteristics like impulsiveness, cravings, temptations to use, and the visual probe task's stimulus timings have been observed to affect attentional biases in opioid users (70). Anderson et al. found attentional biases positively related to impulsiveness, but negatively related to the visual working memory capacity (71). The observations of Water et al. suggest that cravings and temptations to use might affect the magnitude (72). Their study examined participants' affect and cognition before and during a temptation episode and found elevated attentional biases during the temptation episodes, and the magnitude of biases was elevated one hour prior to the temptation episode (72). A temptation episode refers to how individuals who are abstaining from substance use, might experience a sudden urge or craving to use substances, but without relapsing into use (73). Demographic variables, such as gender were also investigated to determine if it accounted for the differences in attentional biases amongst individuals with substance misuse and non-misusers by Fadardi et al., but no associations were found (68).

For Cannabis use disorders, there is also evidence that both the severity of dependence and the quantity of cannabis consumed affect the underlying attentional biases' magnitude. Prior studies, such as that of Field et al. (74), reported that it is not just the frequency of use but also the number of joints smoked that affect attentional biases' absolute magnitude. In two studies by Cousijn, it was reported that attentional biases were mainly amongst heavy users (75,76). Cousijn et al. also highlighted that individual clinically categorised individuals as being dependent exhibited a stronger magnitude of attentional bias than those who were using cannabis heavily but were not dependent (76). In Campbell et al.'s study to differentiate between users and non-users attentional biases, they also reported that the intensity of cannabis used (grams used per week), correlated with the number of errors made during the testing process, and hence affected the magnitude of attentional biases (77).

For Stimulant use disorders, there appears to be a correlation between the severity of the substance dependence and attentional biases like that observed for opioid and cannabis use disorders. Marks et al. measured the fixation time for the computation of attentional biases and reported that only individuals who have had previously misused cocaine had underlying attentional biases (78). They also reported that the magnitude of the attentional biases was correlated with the lifetime use of cocaine (78).

Lastly, for Alcohol use disorders, Field et al. reported how social drinkers tend to have a preferential allocation of attentional processes towards alcohol-related cues in their environment (43). The existence of alcohol-related attentional biases has been reported by Bruce et al. (79). They reported the existence of a more significant alcohol attentional biases amongst heavy drinkers compared to social drinking controls (79). Similar findings were also reported by Field et al., in their sample of 90 adolescent students, of which 38% were heavy drinkers and 36% light drinkers (80). Field et al. reported that attentional biases correlated moderately with the level of alcohol consumption and alcohol cravings (80). So, in summary, it is evident from these studies that attentional biases are present in opioid, cannabis, stimulant, and alcohol disorders, thereby suggesting that the amount and frequency of drug use has an impact on the overall magnitude of attentional biases.

To date, there have been other studies conducted that demonstrated an association between attentional biases and relapse (53). Waters et al. reported that the presence of attentional biases amongst individuals with heroin and cocaine use disorders tend to predict further temptations of drug use (72). Marhe et al. in their study investigating attentional biases during temptations episodes, also reported that attentional biases are predictive of subsequent relapse (81).

1.5.4 Pharmacological Agents and Attentional Biases

The existence of attentional biases has also prompted researchers to evaluate if pharmacological agents could target these biases. Luijten et al., in their systematic review published in 2014, synthesized the evidence-related pharmacological intervention for attentional bias in substance use disorders, which includes stimulant, opioid, and cocaine-dependent individuals (82). The evidence showed that medications

that modulate dopamine do affect the magnitude of attentional biases (82). In the studies included in this systematic review, the pharmacological agents used included that of amisulpride (D2/D3 receptor antagonist), pramipexole dihydrochloride (D2/D3 receptor agonist), haloperidol (D2/D3 receptor antagonist), methylphenidate (dopamine reuptake inhibitor), D-cycloserine (partial glycine-site NMDA agonist), and acute tyrosine or phenylamine depletion (82). There was a reduction in attentional biases after the acute administration of these pharmacological agents (82). However, the reduction in biases were confined to acute effects following a single dose of a particular medication (82). Unfortunately, no long-term studies have been conducted to demonstrate if attentional bias would diminish following longer-term administration of dopamine modulating agents (82).

Other medications, such as Atomoxetine, a pharmacological agent modulating noradrenaline reuptake, is efficacious in reducing attentional biases to cocaine-related cues (83). It is postulated that atomoxetine administration increases noradrenaline levels, particularly in the prefrontal cortex (83). The increase in the noradrenaline levels is associated with increased conscious inhibitory control (83). Despite the promising findings, it should be noted that the study evaluated only the acute effects of a single dose of atomoxetine.

Antidepressant medications, like the selective serotonin reuptake inhibitor, escitalopram have also been evaluated. Liu et al. evaluated the effect of escitalopram on attentional bias in a sample of cocaine-dependent individuals (84). The study by Liu et al. was based on the evidence generated from a preclinical study, which suggested that agonists of the 5-HT_{2C} receptor could affect attentional biases (84). The dosage of escitalopram administered was in the range of 10–20 mg and subjects were followed up for a total of 28 days (84). The selective serotonin reuptake inhibitor is effective in reducing attentional biases only in the acute phase, which was determined by the reduction in attentional bias from baseline that occurred five hours following the administration (84). When Stroop testing was re-administered subsequently, the continued administration of escitalopram did not produce any significant changes in attentional biases from baseline. The acute effects of escitalopram on attentional biases might be due to the increased activation of the 5-HT_{2C} receptors, while the lack of a reduction in attentional biases following chronic administration might be accounted for

by adaptive changes in post-synaptic receptors (84). Liu et al. also pointed out that the chronic administration of escitalopram might have resulted in desensitization of the 5-HT_{1A} auto receptors; hence, the prolonged administration of escitalopram did not result in further increases of serotonin levels (84).

The findings from these studies demonstrate that pharmacological agents help modulate attentional biases when these medications are given acutely. The evidence arising from Liu et al. demonstrates that serotonergic medications' chronic administration does not alter attentional biases (84). There is a need for further studies to evaluate the longer-term efficacy of these pharmacological agents. However, it is also important to consider if these agents should be used, given their risk of side effects, such as extra-pyramidal side effects, amotivation and apathy.

1.5.5 Overview of Research Findings on Attention Bias Modification

There is evidence for the effectiveness of the utility of attentional bias modification. Fadardi & Cox et al. and McGeary et al. reported how attentional bias modification resulted in a significant reduction in alcohol consumption amongst heavy or social drinkers (85,86). Schoenmakers et al. reported how the administration of attentional bias modification led to individuals having longer periods of abstinence (87). In Ziaee et al.'s research, attentional bias modification also helped methadone-maintained individuals reduce their attentional biases toward drug cues, temptations to use, and the number of lapses, as compared to those who only received conventional treatment (88). To date, there is only a single review conducted by Cristea et al. that have examined the evidence for attention bias modification in amongst individuals with tobacco and alcohol use disorders (89). This review had examined 25 randomized controlled trials, 18 of which involved participants with alcohol use disorders, and 7 involved participants with tobacco use disorders (89). In this review, the visual probe task was used in all twelve studies that investigated attentional biases; and it should be noted that the review not only investigated attentional biases, but that of approach biases (89). The review demonstrated that there was evidence for cognitive bias modification on cognitive biases (Hedges' $G = 0.60$) (89). With regards to outcome, there was significant effect on clinical outcomes for alcohol, but not for smoking.

1.5.6 Overview of Technology & Attention Bias Modification

Electronic health (eHealth) refers to the use of Web-based interventions and mobile health (mHealth) refers to the use of mobile devices, such as smartphones and their accompanying apps, for health care (90, 91). In psychiatric practice, both eHealth and mHealth technologies have been adopted to deliver psychological interventions for patients with depression and monitor patients' mood state in bipolar disorders and reduce drinking among individuals with alcohol issues (92, 93). These advances in m-health technologies have also facilitated how conventional attention and cognitive bias modification tasks are being delivered. For example, Wiers et al. evaluated an automated cognitive bias modification program for problem drinkers that was delivered using the Internet (94). In their study, approach and avoidance biases were targeted as part of an online cognitive bias intervention. Wiers et al. observed a reduction in drinking across all the groups, including the group that has received only sham training (94). Despite the negative study's findings, Wiers et al. showed the feasibility of delivering bias modification programs using the Internet (94). However, one of the major limitations of such a delivery mechanism would be that of attrition as half of the recruited participants did not commenced on the intervention and a further half of the sample dropped out during the intervention (94). M-Health technologies have also been used to deliver attentional retraining interventions, as reported by Kerst et al., in which the authors described the use of such interventions amongst individuals who smoke (95).

1.6 Identified Research Gaps

In 2017, I performed a review the existing literature on attentional biases, bias modification, and the impact of technology on disseminating attention bias intervention. This led to the conceptualization of a perspective article, which has been published as Zhang et al. (56) (Appendix 1). This review identified several important research gaps which I wish to address within my doctoral work. Further evaluation of these research gaps is essential to reinforcing the evidence supporting the use of attention bias assessment and modification among individuals with addictive disorders. The key research gaps are described below:

a. Lack of evidence regarding attention bias in individuals with substance use disorders and the effectiveness of bias modification in individuals with Opioid, Cannabis, Stimulant Disorders

There is a growing trend towards the abuse of substances like opioids, cannabis, and stimulants globally, including in Singapore. Unfortunately, the evidence regarding attentional biases, and the effectiveness of bias modification has not been adequately studied for these disorders. As of 2017, only two prior reviews were identified, both with limitations. Christiansen et al. had reviewed studies that involved participants who had been using alcohol, tobacco, cocaine, and cannabis, but failed to specify the inclusion and exclusion criteria and the time frame to which the search was restricted (35). Furthermore, only PubMed and Scopus (and previously published reviews) were searched out, but other databases such as PsycINFO and MEDLINE were not included (35). The other meta-analytical review conducted by Cristea et al. involved only participants with alcohol and tobacco use disorders (89).

There is an urgent need to synthesize the evidence to demonstrate that attention bias exists amongst individuals with opioid, cannabis, and stimulant disorders; and for there to be an understanding of the effectiveness of bias modification. If attention biases are indeed present, this underscores there being a need for bias modification. The information pertaining to the evidence for bias modification will influence the conceptualization and design of subsequent studies seeking to retrain biases amongst these individuals. With this, attention bias modification could then be incorporated into existing treatment programs, potentially as an adjunctive treatment to that of conventional psychotherapies.

b. Absence of formal evaluation of existing mobile and commercially available attention bias interventions

As discussed above, there is evidence of how technology has transformed the delivery of attention bias modification interventions. To date, there remains no prior review that has systematically synthesized the evidence for such interventions for mobile bias modification interventions. Therefore, there is a need to synthesise the literature, highlight the evidence, and comprehensively understand the research findings (i.e., the common functionalities and methods of bias modifications). While my PhD work is

focused primarily on addiction disorder, it is necessary to examine how technology has facilitated cognitive bias modification interventions for a range of psychiatric disorders to identify generic problems and solutions. As cognitive bias and attentional bias modification have been well investigated amongst other disorders like anxiety disorder (Jones et al), it makes sense to include these applications in our evaluations as well, so that the methods and functionalities that render such interventions effective could be identified, and potentially applied to future interventions involving addictive disorders (96).

Several content analyses (Weaver et al., Crane et al., Hoeppner et al. and Ramo et al.) have highlighted the increase in the numbers of commercially available applications for addictive disorders, such as alcohol and cannabis disorder (97-100). Given the richness of this readily available data source, it makes sense to explore commercially available cognitive bias modification interventions and determine their evidence base. The information derived from the synthesis of both the research literature and commercially available applications would aid in guiding the conceptualization of an attention bias modification intervention for the purposes of this PhD.

c. Addressing patient Attrition and Poor Motivation to Train: Is gamification appropriate?

Bias assessment and modification intervention is highly repetitive over time and could potentially reduce motivation to train and attrition from the planned interventions. Some researchers have examined if tasks could be gamified to increase the motivation to use them (101). Boendermaker et al. reported how gamification strategies could be applied to bias modification interventions, and they also described a study investigating a gamified bias modification intervention (102,103). However, there remains no published review that has systematically evaluated all the existing gamified bias interventions. It is important to conduct such reviews to further our understanding of the overall effectiveness of a gamified approach and delineate the gamification strategies that are likely to enhance the effectiveness of the interventions.

d. Further Evaluation of Attention Bias Modification among Illicit Substance Use Disorders is urgently needed in Singapore

As aforementioned, attention bias modification intervention might target implicit processes leading individuals to a lapse or relapse, despite having received efficacious conventional psychological therapies. There has been evidence for the bias retraining for individuals with alcohol use disorders, as highlighted previously by the works of Fadardi & Cox et al. and McGeary et al. (85,86). Some of these prior research, such as that of Wiers et al., Eberl et al. and Manning et al. have reported how they applied bias modification interventions (not limited to the modification of attention biases, but also approach biases) amongst inpatient participants (37, 52, 104). Manning et al. reported the importance of having inpatient participants undertake cognitive bias modification interventions, as these individuals are in the early stages of recovery and abstinence, and cognitive bias modification could capitalize on the initial stages of neural recovery (52). As compared to alcohol use disorders, there is lesser evidence for the effectiveness of attention bias modification for illicit substance disorders.

Whilst there have been recent attempts to investigate such interventions amongst individuals with opioid use disorders (methadone-maintained individuals and individuals with cocaine use disorders, there remained limitations with these studies (88, 105). Whilst Ziaee et al.'s study provided evidence for a three sessions attention control training as compared to a control group; their participants were receiving opioid substitution therapy (88). There remain no studies investigating the effectiveness of such training amongst individuals who are not maintained on opioid substitution therapy, which is the case for almost all patients with opioid use disorders in Singapore. Mayer et al.'s prior study recruited only participants who were using cocaine and reported there being null findings for bias retraining (105). Several reasons could explain the null findings obtained. Firstly, the sample size was modest and hence the study was underpowered (105). Secondly, all participants undertook motivational interviewing before the session for ethical reasons and the provision of motivational interviewing might affect the measurement of baseline bias and have had an impact on the overall treatment (105). Lastly, participants undertook a total of 5 sessions of bias retraining, and the authors reported that 5 sessions might not be sufficient to effect a

change in biases (105). Unfortunately, the authors did not specify the recommended number of sessions (105). There remains a need for further evaluations with regards to how attentional bias modification would benefit individuals with highly prevalent illicit drug use disorders, that of opioid, cannabis, and stimulant use (such as methamphetamine) use disorders, given the evidence there is for alcohol use disorders. Future studies should also take into considerations the findings of existing completed studies, and some of their limitations. It is important to determine the potential of attention bias modification, as a standalone therapy by itself. Moreover, as the treatment approach differs in the Singapore's context, particularly for opioid use disorder (the absence of opioid substitutes), it would be interesting and novel to determine if attention bias modification could help reduce biases amongst these individuals.

Some of the prior works have investigated bias modification amongst participants admitted to a rehabilitation program, such as Eberl et al. and Manning et al. (52,104). This research is based on an alcohol-using population. No trial has investigated attention bias modification amongst an Asian cohort admitted to a rehabilitation program. The differences in genetics, culture, drugs abused, healthcare systems and penal codes warrants there to be further evaluative work, such as that of a feasibility and acceptability study, and a pilot study investigating this.

e. The necessity of considering Co-design and participatory research methods

Recognising the needs of service users/participants is crucial to the development of an efficacious intervention. Most of the existing interventions in healthcare are developed using a top-down approach without patient involvements. This top-down approach assumes that organisations and healthcare professionals are experts who accurately understand patient needs (106). In recent years, the importance of participatory action and design research (PDR) has been recognised increasingly and studies have been undertaken including all relevant stakeholders in the research process and co-create a solution for a problem (106,107). Participant involvement is most common in the following areas: developing and defining the core research questions, the conduct of the research, the collation of research data and the dissemination of data and findings. A prior review of nursing research, between 2000 to 2005, found at least 38% of the research studies have used some of these methods (108). These approaches have been widely used in medical disciplines; for example, in their review, Blair et al. identified

10 studies, involving geriatric patients (109). Such methods have also been adopted for mental health/psychiatry research. O’Conner et al. used a focus group to understand the barriers encountered by individuals living with dementia (110). This approach helped them to co-design a mobile intervention for these individuals. Other researchers, such as Ospina-Pinillos et al. have involved young individuals, aged between 16 to 25 years old, to co-design a solution for a web-based mental health clinic (111). The co-design approach was chosen to ensure that the needs of young people were met and that they had timely access to care. These prior works have demonstrated how co-designing helps in refining existing interventions.

Co-design offers the opportunity perhaps to reduce the impact of users of the repetitiveness of attention bias retraining program and the high attrition rates associated with the interventions. The inclusion of service users’ views on the technology would encourage better engagement and reduce attrition. The integration of existing evidence and theoretical constructs along with co-design is a powerful combination.

1.7 Aims of my Doctoral Research

My doctoral study aimed to develop a mobile attention bias modification intervention that could be used as an adjunct to conventional pharmaceutical and psychological therapies for treatment-seeking Asian individuals with addictive disorders.

1.8 Objectives

The specific objectives of this body of research were to:

1. Determine the evidence base for the existence of attention biases amongst individuals with illicit substance use disorders (opioid, cannabis, and stimulant disorders), and the effectiveness of bias modification (Review 1)
2. Examine the literature on M-Health cognitive bias modification interventions through a systematic review and a content analysis of commercially available applications (Review 2)
3. Systematically synthesize the literature on gamified M-health cognitive bias modification interventions (Review 3) to determine if gamification could be used to enhance acceptability.

4. Conceptualize a Mobile Attention Bias Intervention based on synthesized evidence from the literature (Reviews 1 & 2) and further review of the nature of the visual probe paradigms in the literature in preparation for the conduct of Study 1
5. Conduct a feasibility study amongst Singaporean patients undergoing rehabilitation using the newly conceptualized mobile attention bias modification intervention (Study 1).
6. Refine the Mobile Attention Bias Intervention (Study 2) through a co-design process involving healthcare professionals and patient participants and exploring if gamification strategies identified in Review 3 could be incorporated.
7. Design and conduct a randomized pilot trial to test the intended process of a randomized trial comparing the codesigned app against the conventional app (Study 3).
8. Design the study protocol for a definitive randomized trial.

1.9 Revised Objectives

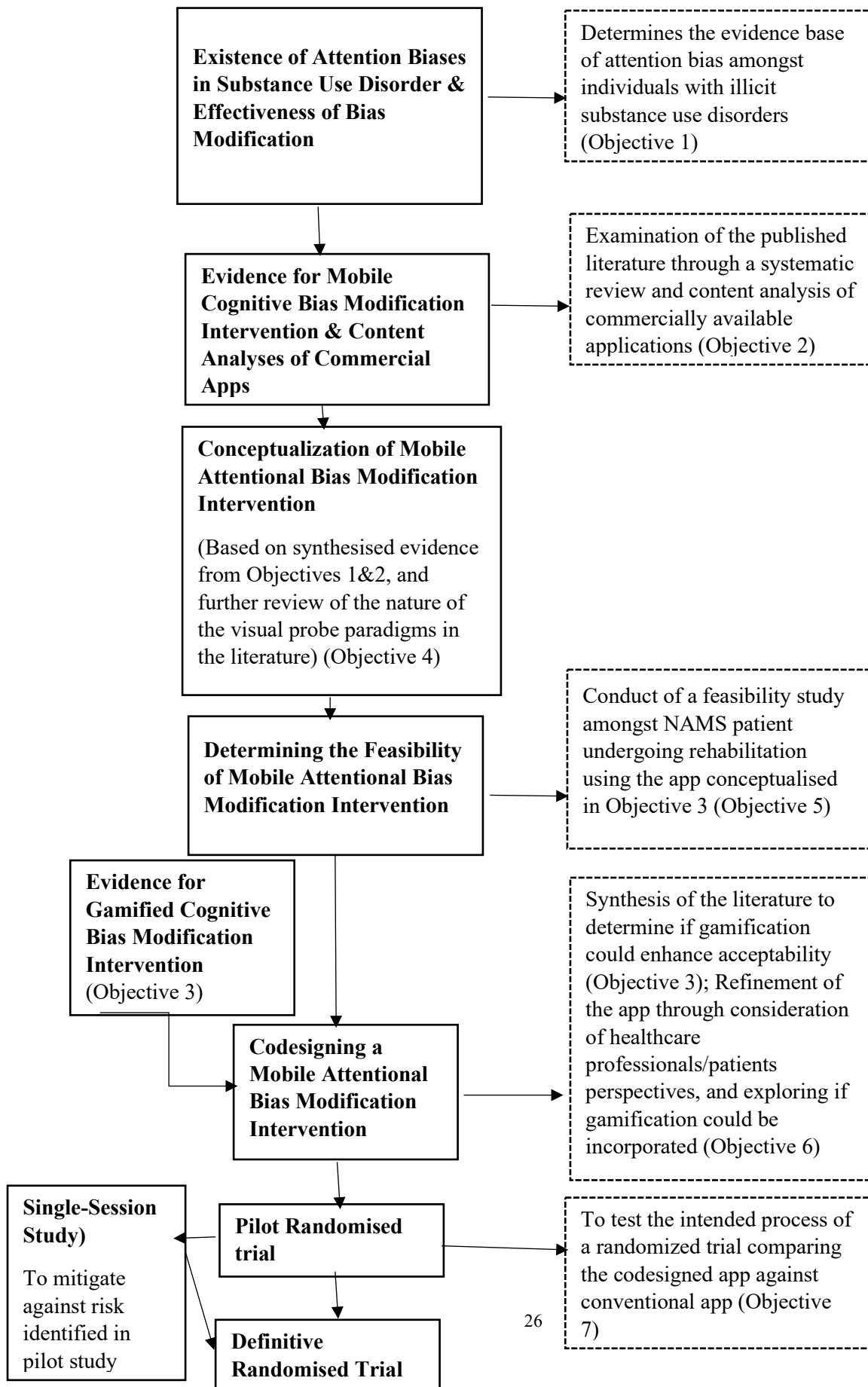
Objective 7 could not be achieved due to the onset of the COVID-19 pandemic and the subsequent expiry of the funding, leading to the suspension of the study. A risk assessment was conducted, and a subsequent study conducted, in order to optimize the methods for the definitive randomised trial. The revised objectives are as follows:

1. Determine the evidence base for the existence of attention biases amongst individuals with illicit substance use disorders (opioid, cannabis, and stimulant disorders), and the effectiveness of bias modification (Review 1)
2. Examine the literature on M-Health cognitive bias modification interventions through a systematic review and a content analysis of commercially available applications (Review 2)
3. Systematically synthesize the literature on gamified M-health cognitive bias modification interventions (Review 3) to determine if gamification could be used to enhance acceptability.
4. Conceptualize a Mobile Attention Bias Intervention based on synthesized evidence from the literature (Reviews 1 & 2) and further review of the nature of the visual probe paradigms in the literature in preparation for the conduct of Study 1
5. Conduct a feasibility study amongst Singaporean patients undergoing rehabilitation using the newly conceptualized mobile attention bias modification intervention (Study 1).

6. Refine the Mobile Attention Bias Intervention (Study 2) through a co-design process involving healthcare professionals and patient participants and exploring if gamification strategies identified in Review 3 could be incorporated.
7. Design and conduct a randomized pilot trial to test the intended process of a randomized trial comparing the codesigned app against the conventional app (Study 3).
8. Conducting a Single-session attention bias modification study to evaluate if a new computational method (Trial-level bias method) could identify more baseline biases, and if a single-session approach could reduce attentional biases, to mitigate against the issues of recruitment and attritions in the pilot study
9. Design the study protocol for a definitive randomized trial

Figure 1.3 provides an overview of the studies involved in this PhD body of work, and how they are related to one another.

Figure 1.3 Overview of Studies involved in this PhD Work



1.10 Contents of the Dissertation

Chapter 1 introduces cognitive biases and identifies the research gaps pertinent to this body of work and describes the aims and objectives of this work. Chapter 2 systematically summarises the evidence for attention bias in opioid, cannabis, and stimulant disorders and the overall effectiveness of bias modification. Chapter 3 provides justifications for exploring mobile technologies in delivering attention bias modification by systematically summarizing the evidence for mobile cognitive bias modification in the published literature; and examining commercially available cognitive bias modification interventions to determine if they adhere to the evidence based. Chapter 4 explores how gamification strategies have been adopted in cognitive bias modification interventions through another systematic review and a content analysis. The information derived from Chapter 4 is used in the application of funding for the subsequent co-design study. Chapter 5 describes a mobile attention bias modification intervention's conceptualisation, based on evidence arising from Chapter 2 &3, and a further review of the visual probe task paradigms in the published literature. Chapter 6 then describes the feasibility and acceptability study of the newly conceptualized mobile attention bias modification intervention to answer the research question of whether such an intervention could be conducted amongst NAMS patients. Chapter 7 addresses the limitations of the mobile intervention highlighted by participants in the feasibility and acceptability study through a codesign process involving patient and healthcare professionals. Chapter 7 also utilizes the evidence from Chapter 4 in determining if gamification strategies could be implemented to address existing limitations of the intervention. Chapter 8 describes the conduct of a pilot study that seeks to refine the definitive randomised trial processes, which seeks to examine the effectiveness of the co-designed intervention against the conventional intervention. Chapter 9 describes a new method of computing attentional biases (trial-level bias score), that might mitigate against the issue of poor detection of biases at baseline. Chapter 9 also compares the trial level bias method of computing attentional biases against the conventional method in NAMS patients. Chapter 10 describes the conduct of a study examining a single session approach towards bias modification, in order to mitigate against the risks of patient attrition. Chapter 11 describes the protocol for the main definitive randomized trial. Chapter 12 summarizes my main findings and the resultant clinical and research implications.

1.11 Originality/Novelty of the Current Work

The work undertaken as a part of my doctoral programme is original and includes the following key features:

- a. This work advances the knowledge and understanding of attention bias and bias modification amongst individuals with highly prevalent illicit substance use disorders, opioid use, cannabis use and stimulant use disorders.
- b. This work explores the effectiveness of existing mobile-based cognitive bias modification interventions and explores if commercially available applications have been conceptualized based on the existing evidence base.
- c. This work attempts to address the clinical problem that of relapses amongst individuals with addictive disorders, by exploring the potential of an attention bias modification intervention in regulating implicit cognitive processes.
- d. This work is the first to explore attentional biases and bias modification amongst an Asian cohort of individuals.
- e. This study's novelty includes the adoption of co-design techniques in refining a conventional intervention to ensure that the intervention is relevant to the specific needs of participants, whilst based on evidence.
- f. The conceptualisation steps and the studies conducted are in line with the MRC (Medical Research Council)'s guidance for how complex interventions ought to be implemented.
- g. This work is the first to demonstrate the temporal variability of attentional biases among individuals with opioid and alcohol use disorders and compares the new computational method (TLBS) against the mean bias method to see if the new method could identify more individuals with baseline biases.
- h. This work also explored the feasibility of a single-session approach in the modification of attentional biases among individuals with either opioid or alcohol use disorders.
- i. The RCT protocol that has been conceptualized is pragmatic and considers alternative approaches for us to recruit the desired sample size.
- j. This work considers a pragmatic approach in the conceptualization of a mobile attention bias modification intervention for individuals with addictive disorders.

Chapter 2 Evidence for Attention Bias

This chapter explores the evidence for attention bias in opioid, cannabis, and stimulant use disorders. The first part of this chapter describes a systematic review of attentional biases and bias modification. Sections 2.2 and 2.3 provide an overview of the methods used in the systematic review. Section 2.4 highlights the study's main findings and limitations. The second part of this chapter describes a secondary systematic review which addresses the limitations of the first review. Sections 2.5 and 2.6 present the methods and results of the secondary systematic review. The chapter concludes with a discussion of the main findings and their implications for this dissertation.

2.1 Introduction

The introductory chapter highlighted the lack of synthesised evidence for attentional biases and effectiveness in highly prevalent illicit drug use disorders (e.g., opioid use, cannabis use and stimulant use). The brief literature overview demonstrated the presence of attention biases amongst opioid, cannabis and stimulant use disorders and the correlation between the nature and frequency of drug use and the magnitude of attentional biases. This chapter seeks to consolidate all the evidence from the literature relating to attentional biases through a systematic review. The secondary aim of the review was to determine the clinical effectiveness of attentional bias retraining. The protocol for the systematic review was formulated and has since been published (112) (Appendix 2). The findings from this review were subsequently published in June 2018 (113) (Appendix 3).

2.2 Methods

2.2.1 Search Strategy

A search was conducted from November 2017 to January 2018 on seven databases from inception to January 2018: PubMed, MEDLINE, Embase, PsycINFO, Science Direct, Cochrane Central and Scopus. The following search terminologies were employed: ('attention bias' or 'approach bias' or 'avoidance bias' or 'cognitive bias') and ('addiction' or 'substance' or 'drug' or 'abuse' or 'dependence' or 'opioid' or 'heroin' or 'cannabis' or 'marijuana' or 'stimulants' or 'amphetamines' or 'cocaine').

2.2.2 Inclusion and Exclusion Criteria

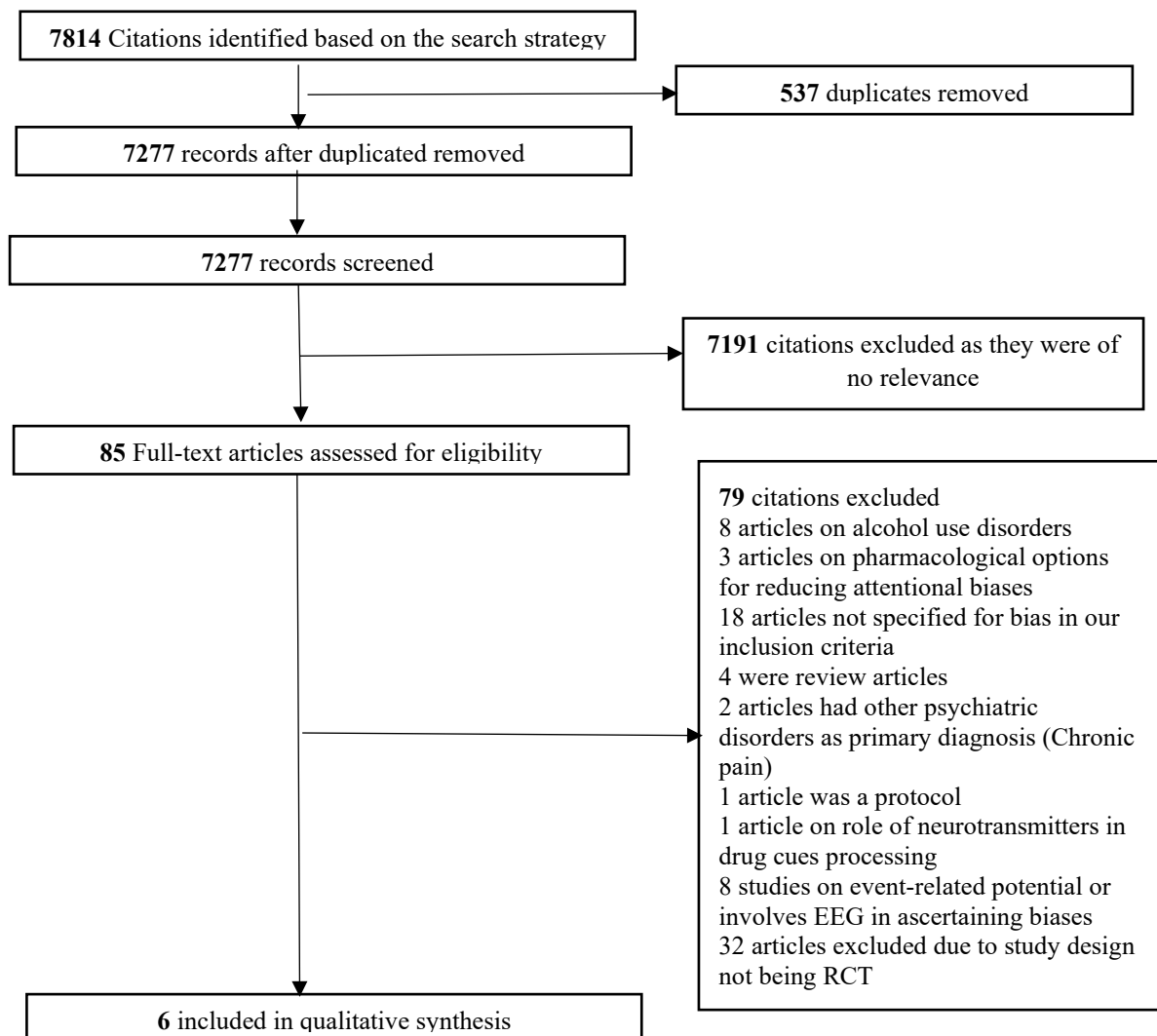
English-language articles that fulfilled the following inclusion criteria were included: (a) presence of attention bias assessed using a validated measure; (b) study participants with a primary diagnosis of opioid use, cannabis use or stimulant use disorder and (c) study design that was a randomised trial. Articles were excluded if (a) they did not include a validated measure for assessing attention bias; (b) study participants were diagnosed with other psychiatric disorders as the primary diagnosis (e.g. depression and anxiety disorders); (c) the studies involved a pharmacological intervention in which medications were utilised to examine their effects on attention bias; or (d) the randomised trial involved a cross-over design, which were excluded due to their high risk of bias.

Given systematic reviews of randomised trials provide the highest level of evidence and because strong inferences can be drawn from the evidence synthesis of randomised trials, this systematic review only considered randomised controlled studies (114).

2.2.3 Articles Selection

Relevant articles were selected independently by two authors (myself and another study team member, a trainee psychiatrist). Articles were first screened based on their titles and abstracts. Shortlisted articles were then evaluated against the inclusion/exclusion criteria. In the event of disagreements regarding the articles' screening based on their titles and abstracts, or if there was no consensus on article inclusion/exclusion, another senior team member (an addiction psychiatrist) was consulted.

The selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) (115). Figure 2.1 provides an overview of the selection process for all articles. The flowchart in Figure 2.1 has been adapted based on the PRISMA 2009 Flow Diagram (115).

Figure 2.1 Overview of the PRISMA diagram for the article selection.

2.2.4 Data Extraction

The following data and information were extracted from each article and recorded on a standardised electronic data collection form: (a) publication details (author(s) and study year); (b) study design and methodology (study design, sample size, types of sample, country, demographics of sample, participants' diagnoses, and diagnostic methodology); (c) attention bias assessment and modification methodology; (d) outcomes of interest (e.g. craving scores, addiction outcomes, effect size for attention bias modification procedure).

2.2.5 Data Analysis and Synthesis

Due to the diversity of the reported outcome measures, a qualitative synthesis was performed.

2.2.6 Quality Assessment

The Cochrane Risk of Bias tool was used for the risk of bias assessment. Risk of bias assessment was conducted for the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases (116). For each of these domains, the risk was judged as high, low, or unclear. High or low risk refers to the extent to which the bias affected the results, while unclear risk refers to how the risk cannot be ascertained due to insufficient details reported in the trial (116,117)).

2.3 Results

Based on the pre-defined search strategy, 7814 citations were identified from the databases; 537 duplicate articles were excluded, 7277 records were screened, and 7192 citations were excluded as they were irrelevant to the topic of interest. Eighty-five full-text articles were downloaded for further evaluation against the inclusion/exclusion criteria. Seventy-nine citations were excluded as they did not fulfil the inclusion criteria, leaving six articles for the eventual qualitative synthesis.

Table 2.1 provides an overview of the included studies' characteristics. Half of the identified articles involved opioid use disorders, and the other half involved cocaine use disorders.

Table 2.1 Characteristics of the included studies

Study	Study Design	Sample Size	Types of Sample	Demographics of Sample	Country	Diagnosis of Sample	Method of Diagnosis	Attention Bias Method	Outcomes
Franken. et al. (118)	Randomised trial	21 heroin-dependent participants 30 control participants	Participants with heroin dependence were recruited from an inpatient treatment centre Participants in the control group were recruited among clinical and administrative staff in the clinic	71.4% males (heroin-dependent) 83.3% (control group) Mean age 31.5 years (heroin-dependent) Mean age 34.8 (control group) Mean self-reported duration of heroin dependence was 93.9 months	Netherlands	Heroin Dependence	Based on the DSM-IV criteria for heroin dependence	Drug Stroop task	Higher overall reaction time for heroin participants as compared to control participants Mean pre-experimental craving was 13.8, mean post masked Stroop was 7.19 and mean post unmasked Stroop was 15.2
Lubman et al. (119)	Randomised trial	16 methadone-maintained opiate addicts 16 age-matched control	Heroin addicts were recruited from local drug services Staff from these services were recruited as controls	Opiate group: mean age 31.4, Male to Female 11:5 Control group: mean age 31.7, male to female 8:8	United Kingdom	Heroin Dependence	ICD-10 and DSM IV	Pictorial Probe Detection Task	Faster reaction times to probes that replaced drug stimuli, indicative of the presence of an attentional bias
Marissen et al. (120)	Randomised trial	110 Participants assigned to either cue exposure therapy or placebo psychotherapy	Abstinent heroin addicts who were admitted voluntarily to an in-patient drug-free therapeutic centre in the Hague	89% males, mean age 34 years old Average age of onset of heroin usage was 21.4 years, most have used heroin for 9.3 years	Netherlands	Heroin Dependence	DSM-IV criteria for heroin dependence	Emotional Stroop Task	Pre-treatment attentional bias predicted relapse at three months follow-up Reduction of attentional biases in both experimental conditions

Study	Study Design	Sample Size	Types of Sample	Demographics of Sample	Country	Diagnosis of Sample	Method of Diagnosis	Attention Bias Method	Outcomes
Montgomery et al. (121)	Randomised trial	32 regular cocaine users and 40 non-users	Student Population at Liverpool John Moores University and the general population in the surrounding areas	Mean age for cocaine users assigned to placebo 19.29, assigned to alcohol 20.23 Mean age for non-users assigned to placebo 19.59, assigned to alcohol 20.0 13 male in cocaine use group 19 male in non-cocaine use group	United Kingdom	Cocaine dependence	Questionnaire	Visual Probe and Modified Stroop task	Cocaine participants who received alcohol had increased attentional bias for cocaine pictures The cocaine Stroop revealed no differences between cocaine users and non-users, and no effects of alcohol in either group
Mayer et al. (105)	Randomised trial	37 participants assigned to either attentional bias modification therapy (ABMT) or control therapy	Not mentioned	ABMT group: 14 male, and 5 female, mean age 37.4 Control group: 10 male and 8 female, mean age 38.9	United States	Cocaine dependence	Structured clinical interview for DSM-IV	Visual Probe task	Presence of attentional bias Attentional bias not subjected to modification by ABMT
DeVito (122)	Randomised trial	38 in treatment as usual plus computer-based CBT (CBT4CBT) 41 in treatment as usual	Recruited from community-based outpatient clinic	46% female, mean age 42.2	United States	Cocaine use disorder	DSM-IV	Computerized drug Stroop test	Stroop testing revealed that participants who have had a longer duration of cocaine abstinence during treatment (3+ weeks) have greater reductions in Drug Stroop effect. Engagement with CBT4CBT intervention also led to a reduction in Drug Stroop effect

2.3.1 Overview of Studies

The six randomised trials were quite varied in terms of their aims and their target participants. One (Mayer et al.) investigated the impact of attention bias modification on attention bias (105). Franken et al.'s had participants undertake a Stroop task to assess attention bias (118). The trial by Lubman et al. employed the pictorial probe task to assess attentional bias (119). The trial by Marissen et al. investigated the effects of cue exposure therapy rather than attention bias modification on attention bias (120). In the remaining two cocaine trials, one (Montgomery et al) evaluated the effects of alcohol administration on attentional bias (121). DeVito et al. evaluated the effects of computer-based CBT as CBT is believed that to strengthen cognitive control processes (122).

2.3.2 Characteristics of three studies for Opioid Use Disorders

The three randomised trials (Franken et al.; Lubman et al.; Marissen et al.) that included participants with opioid use disorders recruited from an inpatient treatment unit, local drug and treatment services, and a drug and rehabilitation therapeutic unit respectively (118-120). The sampled individuals were all seeking treatment and had a mean age in the thirties. All three trials involved a predominantly male cohort. The diagnoses were ascertained using psychiatric assessments, based on either the DSM-IV criteria or the ICD-10 diagnostic criteria. Two of the three trials used the Stroop-based task to assess attention bias (118,120).

2.3.3 Primary and Secondary Outcomes Reported in the Three Studies for Opioid Use Disorder

All three trials reported the presence of attention biases in opioid use disorders. Franken et al. reported that individuals with opioid use disorder had longer reaction times for cues than the controls, while Lubman et al. reported that opioid users tended to demonstrate faster reaction times for probes that replaced drug-related stimuli (118, 119). The included studies reported various secondary outcomes. Franken et al. reported that bias modification led to decreased cravings (118). Marissen et al. reported that baseline attention biases were predictive of subsequent relapses at three months of follow-up and that cue exposure therapy did not significantly reduce attentional biases compared with placebo psychotherapy (120).

2.3.4 Characteristics of Three Studies on Stimulant (Cocaine) Use Disorders

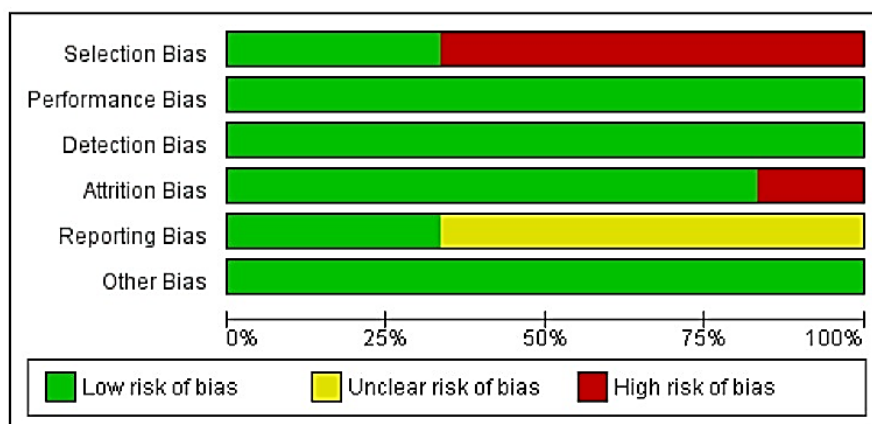
Three studies examined attentional biases amongst individuals with cocaine use disorders. Two of the three trials provided information on their participants' origin. Montgomery et al. recruited a student sample, whereas DeVito et al. recruited participants from community-based clinics (121,122). The participants' mean age ranged from 19.29 years and 42.2 years. Men did not predominate in these trials. Notably, Montgomery et al. trial established the cocaine dependence diagnosis using a questionnaire, whereas the other trials ascertained the diagnosis using a structured clinical interview and DSM-IV criteria (121). The visual probe and Stroop tasks were employed for ascertaining attention biases.

2.3.5 Main Outcomes Reported in Studies for Stimulant (Cocaine) Use Disorders

All three trials reported finding attention biases in individuals with cocaine use disorders. The three trials also involved interventions in modifying attentional biases. Montgomery et al. demonstrated that attention biases toward cocaine-related stimuli were heightened when alcohol was administered, whilst DeVito reported that attentional biases were reduced with CBT intervention (121,122). Notably, Mayer et al. reported that attention bias modification was ineffective in reducing biases (105). In the three included randomised trials, only Mayer et al. evaluated the efficacy of attention bias modification but reported negative findings (105). DeVito et al. evaluated the potential of computer-based CBT in enhancing executive cognitive control processes and reducing attentional biases (122). The search strategy revealed no randomised trials for cannabis use disorders.

2.3.6 Quality and Risk of Bias Assessment

The identified studies conducted risk of bias assessments using the Cochrane Risk of Bias tool. Review Manager 5 (RevMan5) was used to prepare both Figures 2.2 and 2.3. Figure 2.2 provides an overview of the overall risk of each type of bias for all studies. The percentages of low, unclear and high risk of bias were automatically computed by RevMan5 for all included studies. Figure 2.3 provides an overview of the risk of bias assessments in each study.

Figure 2.2 Overview of the overall risk of bias assessment**Figure 2.3** Risk of bias assessment in each of the identified studies ($n = 6$)

	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias
Devito EE et al. (2017)	⊖	⊕	⊕	⊖	⊕	⊕
Franken IH et al. (2000)	⊖	⊕	⊕	⊕	?	⊕
Lubman Dr et al. (2000)	⊖	⊕	⊕	⊕	?	⊕
Marissen M et al. (2006)	⊕	⊕	⊕	⊕	?	⊕
Mayer AR et al. (2016)	⊕	⊕	⊕	⊕	?	⊕
Montgomery et al. (2010)	⊖	⊕	⊕	⊕	⊕	⊕

⊕ : Low Risk of Bias; ? : Unclear Risk of Bias; ⊖ : High Risk of Bias

All six studies demonstrated high risk in selection bias and attrition bias. The study by Franken et al. was graded as at high risk for selection bias due to its recruitment process (inpatient treatment centre for participants and clinics for controls) and discrepancies in educational level, with controls having higher educational levels (118). Similarly, Lubman et al.'s included heroin users with significantly lower intelligence quotients

and higher levels of anxiety and depression than the controls (119). The study by Montgomery et al. also had selection bias, in that the cocaine users had significantly higher scores than non-users on the Alcohol Use Disorder Identification Test (AUDIT) compared with the non-users (121). The trial by DeVito et al. also rated a high risk of selection bias (only participants with Stroop data during preassessment and post-assessment were included) (122) and a high risk of attrition bias (of the original 101 recruited participants, data computation and analysis were only performed on an ultimate sample of 61).

2.4 Critique of Findings

This review's primary objective was to determine the evidence for attention bias among illicit substance use disorders. The six randomised trials included (three of which involved participants with opioid use disorder; the other three involved participants with cocaine use disorder) demonstrated that attentional biases were present. There were similarities in the participants' demographics (treatment-seeking individuals, predominantly men and diagnosis ascertained based on psychiatric assessments) in the three trials with opioid use disorder. Attentional bias was present across all six trials, despite varying assessment methods using either the Stroop or visual probe test. Across the six trials, there was no consensus that attention bias modification was effective. Evidence synthesis for other secondary outcome measures could not be performed given the reported measures' heterogeneity and the small number of trials. The risk of bias assessment for the included trials revealed a high risk of selection and attrition bias.

As there were no identified trials involving cannabis use disorder, the results of this review were unable to address the main research question. In undertaking this review, the decision was made to include only randomised trials for several reasons. The inclusion of randomised trials would ensure that only high-quality evidence was included. Moreover, the inclusion of these trials would enable the determination of the effectiveness of attention bias modification, if it was evaluated. As evident from the research literature, there were intrinsic advantages to including only randomised trials, such as minimising confounding factors by randomising and minimising biases by double-blinded processes (123). This review's main limitation was that there might be other studies investigating the presence of attentional bias and the effectiveness of

attention bias modification but were excluded due to their study design. The present review did not consider the articles identified by the review by Christiansen et al. because the study design was not a randomised controlled trial (47). The pursuit of scientific rigour has resulted in the exclusion of the above-mentioned studies. Moreover, even though randomised trials were included, the included studies have had high risk of bias (especially attrition and selection biases). Randomisation has potentially not minimised the confounder risk.

Other researchers, such as Shirer et al., have highlighted the need to include other trial designs, given that the additional information derived could help in clinical reasoning and provide a solid foundation for causal inferences (123). Peinemann et al. also recommended that other study designs be considered depending on the clinical questions that needed answering (124). Taking these into consideration, restricting the inclusion criteria to include only randomised trials would result in a significant number of observational studies being excluded, as demonstrated by Christiansen et al.'s review (47). Given that many of these substances are globally considered illicit, it is potentially difficult for researchers to conduct randomised trials due to the ethical and legal concerns associated with a randomised trial.

2.5 Secondary Study Undertaken in Response to Critique of Findings

Recognizing the previous review's limitations, a second systematic review was undertaken to improve on the inclusion of evidence synthesised. The search strategy, article selection and statistical analysis were like those of the previous review. The search timeframe was also November 2017 to January 2018, searching the databases from inception to January 2018. The differences were in the methods relating to the definitions of the inclusion/exclusion criteria.

2.5.1 Revised Inclusion and Exclusion Criteria

The inclusion criteria were (1) publication in English only and (2) inclusion of participants with a primary diagnosis of opioid, cannabis, or stimulant use disorder. The exclusion criteria were (1) participants with other psychiatric disorders as a primary disorder or (2) the inclusion of a pharmacological intervention that examined medications to determine their effects on cognitive biases. All types of study designs were included.

The findings from this review were published in August 2018 (125) (Appendix 4).

2.6 Results

A total of 7,814 citations were extracted from Embase, PsycINFO, Science Direct, Scopus, MEDLINE, and PubMed, of which 537 duplicated articles were removed, leaving 7,277 citations. Further screening removed 7,192 citations deemed irrelevant. Eighty-five full-text articles were downloaded and evaluated against the inclusion/exclusion criteria. Forty-seven citations were excluded for reasons documented in Figure 2.4. Thirty-eight articles were selected for this qualitative synthesis. Figure 2.4 provides an overview of the current review's article selection process and was prepared in accordance with PRISMA guidelines (115). Tables 2.2-2.5 provide an overview of the included studies' core characteristics ($n = 38$).

Eleven articles involved participants with opioid use disorder, 16 involved participants with cocaine use disorder, nine involved those with cannabis use disorder and two involved participants with other disorders (e.g. drug-dependent participants with either cocaine, cannabis or opiate dependence or participants with alcohol, cannabis, amphetamine or GHB use disorders). Of the 11 articles involving participants with opioid use disorder, three were randomised trials, seven were cross-sectional studies and one was a longitudinal study. Of the 16 articles involving participants with cocaine use disorder, three were randomised trials, 11 were cross-sectional studies, one was a pilot study and one a case-controlled study. Of the nine articles involving participants with cannabis use disorder, two were case-control studies, and seven were cross-sectional studies.

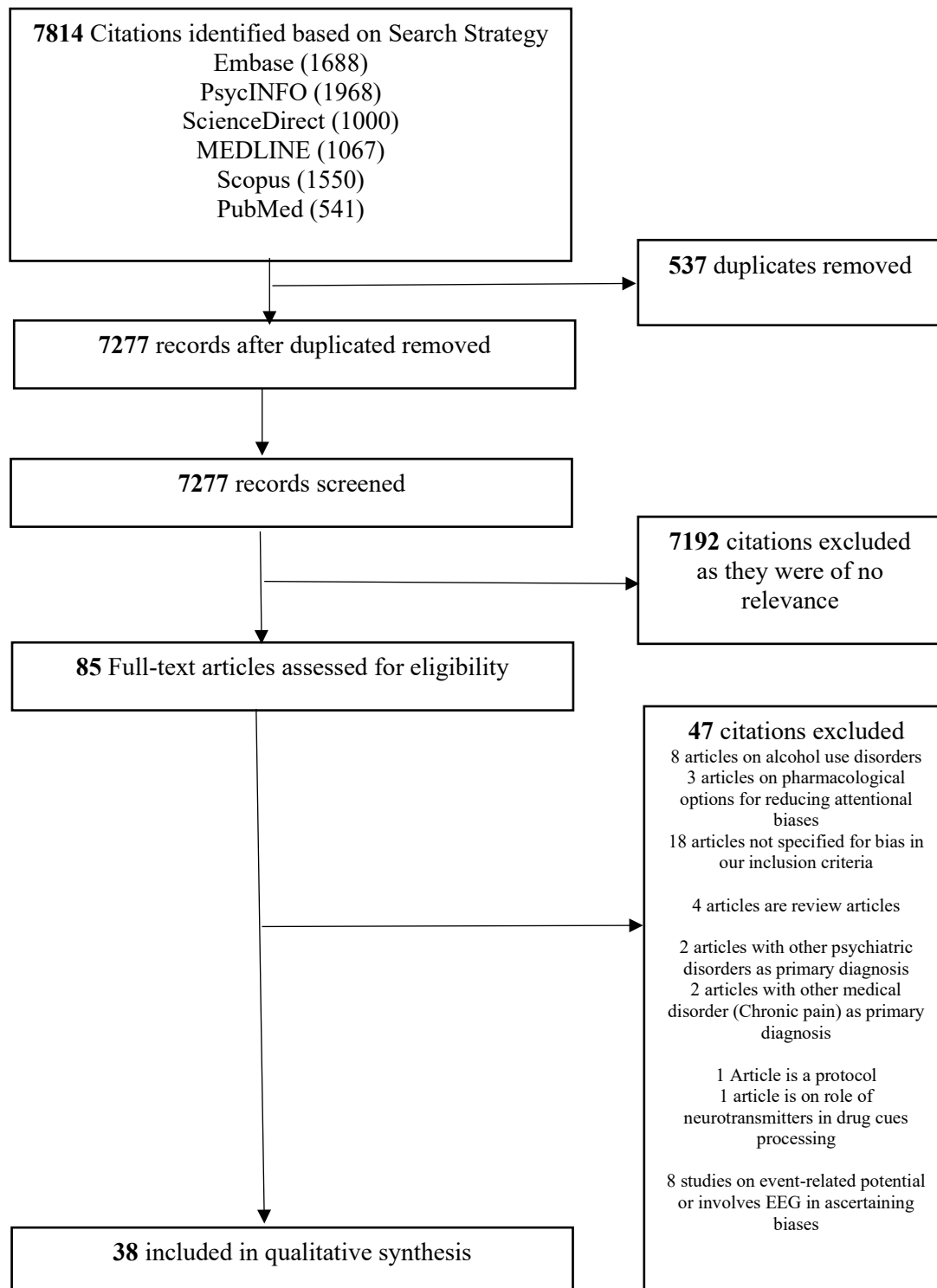
Figure 2.4 Flowchart of the article selection process

Table 2.2 Characteristics of Studies for Opioid Use Disorder (n=11)

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
OPIOID USE DISORDERS									
Franken et al. (118)	Randomised trial	21 heroin dependent participants 30 control participants	Participants with heroin dependence were recruited from an inpatient treatment center Participants in the control group were recruited among clinical and administrative staff in the clinic	71.4% males (heroin dependent) 83.3% (control group) Mean age 31.5 years (heroin dependent) Mean age 34.8 (control group) Mean self-reported duration of heroin dependence was 93.9 months	Netherlands	Heroin Dependence	Based on the DSM-IV criteria for heroin dependence	Drug Stroop task	Higher overall reaction time for heroin participants as compared to control participants Mean pre-experimental craving was 13.8, mean post masked Stroop was 7.19 and mean post unmasked Stroop was 15.2
Lubman et al. (119)	Randomised trial	16 methadone maintained opiate addicts 16 age-matched control	Heroin addicts were recruited from local drug services Staff from these services were recruited as controls	Opiate group: mean age 31.4, Male to Female 11:5 Control group: mean age 31.7, male to female 8:8	United Kingdom	Heroin Dependence	ICD-10 and DSM IV	Pictorial Probe Detection Task	Faster reaction times to probes that replaced drug stimuli, indicative of the presence of an attentional bias

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
Marissen et al. (120)	Randomised trial	110 Participants assigned to either cue exposure therapy or placebo psychotherapy	Abstinent heroin addicts who were admitted voluntarily to an in-patient drug-free therapeutic center in the Hague	89% males, mean age 34 years old Average age of onset of heroin usage was 21.4 years, most have used heroin for 9.3 years	Netherlands	Heroin Dependence	DSM-IV criteria for heroin dependence	Emotional Stroop Task	Pre-treatment attentional bias predicted relapse at 3 months follow-up Reduction of attentional biases in both experimental conditions
Bearre et al. (70)	Cross-sectional study	60 participants	Recruited from a harm reduction program (methadone maintenance or needle exchange)	44 participants on methadone maintenance, 16 on needle exchange program Mean age 32 years, mean 7.07 months of heroin use	United Kingdom	Heroin dependence	Not mentioned	Flicker change blindness paradigm	Attention bias increase as the monthly frequency of heroin use increases
Fadardi et al. (68)	Cross-sectional study	53 drug abusers with 71 non-abusers as controls	Drug abusers were recruited from a local drug-use services clinic and were on methadone maintenance therapy Controls were students, academic staff and	Drug abusers: 100% male, mean age was 36.57 years Control: 54% male, mean age 26.62 years	Iran	Opiate abuse	Not mentioned	Persian Version of classic and addiction Stroop tests	Higher attentional bias for drug-related stimuli than non-abusers

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
			other personnel of Ferdowsi University of Mashhad and people from the local community who were visiting the university						
Waters et al. (72)	Longitudinal study	68 heroin dependent inpatients	Addiction treatment center	85.3% Males Mean age 40.87 Age of first heroin use was 22.34 Total years of heroin use was 14.13	Netherlands	Heroin Dependence	DSM-IV criteria for heroin dependence	Drug Stroop task	Attentional biases to drug cues were elevated during temptation episodes
Zhou et al. (126)	Cross-sectional study	22 male abstinent heroin abusers 20 healthy males	Recruited from a legal rehabilitation center in Yunnan Province, China	All males Mean age 31.45	China	Opioid dependence	DSM-IV criteria for heroin dependence	Pull/Push task (Based on Approach/Avoidance Task rationale)	Abstinent individuals had higher tendencies to approach heroin-related stimuli, and avoidance tendencies toward heroin stimuli were reduced

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
Anderson et al. (71)	Cross-sectional study	17 opioid dependent patients 17 controls	Opioid dependent patients were from local methadone clinic Controls recruited from newspaper advertisements and flyer postings	Patients: mean age 44.4; male to female 9:8 Control: mean age 42.9; male to female 9:8	United States	Opioid Dependence	Structured clinical interview for DSM-IV (SCID-I)	Attentional Visual Search Task	Patients in treatment for addiction experience greater difficulty ignoring stimuli associated with non-drug reward.
Charles et al. (59)	Cross-sectional study	23 opioid dependent 21 healthy controls	Those prescribed with opioid substitution within the National Health Service	Mean age for Patient group (ABM-away) 43.91, (ABM-control) 45.17 Control group (ABM-away) 41.00, ABM-Control 38 Gender M:F for patient group ABM-away 10:1, ABM-control 10:2 Control group ABM-away 8:3, ABM-contor 7:3	United Kingdom	Opioid Dependence	Not mentioned	Visual Probe Tasks	No baseline differences in attentional biases between control and patient group No change in AB following bias modification Treatment adherent patients who did not use illicit opiates on top of their prescribed opiates had statistically significantly greater attention bias away from substance-related stimuli

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
Ziaee et al. (88)	Cross-sectional	24 in experimental group received Drug Attention Control Training Program in addition to treatment as usual 24 in control group received only treatment as usual	Participants were drug abusers who were undergoing methadone maintenance therapy in a drug-abuse clinic	Mean age of experimental group was 33.17; mean age of control group was 38.75 The drugs that participants most commonly abused were opium, crystal and opium sap	Iran	Drug abuse and on methadone maintenance therapy	Not mentioned	Drug Stroop test	Experimental group showed reduction in attention bias for drug related stimuli, temptations to use, doses of medicine, and number of relapses; increases on the Readiness to Change Questionnaire and 2 subscales of the Situational Confidence Questionnaire
Zhao et al. (127)	Cross-sectional	30 heroin dependents 39 healthy controls	Heroin dependents were from a methadone clinic Controls were service workers and security guards from a university	In heroin group: mean age 39.83, male to female 2:1 In control group: mean age 41.42, male to female 9:10	China	Heroin dependence	DSM-IV	Visual probe task with concurrent eye movement monitoring	Heroin group reacted faster to probes associated with substance-related pictures than neutral pictures, and they directed more initial fixations and maintained longer initial fixation durations toward substance-related pictures than neutral pictures.

2.6.1 Characteristics of Studies for Opioid Use Disorder (n=11)

Table 2.2 provides a summary of the characteristics of studies for opioid use disorders. Three studies (Franken et al., Marissen et al., and Zhou et al.) recruited participants from an inpatient treatment facility (118,120,126). The remaining studies ($n = 8$) recruited outpatients or attendees of a harm reduction programme. Six studies [Bearre et al. (70), Fadardi et al. (68), Anderson et al. (71), Charles et al. (59), Ziaee (88), and Zhao et al. (127)] included participants who were undergoing methadone maintenance therapy. The study by Ziaee et al. failed to provide information on gender ratios for the cohort (88). All other studies predominantly included men (mean age 30 to 45 years). Most of the included studies were conducted in Europe ($n = 6$), with the remaining studies conducted in the China ($n = 2$), Iran ($n = 2$) and United States ($n = 1$). The opioid use disorder diagnosis was ascertained using DSM criteria for almost all studies. Only four studies [those of Bearre et al. (70), Fadardi et al. (68), Charles et al. (59), and Ziaee et al. (88)] failed to report how the diagnosis was ascertained. To assess attention bias, five studies used the Stroop task; two used the visual probe task and the rest used the visual probe task with concurrent eye tracking ($n = 1$), approach and avoidance task ($n = 1$), attentional visual search ($n = 1$) and the flicker change blindness paradigm ($n = 1$).

2.6.2 Primary and Secondary Outcomes Reported in the Studies on Opioid Use Disorder

Ten of the 11 studies reported the presence of biases in their participants, except Charles et al., who reported no baseline attentional differences between healthy controls and opioid-dependent participants (59). Studies that assessed attention bias using the Stroop task reported a higher overall reaction time or enhanced attentional biases for drug-related stimuli, especially among opioid-using participants and that attentional biases for drug-related cues were heightened when participants had temptation episodes (68, 72, 118). Studies that assessed attention bias using the visual probe task reported that reaction times for opioid-using participants were faster when they had probes that replaced drug-related stimuli. The only study that paired the visual probe task with concurrent eye tracking demonstrated that opioid-using participants not only had faster reaction time to drug-related probes, but also exhibited a higher number of initial

fixations and maintained fixations on drug-related probes or images (127). For the approach and avoidance task, Zhou et al. reported that former opioid users had a greater tendency to approach heroin-related stimuli and a reduced tendency to avoid these stimuli (126). The study using the flicker change blindness paradigm reported an association between attention biases and the monthly frequency of heroin use (70). The study assessing attentional bias using an attentional visual search showed that attention biases were present and that their presence would cause opioid-using participants to have heightened attention for other non-drug-related reward probes (71).

Four of the included studies reported other secondary outcomes following attention bias assessment and modification and provided evidence for bias modification's potential effectiveness. Franken et al. reported a correlation between reaction times and self-reported cravings for heroin (118). Ziaee et al. found that bias modification was associated with a reduction in several outcome parameters, including temptation to use, medication dose, and number of relapses (88). Marissen et al. reported findings similar to those of Ziaee et al. concerning relapse, as the former found that baseline attentional biases could predict relapse at three-month follow-ups (88,120). Regarding the effectiveness of the interventions, Marissen et al. reported a reduction in attentional biases amongst individuals who received either cue exposure therapy or placebo psychotherapy (120).

Table 2.3 Characteristics of Studies for Cannabis Use Disorders

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
CANNABIS USE DISORDERS									
Field et al. (128)	Case control	17 regular cannabis users 16 non-users	Students and Staff at the University of Southampton	5 males, 12 females in the group of cannabis users Mean age of 22.4 years Median length of time cannabis smoked 3 years 4 males, 12 females in control group. Mean age 20.9 years.	United Kingdom	Cannabis	No mention of any diagnostic tools	Visual Probe Task	High levels of craving associated with significant attention bias for cannabis-related words
Field et al. (74)	Cross-sectional study	28 recreational cannabis users, including 15 in the “dependent” group and 13 in the “non-dependent” group	Students or staff at the University of Liverpool	6 female, 22 male Mean age was 21.9 years	United Kingdom	Cannabis Dependence	Scores on the Cannabis Severity Dependence Scale	Drug Stroop task	Significant attention bias in the cannabis group No association between attention bias and frequency of cannabis use or subjective craving
Field et al. (49)	Case control	23 regular cannabis users 23 non-user controls	Students and staff at the University of Liverpool	Cannabis users mean age was 23.04 Non-users mean age was 21.30 Gender ratio for Cannabis users: 14:9 (M:F) Gender ratio for non-users 8:15 (M:F)	United Kingdom	Cannabis abuse	Self-report usage of drugs	Visual Probe task with concurrent eye movement monitoring	Regular cannabis users had biases to maintain gaze on cannabis cues, and faster approach responses to cannabis cues

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
Cane et al. (129)	Cross-sectional study	17 marijuana-smokers 15 non-marijuana smokers	Students from the University of Kent	Not provided	United Kingdom	Cannabis dependence	Screening questionnaire	Drug Stroop task	Mean reaction time was significant for the marijuana group (Mean time for marijuana words was 984ms, neutral words was 895ms).
Cousijn et al. (75)	Cross-sectional study	32 heavy cannabis users and 39 non-using controls	Recruited through advertisements on the Internet and in Cannabis outlet (coffee-shops)	34% females for heavy cannabis users, mean age 21.2 37% female for controls, mean age 22.0	Netherlands	Cannabis dependence	Cannabis Use Disorder Identification Test and Structured Diagnostic Interview (MINI)	Approach and Avoidance Task	Heavy cannabis users had approach bias for cannabis as compared to controls. Approach bias was predictive of cannabis use at 6 months follow-up.
Cousijn et al. (76)	Cross-sectional Study	42 heavy cannabis users with intentions to use 45 heavy cannabis users shortly after cannabis usage	Recruited in five different cannabis outlets	82 males, 8 females Aged 18-59	Netherlands	Cannabis dependence	Cannabis Use Disorder Identification Test-Revised	Approach and Avoidance Task	Heavy cannabis users with the intention to use did not show a cannabis approach bias, whereas intoxicated cannabis users did show an approach bias regardless of image category. Moreover, craving was negatively associated with the approach bias, and no relationships were observed between the cannabis approach bias, satiation, prior cannabis use, and response inhibition
Cousijn et al. (130)	Cross-sectional study	27 heavy cannabis users 26 controls	All recruited via Internet advertisement and Amsterdam coffee shops	30% females in cannabis group, 38% females in control group Mean age 24.0 years in cannabis group Mean age 25.3 years in control group	Netherlands	Cannabis dependence	Cannabis Use Disorder Identification Test-Revised	Classical and Cannabis Stroop test	Cannabis smokers as compared to control group have stronger attentional bias for cannabis word Within the group of cannabis users, those who were clinically recognized as dependent showed a stronger attentional bias than the heavy, non-dependent users. Cannabis users who

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
									displayed reduced cognitive control (as measured with the classical Stroop task) showed increased session-induced craving. Cognitive control did not appear to modulate the relationship between attentional bias to cannabis words (cannabis Stroop task) and cannabis dependence.
Metrik et al. (131)	Cross-sectional	93 participants	Recruited from community	34.4% female	United States	Cannabis dependence	SCID-IV-NP for assessment of cannabis dependence	Marijuana Stroop Test	Presence of Attention bias to marijuana words (mean time was 752.89) vs. control (721.88) $p < 0.001$
Vujanovic et al. (132)	Cross-sectional	12 adults with cannabis use disorders 13 controls	Recruited via local advertisements	8 female Mean age 31, range 22-45	United States	Cannabis use disorder	Screening test and structured clinical interview for DSM-IV Axis I disorder	Pictorial stimuli attention bias task	Cannabis use disorders group showed greater attentional bias to cannabis cues at the 125-ms probe time Cannabis use disorders group also reported greater perceived stress and post-task stress scores

2.6.3 Characteristics of Cannabis Use Disorder Studies ($n = 9$)

Table 2.3 provides an overview of the characteristics of cannabis use disorder studies. Four studies [Field et al. (49,74, 128) and Cane et al. (129)] recruited students; the others ($n = 5$) recruited through advertisements or from cannabis outlets. No study recruited participants from inpatient treatments or rehabilitation facilities. Most sampled participants were men. The participants' mean ages ranged from 20 years to early 30s. Seven of the studies were conducted in Europe, and two in the United States. The diagnostic methods varied, with one study Field et al. (49) using self-reported information, four studies [Field et al., (74), Cane et al., (129), and Cousijn et al. (76,130)] using questionnaires, and the remainder (Cousijn et al. (75), Metrik et al. (131), and Vujanovic et al. (132)] using structured interviews. In the bias assessments, four studies used the Stroop task; the remainder used the visual probe task ($n = 1$), the visual probe task with concurrent eye tracking ($n = 1$), the pictorial attention bias task ($n = 1$) or the approach and avoidance task ($n = 2$).

2.6.4 Primary and Secondary Outcomes Reported in the Cannabis Use Disorder Studies

All studies provided evidence of the presence of bias. One study that assessed attention bias using the Stroop task reported mean reaction times for cannabis or marijuana stimuli greater than those for neutral stimuli (129). Stroop-based testing also helped differentiate users who consumed varying amounts of cannabis, those who were clinically dependent had a stronger attentional bias than the non-dependent (76). The visual probe task, alone or with concurrent eye tracking, provided direct and indirect evidence of attention bias; regular cannabis users exhibited bias in maintaining gaze on cannabis cues and increased reaction times for cannabis cues (49). As in the visual probe task, the pictorial stimuli attention bias task also reported attentional bias among cannabis users, which were most prominent when the probe was presented for 125 ms (shorter than the normal duration of 500 ms). Among the studies using the approach and avoidance task, one reported the presence of approach bias among heavy users (individuals who used cannabis 10 or more days a month). In contrast, the other study reported no approach bias in heavy users but found an approach bias for cannabis cues only among those users who were intoxicated when testing.

There is mixed evidence for the association between attention bias and cravings. Field et al. reported that high levels of cravings were associated with attentional biases (128), but in a later study, Field et al. reported observing no association between attention biases and cravings (74). Cousijn et al. also reported the lack of an association between approach biases and cravings (130). One study, Cousijn et al. reported approach bias to be a predictor of relapse (75).

Table 2.4 Characteristics of Studies for Stimulant Use Disorder

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
STIMULANT USE DISORDERS									
Franken et al. (133)	Pilot Study	16 cocaine dependence or cocaine abuse individuals	Addiction treatment department of a psychiatric hospital	13 males, 3 females Mean age was 26.4 years Mean cocaine abstinence was 184 days Mean age of first cocaine use was 18.6 years Mean years of regular cocaine use was 5.7 years	Netherlands	Cocaine abuse/dependence	DSM-III-R criteria for cocaine dependence or cocaine abuse	Reaction time experimental task	Attentional bias was present in patients with higher scores on the obsessive cocaine thoughts and higher craving scores.
Hester et al. (134)	Case control	23 cocaine users with 23 matched controls	Not available	23 non-drug using participants (7 female), mean age 39.4 years 23 active drug using participant (7 female, mean age 40.3)	United States of America	Cocaine dependence	Not available	Emotional Stroop Task	Mean reaction time for cocaine words for cocaine users (922.7ms), for controls (772.2ms). Significant attention bias for active cocaine users
Vadhan et al. (135)	Cross-sectional study	17 cocaine-dependent treatment seeking males 20 cocaine-dependent	Recruited from two clinical treatment trials of combination pharmacotherapy and cognitive-behavioral relapse prevention therapy Non-treatment seekers were recruited	Mean age of treatment seekers was 42.2, mean age of nontreatment seekers was 40.4	United States	Cocaine Dependence	DSM-IV criteria, Structured Clinical Interview	Drug Stroop task	Treatment seeking participants have increased response latency when presented with cocaine-related words. Non-treatment seeking participants did not demonstrate this.

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
		nontreatment seeking males	from behavioral pharmacology studies						
Hester et al. (136)	Cross-sectional Study	16 active cocaine users	No mention of source of recruitment, but participants were retained in the study if they had used cocaine in the past 72 h.	Mean age 41, Mean education 11.6 years	Australia	Cocaine dependence	Not mentioned	Working Memory task that manipulated attention by varying behavioral contents	Cocaine users had significantly poorer attentional control under high working memory demands, suffering both increased response times and reduced recall accuracy, with this effect more pronounced for cocaine stimuli
Montgomery et al. (121)	Randomised trial	32 regular cocaine users and 40 non-users	Student Population at Liverpool John Moores University and the general population in the surrounding areas	Mean age for cocaine users assigned to placebo 19.29, assigned to alcohol 20.23 Mean age for non-users assigned to placebo 19.59, assigned to alcohol 20.0 13 male in cocaine use group 19 male in non-cocaine use group	United Kingdom	Cocaine dependence	Questionnaire	Visual Probe and Modified Stroop task	Cocaine participants who received alcohol had increased attentional bias for cocaine pictures The cocaine Stroop revealed no differences between cocaine users and non-users, and no effects of alcohol in either group.
Liu et al. (137)	Cross-sectional study	37 cocaine-dependent subjects, 32 controls	Recruited from an ongoing neuroimaging study and via newspapers advertisements	Cocaine dependent subjects used cocaine for a mean of 13.64 years	United States	Cocaine dependence	Structured clinical interview for DSM-IV (SCID-I)	Cocaine Stroop Task	Cocaine-dependent subjects showed attentional bias to cocaine-related words, increased impulsivity, and poor inhibitory control compared with controls. The attentional bias was associated

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
									with inhibitory control in cocaine-dependent subjects but not in control subjects.
Tull et al. (138)	Cross-sectional study	30 cocaine dependent patients with PTSD, 30 cocaine dependent without PTSD	Residential substance use disorder treatment center	Mean age cocaine with PTSD was 44.57, cocaine without PTSD was 44.27 Male in cocaine with PTSD was 26.7%, in cocaine without PTSD 83.3%	United States	Cocaine Dependence	Not mentioned	Visual Dot probe task	Differences in attentional bias following script intervention (neutral or trauma script) Non-PTSD participants have greater attentional bias following neutral script than PTSD participants This effect was reversed following trauma script exposure, with PTSD participants exhibiting a greater attentional bias toward the location of cocaine imagery than non-PTSD participants.
Carpenter et al. (139)	Cross-sectional Study	25 individuals	Active cocaine users seeking treatment at Columbia University's Substance Treatment and Research Service	Mean age 37 years	United States	Cocaine dependence	Structured clinical interview for DSM-IV (SCID-I) and independent psychiatric examination	Drug Stroop	Attention bias toward cocaine related stimuli not demonstrated Stronger implicit beliefs about the positive effects of cocaine use prior to treatment were associated with poorer treatment outcome when an escalating voucher-incentive program was in place. An attentional bias for cocaine-related stimuli was associated with better treatment outcome when an escalating voucher-incentive program was removed. No association between cocaine

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
									use beliefs and treatment outcome was found when beliefs were measured with self-report instruments.
Marhe et al. (81)	Cross-sectional study	34 cocaine dependent inpatients	Recruited from an addiction treatment center	Mean age 38.7 85% males 11.4 years of using cocaine	Netherlands	Cocaine dependence	DSM-IV criteria for cocaine dependence	Cocaine Stroop test	Presence of attentional bias, with cocaine dependent patients responding slower to cocaine stimuli
Bardeen et al. (140)	Cross-sectional study	22 cocaine dependent patients with BPD 36 cocaine dependent patients without BPD	Community based residential substance use disorder treatment facility	26 females, mean age of 44.5 years	United States	Cocaine dependence	DSM-IV criteria for cocaine dependence	Dot-probe task	Males with BPD have higher attentional bias scores following a post trauma script intervention
Kennedy et al. (141)	Cross-sectional study	35 individuals	Substance abuse and treatment program	20 non relapsers, mean age 43.7 15 relapsers, mean age 43.0	United States	Cocaine dependence	Structured clinical interview for DSM-IV	Stroop tasks	Attention bias was present, with cocaine-dependent subjects having increased reaction time for personal drug use words (928.6ms) vs. neutral words (897.2) The level of attentional bias for cocaine-use words was not predictive of eventual relapse

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
Dias et al. (142)	Cross-sectional study	46 cocaine dependent subjects 41 healthy controls	Recruited by a variety of media advertisements	cocaine dependent group Mean age was 46.3 Control mean age was 40.0 cocaine dependent group %Male was 84.8%, Control %Male was 51.2	United States	Cocaine dependence	DSM-IV (SCID-1)	Eye-tracking cocaine attentional bias task	Presence of attentional bias toward cocaine cues as cocaine dependent subjects made more anti-saccade to cocaine cues
Mayer et al. (105)	Randomised trial	37 participants Assigned to either attentional bias modification therapy (ABMT) or control therapy	Not mentioned	ABMT group: 14male, and 5 female, mean age 37.4 Control group: 10 male and 8 female, mean age 38.9	United States	Cocaine dependence	Structured clinical interview for DSM-IV	Visual Probe task	Presence of attentional bias Not subjected to modification byABMT
Marks et al. (143)	Cross-sectional study	20 cocaine dependence 20 cocaine and alcohol dependent	Recruited through word of mouth and postings on community bulletin boards	Cocaine mean age 43.4 Cocaine alcohol mean age 43.4 6 females in each groups	United States	Cocaine and alcohol dependent	Structured clinical interview for DSM-IV	Eye-tracking cocaine attentional bias task	Cocaine dependent had attentional bias toward cocaine Cocaine-alcohol dependent has attentional bias toward both cocaine and alcohol.
Devito et al.(122)	Randomised trial	38 in treatment as usual plus computer-based CBT (CBT4CBT) 41	Recruited from community based outpatient clinic	46% female, mean age 42.2	United States	Cocaine use disorder	DSM-IV	Computerized drug Stroop test	Reductions in Drug Stroop Effect across treatment were associated with greater engagement with CBT4CBT-specific treatment components

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
		in treatment as usual							
Sharma et al. (144)	Cross-sectional study	Study 1 52 participants, 27 of which were regular marijuana users and 25 were not marijuana users Study 2 16 participants	Recruited through social networks and known to be marijuana smokers or non-users Recruited from two local Narcotics Anonymous Fellowships	Mean age 31 years old 38 males 13 males, 3 females, with ages of 25 to 41	United Kingdom	Cannabis dependence Cocaine dependence	Self-report Self-report	Drug Stroop task	A slowdown in responding to the color of non-words that were paired with cocaine-related images compared with non-cocaine related images. The slowdown was also characterized as a carryover effect, with the largest effect occurring on trials following the addiction-associated non-word. No effects were found for marijuana images associated with non-words.

2.6.5 Characteristics of Stimulant Use Disorder Studies ($n = 16$)

Table 2.4 provides an overview of the characteristics of the studies for stimulant use disorders. Eight studies [Franken et al. (133); Vadhan et al. (135), Tull et al. (138), Carpenter et al. (139), Marhe et al. (81), Bardeen et al. (140), Kennedy et al. (141), Devito et al. (122)] recruited clinical or treatment-seeking cohorts, one study Montgomery et al. (121) recruited a student sample, and five studies [Hester and Garavan (136); Liu et al. (137), Dias et al. (142), Marks et al. (143), and Sharma et al. (144)] recruited a cohort of participants from the community. Amongst the studies, there was a predominance of male participants. The studies' mean age range from 20 to 45 years, with only one study Montgomery et al. including an adolescent cohort (mean age 19 years) (121). Twelve, four and one of the included studies were conducted in the United States, Europe and Australia, respectively. To diagnose stimulant use disorder, most studies (12 out of 17 studies) used the diagnostic criteria, two studies used a questionnaire or self-report, and three studies provided no information regarding the diagnostic methods. Eight studies employed Stroop testing, one study used a reaction time experimental task, one study used a working memory task, four studies used the visual probe task, and two studies used the visual probe task with eye tracking.

2.6.6 Primary and Secondary Outcomes Reported in Stimulant Use Disorder Studies

All included studies reported the presence of biases, except the one by Carpenter et al., which failed to demonstrate an attention bias in their sample of cocaine users (139). Two studies reported that the severity of the underlying dependency affected the resultant biases [Franken et al. (133) and Liu et al. (137)]. Studies that assessed attention bias using the visual probe with eye-tracking to evaluate attentional bias demonstrated that the cocaine-using cohort exhibited gaze preferences toward cocaine-related stimuli. Concerning secondary outcomes, Franken et al. reported that attentional bias was elevated in patients who had higher craving levels (133). Liu et al. observed that attentional bias amongst cocaine users was associated with heightened impulsivity and poorer inhibitory control (137). Marks et al. suggested the generalization of attentional bias for cocaine-related stimuli to that of alcohol-related stimuli (143). Mayer et al. reported that there was no effect of attention bias modification in reducing cocaine-related attentional biases (105).

Table 2.5 Characteristics of studies with a heterogenous sample of participants

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
MIXED COHORT									
Carpenter et al. (145)	Cross-sectional study	80 drug dependent individuals	All were illicit drug users enrolled in one of the six randomized trial combining coping skills relapse prevention and pharmacotherapy	62 males, 18 females 45 participants (cocaine), 25 participants (marijuana), 10 participants (heroin) Mean age 39.9 years	United States of America	Cocaine, Marijuana and Heroin dependence	DSM-IV dependence criteria Structured psychiatric interview	Drug Stroop Test	All groups had slower reaction times when presented with cocaine words.
Van Hamel et al. (146)	Cross-sectional	78 adolescents with substance dependence 64 healthy controls	Addiction care facility	Substance dependence group mean age 19.5 Control group mean age 19.0	Netherlands	Alcohol, Cannabis, Amphetamine or GHB Use disorder	Self-reported substance usage and severity of usage	Visual Probe task	Attentional bias for stimuli presented at 500ms and 1250ms. Higher severity of dependence, increased AB

2.6.7 Outcomes Reported in Studies with a Heterogeneous Samples

Table 2.5 provides an overview of studies with heterogeneous participant samples.

Two studies [Carpenter et al. (145) and Van Hamel et al. (146)] examined groups with heterogeneous diagnoses and included drug-dependent participants with cocaine, cannabis, opiate dependence, alcohol, cannabis, amphetamine or GHB use disorders. The Stroop and visual probe task were employed to assess attentional biases, and both trials demonstrated the presence of attentional biases.

2.7 Synthesis of Findings and Critiques

As mentioned in the Introduction (Section 1.6), this review addresses the gap in previous reviews regarding the evidence base for attentional biases amongst illicit substance use disorders, i.e., that of opioid, cannabis, and stimulant disorders. Whilst the work by Field and Cox provided evidence for the presence of cognitive biases in opiate and cocaine use disorders; the evidence synthesis was from a limited number of studies (36). In their critical review, Leeman et al. provided evidence for attentional biases only in cocaine use disorders (53). This review provided evidence that biases are present among individuals with opioid, cannabis, and stimulant use disorders. This review has justified the evidence base and synthesised the findings for cannabis use disorders and attentional biases. Of the 38 studies, only two reported no positive findings. One of the studies attributed this finding to the fact that presenting opioid-related stimuli might have appeared to be novel to the control sample (59).

No prior review (Field & Cox et al. (36), Leeman et al. (53)) synthesised evidence for the presence of attentional biases for individuals with cannabis use disorders. Evidence synthesis for this is of particular importance, given that cannabis use has been increasingly globally, and that an estimated 10% of regular cannabis users do eventually develop dependence (132). Apart from the risk of developing an addictive disorder, cannabis use has been associated with a heightened risk of developing other psychiatric disorders. Thus, identifying the presence of cognitive bias in individuals with cannabis use disorders signifies a need for interventions to deal with these unconscious processes. Moreover, cognitive bias assessments could help differentiate individuals who are clinically dependent on cannabis and those who use cannabis recreationally, as it has been demonstrated that individuals who are clinically dependent have stronger attentional biases.

Our synthesis of the published literature demonstrated biases in individuals who are kept on opiate substitution therapy. The presence of biases among such individuals implies that while pharmacological interventions might help stabilise lifestyles and minimise harm associated with illicit use, it has no effect on factors that could still predispose to a lapse or relapse. Drug-related stimuli have been proposed as ‘cognitive intermediates’ before a lapse or relapse because such salient stimuli activate unconscious processes, leading to increased attention, but leave individuals with fewer resources to apply learned coping strategies. The evidence to date demonstrates that pharmacological agents for opioid use disorders do not reduce attentional biases, and psychological interventions need to be considered instead. Heitman et al. proposed considering cognitive bias modification as an adjunct to conventional psychotherapy (147). The authors were interested in investigating the effectiveness of an Internet-based cognitive bias modification intervention in terms of efficacy and cost, which would be delivered as an adjunct to standard treatment for individuals with alcohol or cannabis use disorders (147).

The second review presented addressed the first review’s limitations (which included only randomised trials) and expanded the evidence base previously identified for attentional biases among individuals with opioid, cannabis, and stimulant disorders. A risk of bias assessment cannot be undertaken for this study, given the study types and lack of a unified assessment tool. While this review’s original design also consisted of identifying the evidence for bias modification, this was not accomplished, as most of the studies focused primarily on bias assessment. The meta-analysis by Cristea et al. was the only other study that examined the evidence for attentional bias modification before these two recent reviews (89). The meta-analysis included 25 randomised trials, 18 of which were trials involving alcohol use disorders and seven were trials involving tobacco use disorders. The authors reported that the intervention had a moderate effect (effect size, Hedges $G=0.60$) on cognitive biases following bias modification. However, the moderate effect of bias modification on cognitive biases did not generalise to other addiction outcomes or cravings. The meta-analysis by Cristea et al. was subsequently criticized by others (89, 148). Wiers et al. also reported that their meta-analysis was biased because it had synthesised information arising from both experimental laboratory studies and randomised controlled trials (148). Wiers et al. indicated that the meta-analysis was biased because it had synthesised information from experimental

laboratory studies and randomised controlled trials (148). The authors indicated that when the studies were clearly differentiated (i.e., classified into experimental laboratory studies and randomised trials), there was a small but robust effect of bias modification when the bias intervention was administered concurrently with existing treatment in clinical settings. More recently, Boffo et al. undertook a Bayesian meta-analysis investigating cognitive bias modification for behavioural changes among participants with alcohol and smoking disorders (149). The authors reported that cognitive bias modification had a small effect on cognitive biases (effect size 0.23) and relapse rates (-0.22) (145). From these studies, bias modification appeared to have some effect on cognitive biases, but the examination was limited to alcohol and tobacco use disorders. The findings that attentional biases are present (based on the completed reviews) indicate that further investigation is needed into the effectiveness of bias modification in opioid, cannabis, and stimulant use disorders.

2.8 Implications for Further Studies

The systematic reviews undertaken as part of this doctoral research provide evidence of cognitive bias among individuals with opioid use, cannabis use and stimulant use disorders. Table 2.6 summarises the evidence derived from the completed systematic reviews.

Table 2.6 Overview of Evidence

Substance Use Disorder	Countries of Sampled Participants	Presence of Attention Bias	Attention Bias Modification
Opioid	Europe (n=6) United States of America(n=2) Iran (n=2) China (n=2)	10/11 studies reported presence of attention bias	1 study reported positive findings for Attention Bias Modification 1 study reported negative findings following cue exposure versus placebo therapy
Cannabis	Europe (n=7)	9/9 studies all reported the presence of attention bias	No studies discussed effectiveness of bias modification
Stimulant	United States of America (n=12) Europe (n=2) Australia (n=1)	15/16 studies reported the presence of attention bias	1 study reported negative findings for attention bias modification

My reviews were conducted in 2017. When preparing this dissertation, a further literature search was performed, which revealed two further reviews in this field.

Hietmann et al. conducted another systematic review in 2018 examining attention bias modification effectiveness (150). In particular, the authors sought to determine whether attention bias modification decreased symptoms of addictive behaviours and effected changes in attentional biases (150). Both randomized and non-randomized trials up to 2016 were searched for in the literature (150). They identified 18 studies, with most of the studies for alcohol and nicotine disorders and only 3 studies for opioid use (150). The authors reported evidence for multi-session attention bias modification for alcohol disorders, and amongst the studies involving opioid use, only one (Ziaee et al.) reported a change in attentional bias (88, 150). In another subsequent review by MacLean et al. in 2018, they identified 21 studies and reported that individuals using opioids, as opposed to healthy controls, demonstrated an attentional bias and that even participants who were enrolled in medication-assisted therapy (methadone and buprenorphine) also demonstrated a robust baseline attentional bias (151). The authors also highlighted the possibility of opioid abusers having a greater attentional bias than individuals with other substance use disorders (151). The modality of opioid administration might affect these baseline biases (151).

The findings from these newly identified reviews and my own completed systematic review strengthened my decision for the planned work in exploring an intervention for bias modification among highly prevalent illicit drug use disorders in Singapore, which are encountered clinically at NAMS. Treatment-seeking individuals enrolled in inpatient detoxification and rehabilitation programmes at NAMS might have underlying attentional biases that can be targeted, an approach that has not been explored by any form of psychological therapy to date. With the findings described above, this approach warrants investigation, given targeting these biases could help individuals in their recovery. As evidenced by Table 2.6, there have been no studies in Asia that have investigated the potential of attention bias intervention. It makes sense to determine if our cohort would also benefit.

Chapter 3 Review of Mobile Attention Bias Interventions

Introduction

This chapter begins with an overview of how advances in web and mobile technologies have been applied to deliver cognitive bias modification interventions. Section 3.2 explains the rationale for a systematic literature review of mobile cognitive bias modification interventions and subsequent content analyses of commercially available cognitive bias modification interventions. Section 3.3 describes the methods and results. Section 3.4 discusses the main findings. The chapter concludes with a discussion of the implications of the findings for the overall PhD dissertation.

3.1 Technological Advances and its Implications for Interventions

3.1.1 e-Health/ Web Technologies and Cognitive Bias Modification Interventions

E-health or electronic health refers to the use of web-based interventions for healthcare (90). In psychiatry, eHealth technologies are being used to deliver psychological interventions for conditions such as depression and bipolar disorders, monitor the mood state of patients and reduce drinking among individuals with alcohol use disorder (92, 93). Advances in web-based technologies have transformed the delivery of conventional attention bias modification interventions. In most published interventions, the nature of the web interventions does not differ from the conventional computerised task; the technology is used to facilitate the delivery and not augment the intervention (94). For example, Wittekind et al. (2015), utilized an online platform (Questback) for delivering the intervention (152). However, the intervention did not differ from the conventional approach and avoidance task (152).

From my prior scoping review of web-based cognitive bias modification intervention, there has been four studies demonstrating the application of web technologies for addictive disorders (153). A scoping review of web-based cognitive bias modification interventions was undertaken, given that the intent was to determine the scope and to map out the available literature for web-based interventions, specifically those for addictive disorders (153). This approach is consistent with the recommendations of Zachery et al., in which scoping reviews are indicated to identify the types of available evidence in a given field; to clarify key concepts/definitions; to examine how research

can be conducted; to identify key characteristics or factors related to a concept; to act as a precursor to a systematic review; and to identify and analyses knowledge gaps (154). Scoping reviews are quicker to conduct than conventional systematic reviews and are essential in synthesising the available evidence in the rapidly advancing field of web-enabled cognitive bias modification interventions (154).

Table 3.1 provides an overview of the characteristics of the four studies found. Two of the studies were for alcohol use disorders (94, 156), which involved 58 and 136 participants, respectively. They found no clear benefit for cognitive bias modification. Of the two studies involving smoking disorder, only one (152) reported a reduction in the number of cigarettes smoked and in smoking compulsion amongst their participants, and the other reported there being no effect of the intervention on the maintenance of abstinence. Although there have been negative findings regarding the utility of web technologies for delivering cognitive bias modification interventions for individuals with addictive disorders, web-based cognitive bias modification has been reported to be effective for other psychiatric disorders, such as social anxiety (157, 158).

Table 3.1 Characteristics of Studies involving Web-based bias interventions for Addictive Disorders.

Study & Country of Study	Study Design	Sample Size	Demographics of Sample	Mechanism of Recruitment	Psychiatric Diagnoses	Method of Diagnosis	Attention or Cognitive Bias Task	Primary Outcomes	Secondary Outcomes
Addictive Disorders									
Wiers et al. (94) Country: Netherlands	Randomised trial with four experimental conditions compared against sham training control.	136 problem drinkers 17 assigned to AACTP, 27 assigned to ATT100 Explicit, 35 assigned to ATT100 implicit, 33 to ATT90 implicit, 24 to ATT50 control	Average age of 46.1, 48.1, 46.9, 49.4 and 48.7 respectively Gender ratio(Females to Males): 9:8; 10:27; 14:21; 14:19; 15:9.	Via newspaper and online advertising and a website	Alcohol Use Disorder	Alcohol Use Disorders Identification test and alcohol consumption based on the self-reported timeline follow-back procedure.	Attention Control Training and Approach Bias Re-training	Bias present and subjected to manipulation	Reduction in drinking in all intervention arms (attention control training, approach bias retraining and sham control). No evidence of stronger reduction of alcohol consumption following active training as compared to sham training.
Wittekind et al. (152) Country: Hamburg, Germany	Randomised trial with two experimental conditions (Approach avoidance task, AAT) and a waitlist control.	257 participants, 87 allocated to standard AAT, 85 allocated to modified AAT and 85 allocated to waitlist control group	Standard AAT: Age of 44.30, 54 females, 33 males, 24.27 years of smoking, 20.31 cigarettes per day Modified AAT: Age of 43.65, 56 females, 29 males, 25.09 years of smoking, 20.13 cigarettes per day Control group: Age of 41.55, 47 females, 38 males, 22.62 years of smoking, 20.52 cigarettes per day	Invitation to participate posted in several smoking-related Internet forums	Tobacco Use Disorder	Questionnaire (Fagerstrom Test for Nicotine Dependence & Cigarette Dependence Scale-12).	Approach and avoidance task (only avoidance task used as intervention)	Bias present and subjected to manipulation	Significant reduction in number of cigarettes smoked and compulsion among participants who received intervention versus control Reduction of cigarette dependence and compulsive drive for smoking most significantly in those assigned to the standard AAT.

Elfeddali et al. (155) Country: The Netherlands	Randomised trial involving either 6 sessions of bias modification or placebo training over 2 weeks	434 participants, 224 assigned to ABM group and 210 assigned to control group	68.9% female, average age 40.76years, average consumption 17.78 cigarettes, 91.7% have had made quit attempts ABM group mean age 40.96, 67.4% females, 17.49 cigarettes per day Control group mean age 40.54, 70.5% female, 18.09 cigarettes per day	Online Recruitment with advertisement on online international news pages referring to a website.	Tobacco Use Disorder	Questionnaire (Fagerstrom Test for Nicotine Dependence)	Attention Bias Modification (Visual Probe task) Approach bias using reaction time paradigms	Significant attentional bias towards smoking-related cues among heavy smokers, whilst bias was not significant in light to moderate smokers. Significant approach bias for cigarette related stimuli	Non-significant results for multiple-session ABM interventions. Web-based, multiple-session ABM intervention was not effective in ensuring continued abstinence. ABM training effects did not generalize to that of approach bias.
Cogle et al. (156) Country: United States	Randomised trial involving either eight web-based sessions of interpretation bias modification for hostility or a healthy video control condition	58 individuals, with 30 receiving Interpretative bias modification for hostility (IBM-H) and 28 receiving healthy video control condition (HVC)	Mean age of sample was 40.71 years, 69.0% female IBM-H: 70% females, mean age 39.33 years HVC: 67.9% females, mean age 42.18 years	Craigslist, Reddit, bus advertisement, doctor referrals and filers posted around the local community	Alcohol Use Disorder with elevated trait anger	Endorsement of 4 out of the 11 symptoms of DSM-5 modified alcohol module of the Mini International Neuropsychiatric Interview Trait anger based on the State-Trait Anger Expression Inventory-2 (STAXI-2)	Interpretative bias modification for hostility	Greater reduction in interpretative bias in the intervention as compared to the control group.	IBM-H lead to greater reduction in trait anger than HVC. IBM-H also led to reductions in anger expression. Both groups (intervention and control) groups reported a reduction in alcohol consumption.

3.1.2 mHealth/Mobile Technologies and Implications for Addictive Disorders

mHealth, or mobile health, are the terms used when mobile devices, such as smartphones and their accompanying apps, are used for health care (92). The increasing popularity of mHealth technologies in healthcare has led to them being considered tools for addressing addictive disorders. Smartphone applications are increasingly popular, serving as promising tools for the primary and secondary prevention of addictive disorders (92). Applications can augment classical interventions (92). Mobile applications can also help overcome geographic barriers and the stigma associated with seeking help (92). There are also some economic advantages for the users, given the cost associated with using an application is usually minimal as a significant proportion of applications are free to download (92). A mobile application eliminates the need to always be connected to the Internet to receive the intervention, enabling access anywhere and at any time.

It is expected that with time, there will be increased research evaluations of these tools, as well as a corresponding increase in the number of commercial applications made available to individuals. Regarding research evaluations, Gajeck et al. reported the effectiveness of the Alcohol-Comprehensive Health Enhancement Support System (ACHESS), a smartphone app that supports patients in recovering from alcoholism. This application was conceptualised based on the self-determination theory (159). The application helps equip individuals with cognitive behavioural skills for relapse prevention (159). The Location-Based Monitoring and Intervention System for Alcohol Use Disorders (LBMI-A) is another app based on motivational enhancement, relapse prevention and community reinforcement theories (160). The assessment function of the LBMI-A app is a brief motivational intervention tool; the high-risk location functionality is based on principles of relapse prevention; the identification of supportive individuals is based on the Community Reinforcement and Family Training approach, and the craving functionality is based on cognitive behavioural theory (160). A randomised trial evaluating ACHESS found that individuals with access to the app had significantly fewer risky drinking days for one year than controls, and a pilot study involving LBMI-A showed that the app helped individuals reduce heavy drinking (159, 160).

Alongside the development and evaluation of apps in research setting evaluations, there has been an increase in the number of commercial applications for addictive disorders, as documented in the content analyses by Weaver et al., Crane et al., Hoeppner et al. and Ramo et al. (97-100). Weaver et al. evaluated apps from Apple iTunes and Google Play Store (97). The apps were identified using the search term ‘alcohol’. Only the top 250 apps on each store were included, giving a total of 384. Fifty percent of the sampled applications were entertainment applications, and only a minority (11%) were applications that provided information about health or methods to reduce alcohol consumption. Two years later, Crane et al. reviewed alcohol-related applications available in the United Kingdom to identify those that used behavioural change techniques and found 662 unique applications (98). As with Weaver et al., a minority (13.7%) of these applications assisted in alcohol reduction, with most (53.9%) for entertainment (98). Crane et al. (2015) reported that the most utilised behavioural change techniques were those enabling individuals to self-record their behaviours (54.1%), followed by the provision of information on excessive usage of alcohol (42.6%), feedback on performance (41.0%), and options for alternative and subsequent support (24.6%) (98). A third content analysis was published (Hoeppner et al.) which examined 266 Android Store applications apps to determine whether alcohol apps provided any form of tailored messages and to describe their standard functionality (99). Approximately two-thirds of the apps (60%) provided some mechanism for tailoring feedback. The most common form of tailored messages was based on drinking, demographics, and time (99), but only a minority provided tailored feedback based on triggers (1.9%) or pre-set goals (0.8%). The most common tools were blood alcohol concentration calculators, apps that provided information, tracking calendars and motivational apps. A similar focus on information or entertainment was observed in reviews of apps for cannabis use disorder. Ramo et al., using the search terminologies “cannabis” and “marijuana”, found 27.0% of identified applications to focus on the provision of information and 20.3% on entertainment (100). Table 3.2 summarises the key findings of these content analyses.

Table 3.2 Summary of the Key Findings of previously concluded content analyses

Review Articles	Weaver et al. (97)	Crane et al. (98)	Hoeppner et al. (99)	Ramo DE et al. (100)
Main Substance Disorder	Alcohol	Alcohol	Alcohol	Cannabis
Keywords Used	Alcohol	Alcohol	Drinking, Drink, Alcohol, Alcoholism, Sobriety	Cannabis, Marijuana
Application Stores Searched	Apple iTunes & Google Android Store	Apple iTunes & Google Android Store	Google Android Store	Apple iTunes & Google Android Store
Number of applications included	384 applications identified, but only the top 250 applications included for the review	Only initial 200 results considered, with 4 searches conducted, a total of 800 results considered. 662 applications included in final review	266 applications	342 applications from Apple App Store; 500 applications from Google Store
Key Findings	50% of applications were entertainment applications 11% provided information about health or methods to reduce drinking Analysis of blood alcohol concentration applications revealed these applications to be inaccurate	13.7% of applications helped in alcohol reduction 53.9% entertainment applications	60% of applications provided some mechanism for tailoring of feedback. Most common form of tailored feedback were triggers or pre-set goals. Most common tools were blood alcohol concentration calculators, applications that provided information, tracking calendars and motivational applications	27% of applications provided information 20.3% were entertainment applications

3.1.3 mHealth Technologies and Cognitive Bias Interventions for Addictive Disorders

As discussed previously, web-based bias interventions have been investigated for only alcohol and tobacco addictive use disorders (94,152). Despite there being no conclusive evidence for their overall effectiveness, other researchers have investigated mobile-based bias modification interventions for addictive disorders. Kerst et al. examined the delivery of attentional retraining using a smartphone device (personal digital assistant) (161). Given the proliferation of commercially available health apps (as highlighted above) and the increased recognition of the role of attention bias in addiction disorders, more scientifically evaluated and commercially developed apps aimed at manipulating attention bias are expected.

3.2 Rationale for Review 2 focusing on mHealth cognitive bias modification interventions in the literature and on commercial stores

Review 2 was planned and conducted to determine the evidence base for mHealth cognitive bias modification interventions. There have been no prior reviews that have synthesised the scientific evidence for mHealth cognitive bias modification interventions. A current understanding is warranted, to inform and guide the future development of similar interventions, and the synthesis needs to be broad-based (and expanded to all psychiatric disorders) because it will help determine whether a mobile approach should be considered for bias modification interventions. Moreover, addiction is a niche subspeciality of psychiatry, and there are likely few publications relating to cognitive bias modification interventions. A broader-based search allows for a better understanding of the evidence base and factors (such as the type of bias modification task) that would render the intervention successful.

Given the exponential growth in the number of commercially available applications, there is a need to determine whether scientifically evaluated applications can successfully be commercialised. This success would be an indicator of a strong collaboration between academics and developers. Forging such a collaboration is also one of the objectives of this doctoral thesis to develop a new mobile intervention targeting attentional biases in addictive disorders. The growth of commercially

available applications and the limitations highlighted by the previous content analyses indicate the need for determining the evidence base of commercially available applications. Commercially available cognitive bias modification applications that are not evidence-based would have implications for future scientific work and clinical care. Developers keen on developing cognitive bias interventions should be mindful that their application needs to be grounded in evidence-base; and clinicians who might recommend commercial apps should be mindful of their poor evidence base. The completed systematic review and content analyses were published in May 2018 and are available in Appendix 5.

3.3 Methods for Review 2

This section defines and further elaborates the methods used to address the objectives of Study 2, which were to review mobile cognitive bias modification interventions from the published literature and those which are on the commercial apps stores.

3.3.1 Phase 1: Identifying Attention and Cognitive Bias Modification Apps in the Literature

To achieve the primary objective, PubMed and MEDLINE were searched for articles published from 2000 to 24 September 2017. An updated search was subsequently performed from April 14 to 17 April 2018, on PubMed, MEDLINE, PsycINFO and Scopus. The year 2000 onwards was selected because few people had access to personal digital assistants and mobile phones before this date. We used the search terms ‘attention bias’ OR ‘cognitive bias’ AND ‘smartphone’ OR ‘smartphone application’ OR ‘smartphone app’ OR ‘mobile phones’ OR ‘mobile application’ OR ‘mobile app’ OR ‘personal digital assistant.’ Only English-language articles were included.

The inclusion criteria were (1) the cognitive bias modification must have been delivered using a mobile device (mobile phone, smartphone or personal digital assistant) and (2) delivery was in the form of a specific app or game. Articles were excluded if they only described how a web-based intervention ran on a mobile device.

All articles were initially screened by two independent authors based on titles and abstracts. Full copies of the shortlisted articles were then evaluated against the inclusion/exclusion criteria. Disagreements were resolved by discussion with a third

author. The inclusion/exclusion rationale was recorded on an electronic form, together with the following information: (1) publication details (author names and publication year), (2) specific condition targeted, (3) description of the intervention, (4) delivery method for attention bias or cognitive bias modification and (5) main outcome and findings.

3.3.2 Phase 2: Identification of Commercially Available Apps

A manual cross-sectional search was conducted between September 15 and 25, 2017 on the apps stores iTunes (Apple Inc, Cupertino, CA, USA) (162) and Google Play (Google LLC, Mountain View, CA, USA) (163). The search terms used were “attention bias” and “cognitive bias.” The manual search was simultaneously supplemented in the same period with the use of a mobile app search engine, 42matters (42matters AG, Zurich, Switzerland) (164), to globally search for all available apps globally. If the app was available for free and in a paid version, the latter was analysed, as paid versions typically have more functionality (158).

The following information was extracted from the identified apps and recorded in a standardised electronic data collation form: (1) app name, (2) general description of the app, (3) method of attention or cognitive bias modification, (4) other functionality, (5) range of total downloads, (6) app rating, (7) reference source and (8) last modification date. For the attention or cognitive bias modification method, we recorded the tool used (e.g., visual probe task, dot-probe task, and visual search).

To determine whether the apps identified had been evaluated scientifically, each extracted commercial app was compared against those apps identified from the literature review conducted in Phase 1. The references cited in either the app description or within the app itself were further assessed to determine whether it had been scientifically evaluated. The app developers were contacted via email on November 5, 2017, requesting further information regarding the app’s scientific evaluation.

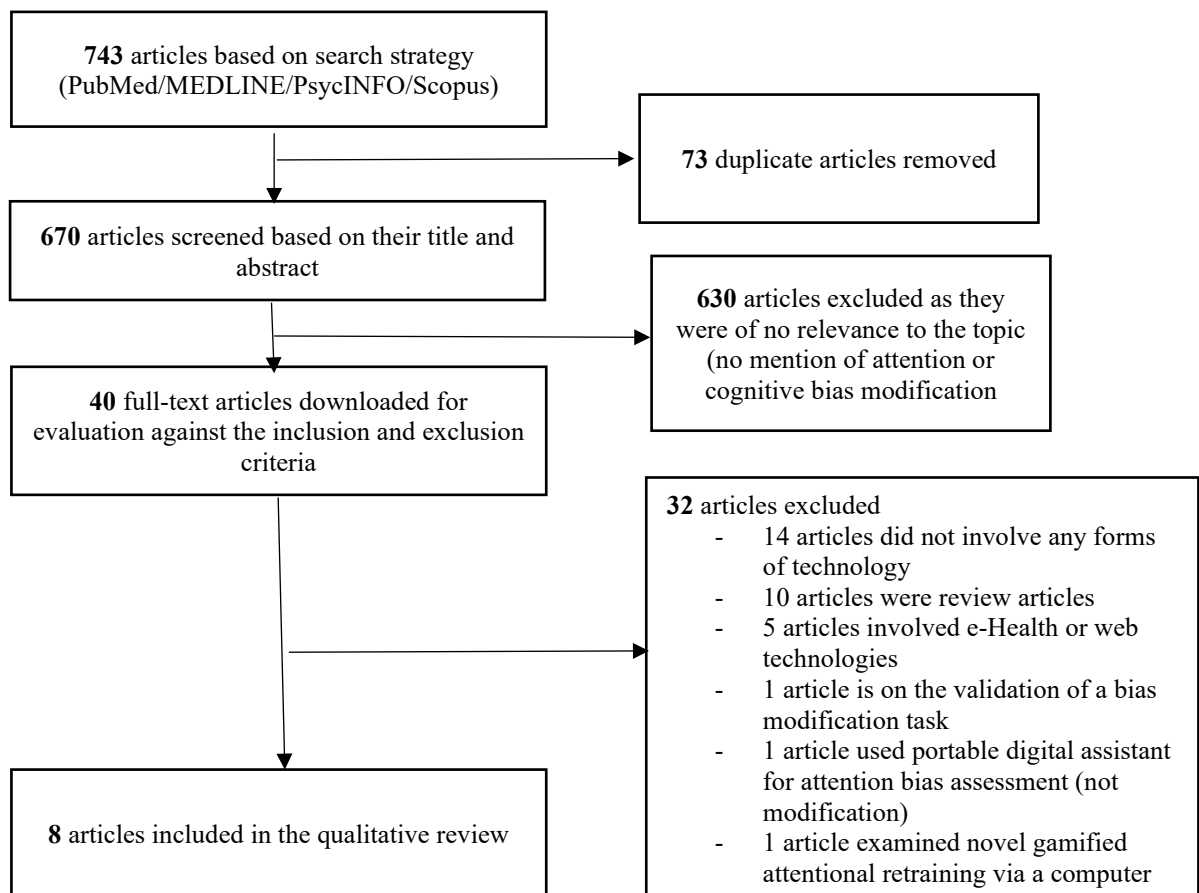
3.3.3 Phase 3: Availability in App Stores of Apps in Published Literature

For the apps with published evaluations, the manual search of the app stores was repeated using the same process indicated in subsection 3.3.2.

3.4 Results

Figure 3.1 provides an overview of the study selection process, prepared according to PRISMA guidelines (115). Our initial and updated search identified 743 citations, 73 of which were duplicates. The remaining 670 articles were screened by title and abstract. Forty full-text articles were then downloaded and evaluated against the inclusion/exclusion criteria, resulting in eight articles suitable for qualitative review.

Figure 3.1 Overview of the Study Selection Process



The articles described the use of mHealth apps in delivering attention or cognitive bias modification for the following conditions: insomnia ($n = 1$), social anxiety ($n = 1$), anxiety disorder ($n = 3$), alcohol use disorder ($n = 1$) and tobacco use disorder ($n = 2$). Table 3.3 summarises the included studies' main characteristics.

Table 3.3 Overview of Attention and Cognitive Bias Modification Apps in the published literature

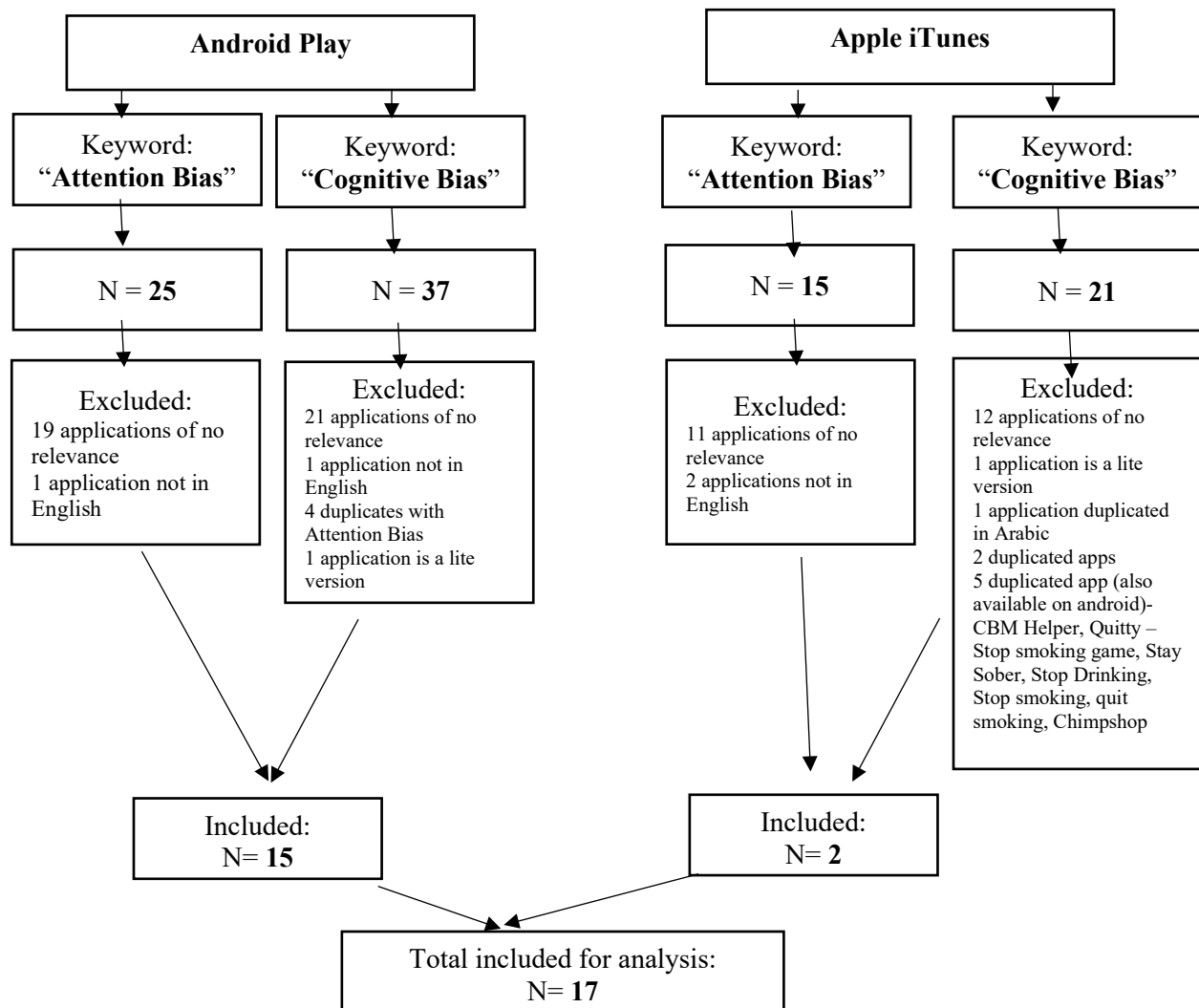
Reference	Condition targeted	Description of intervention	Method of ABM	Main outcomes reported	Availability in commercial stores
Clarke et al. (165)	Insomnia	ABM task involving 48 word pairs comprising sleep-related threat words paired with nonthreat words.	Dot-probe task	The primary outcome measured was whether the delivery of attention bias task could help reduce symptoms of insomnia and cognitive symptoms of presleep arousal. Participants who received ABM training reported significantly lower presleep arousal and better overall sleep quality. Those assigned to the ABM condition also fell asleep faster and woke less often during the night (based on electrophysiological measures)	No
Yang et al. (166)	Social anxiety	CBM-A task involving the presentation of 2 faces as stimulus. CBM-I ^c task based on the presentation of ambiguous scenarios. Attention and interpretation modification involving half the tasks for CBM-A and CBM-I.	Dot-probe task, CBM-I	The main outcome was to compare the effectiveness of 3 types of training program. Delivering cognitive bias modification via smartphone device is feasible. CBM-A and attention and interpretation modification was not effective as measured by the dot-probe attention bias scores.	No
Dennis et al. (167)	Anxiety	Gamified ABM app	Dot-probe task	The main outcome of the study was to determine whether the gamified ABM task could help reduce threat bias, anxiety, and the stress reactivity of trait anxious individuals, in a way similar to that of laboratory-based bias modification. The single session helped reduce subjective anxiety and stress reactivity. Long-training bias modification helped reduce threat bias and difficulties with disengagement.	No
Dennis-Tiwary et al. (168)	Anxiety	Gamified ABM app (Personal Zen)	Dot-probe task	Subjective anxiety and stress responses measured following the intervention showed that there was no difference in overall self-reported anxiety symptoms. However, behavioral performance improved during the stress task among female participants.	No

Reference	Condition targeted	Description of intervention	Method of ABM	Main outcomes reported	Availability in commercial stores
Kerst et al. (161)	Smoking	Attention retraining via personal digital assistant in natural environment	Modified visual-probe task	The main outcome examined was whether delivering attention retraining on a personal digital device in the natural environment could help reduce attention bias and overall cravings for smoking. Attention bias decreased in the intervention group and overall craving decreased in the intervention group.	No
Denis-Tiwary et al. (169)	Anxiety and stress	Gamified ABM app (Personal Zen)	Dot-probe task	Biobehavioral indices of prenatal stress and anxiety were reduced following the intervention.	No
Cox et al. (170)	Alcohol	Gamified ABM app (ChimpShop)	Not specified	The main outcome measured was the amount of drinking. The intervention reduced drinking in problematic drinkers by 60%.	Yes
Robinson et al. (171)	Smoking	Attention bias retraining	Visual-probe task	Attentional biases in smokers were reduced. Reduction in attention biases did not reduce craving or biological measures of smoking.	No

All but one of the trials used either the dot-probe or visual probe task, the exception was for one study that used cognitive bias for interpretation intervention and another that did not specify the task applied. Regarding outcomes, seven studies reported effectiveness; only one reported no effect (166). Bias modification helped improve insomnia symptoms and cognitive symptoms of pre-sleep arousal (165); reducing subjective anxiety (167); improving stress task performance (168); reducing attentional biases for cigarettes (161, 171); reduce alcohol consumption (170); and reducing prenatal stress and anxiety (169). However, Yang et al. reported that bias modification was not effective, as the bias scores among participants with social anxiety disorders were not reduced (166). Only one of the apps identified was commercially available on the app stores (based on our phase 3 search).

In Phase 2, 15 apps from Google Play and two apps from iTunes were retrieved; five of these apps were available in both stores. The flowchart in Figure 3.2 shows the app selection process from the commercial stores.

Figure 3.2 App Selection Process from the Commercial Stores



Commercial apps were downloaded for further evaluation ($n = 17$). Table 3.3 summarises the main characteristics of the commercially available attention or cognitive bias apps. Of the 17 apps, 10 were free to download. Most of these apps claimed targeted a specific condition, such as stress ($n = 7$), anxiety ($n = 3$), tobacco ($n = 3$), alcohol use disorders ($n = 2$) and grief ($n = 1$). One app (Bias Modification) did not specifically mention the app description or the targeted condition in the app. Most ($n = 11$) used attention visual search in bias modification, with only two apps adopting the cognitive bias modification for interpretation method. Four apps used bias modification methods that differed from the visual probe, cognitive bias modification and attention visual search tools. For the Quitty

app, the bias modification task involved using a tobacco product as a projectile to hit other objects. For the Stop Smoking-Quit Smoking, Stay Sober, Stop Drinking and ChimpShop apps, the paradigm involved an avatar running through an environment and bias was retrained by avoiding the substances. There were limited additional functionality for most apps, but five apps included a questionnaire or other functionality, such as the ability to customise images (Spot Smile, brighten your day app) or the addition of reminders (AntiAnxiety), to allow for app customisation by individual users. Only four apps included or stated a reference source within the app, of which one has been previously evaluated (ChimpShop). On the Android platform, two of the apps had been downloaded between 10,000 and 50,000 times. Contacting the developers to determine whether their apps had been previously evaluated, resulted in three replies (Quitty, Happytap and AntiAnxiety), but none of the developers could offer evidence demonstrating that their app had been independently evaluated.

Table 3.4 Characteristics of Attention Bias Commercial Applications

App Name	App Description	Bias Assessment	Main Condition Targeted	Other Functionalities	Range of Downloads	App Rating (Out of 5)	Reference Source	Last modified
Android apps								
Psych Me Up! (Free App)	Tool for stress reduction and improving self-confidence, performance and productivity. Training attention to a smiling face can reduce stress and anxiety. This tool of cognitive bias modification can boost self-confidence and esteem	Attention Visual Search	Stress	Questionnaire Quiz	10000-50000	3.0	Mind habits No reference sources for the task and the evidence underlying the task provided in the description	24 th March 2013
Spot Smile, brighten your day (Free App)	Based on Cognitive bias modification. By focusing on smile images, it can subtly retrain your brain to shift attention away from nasty images towards pleasant images. A growing body of research shows that shifting negative biases is easy and has effects on how well people cope with a stressful situation.	Attention Visual search -	Stress	Ability to add own images to the Bias modification task	5000-10000	4.6	Make Good Apps No attribution to any reference sources	4 th October 2015
AntiAnxiety (Paid App – \$3.99)^	Use CBM to train you to ignore negative stimuli that would cause stress in social situation. Deals with interpretative bias – People suffering from anxiety are prone to interpret uncertain situations more negatively.	Cognitive Bias Modification for Interpretation	Social Anxiety	Ability to add 3 training reminder notification	500-1000	4.0	Great Bytes Software Claimed to have its basis based on research from McNally Laboratory, Harvard University	22 nd February 2014
Happytap (Paid App – \$2.43))^	Marketed as a research-based game to help lighten mood. Based on CBM tool of attention training in experimental psychology. The task is designed to reduce attention (bias) against rejection and pessimism and increase attention towards acceptance and optimism	Attention Visual search	Stress	Nil	100-500	Nil	SuperEgo AS No attribution to any reference sources	22 nd January 2016
Bias Modification (Free App)	The game makes you happier and it is backed by scientific research Cognitive Bias modification has been shown to help overcome the tendency to	Assessment phase based on Cognitive Bias Modification	None stated	Nil	100-500	4.3	Tyrsk Reference attributed to Wikipedia article on Cognitive Bias Modification	5 th June 2017

	focus on negative or threatening social cues.	ion for Interpretation						
HappyFace (Free App)	A simple game that uses cognitive bias modification to reduce social anxiety and improve personal well-being	Attention Visual search	Social Anxiety	Nil	10000-50000	4.1	NA Reference attributed to BBC Horizon Programme	20 th January 2014
Happy Faces (Free App)	Boost your mood and reduce stress and anxiety with Cognitive Bias modification	Attention Visual search	Stress & Anxiety	Ability to add own images	1000-5000	4.0	Mental Mint No attribution to any reference sources	18 th January 2016
Quitty (Also available as a standalone Apple App) (Paid App: \$2.99)^	A game designed to help you quit smoking Scientifically based on cognitive bias modification and hypnotic techniques	Not based on conventional tools In the game play, a tobacco product is used as a projectile to hit other objects.	Smoking	Nil	100-500	4.3	Playing for Health No attribution to any reference sources	28 th August 2017
CBM Helper (Also available as a standalone Apple App) (Paid App: \$6.06)^	The application will allow the user to alter their natural bias and look for more favourable outcomes. Therapy tool for cognitive bias modification for clients with anxiety disorders.	Attention Visual search	Stress, Depression and PTSD	Nil	100-500	2.9	Achieving Greatness No attribution to any reference sources	9 th September 2017
StopSmoking-Quit smoking (Also available as a standalone Apple App) (Free App)	StopSmoking is a mobile runner game which helps you to quit smoking in a fun and interactive way.	Not based on conventional tools In the game play, the intention is to avoid hitting	Smoking	NA	1000-5000	4.4	Optimum Design No attribution to any reference sources	18 th October 2016

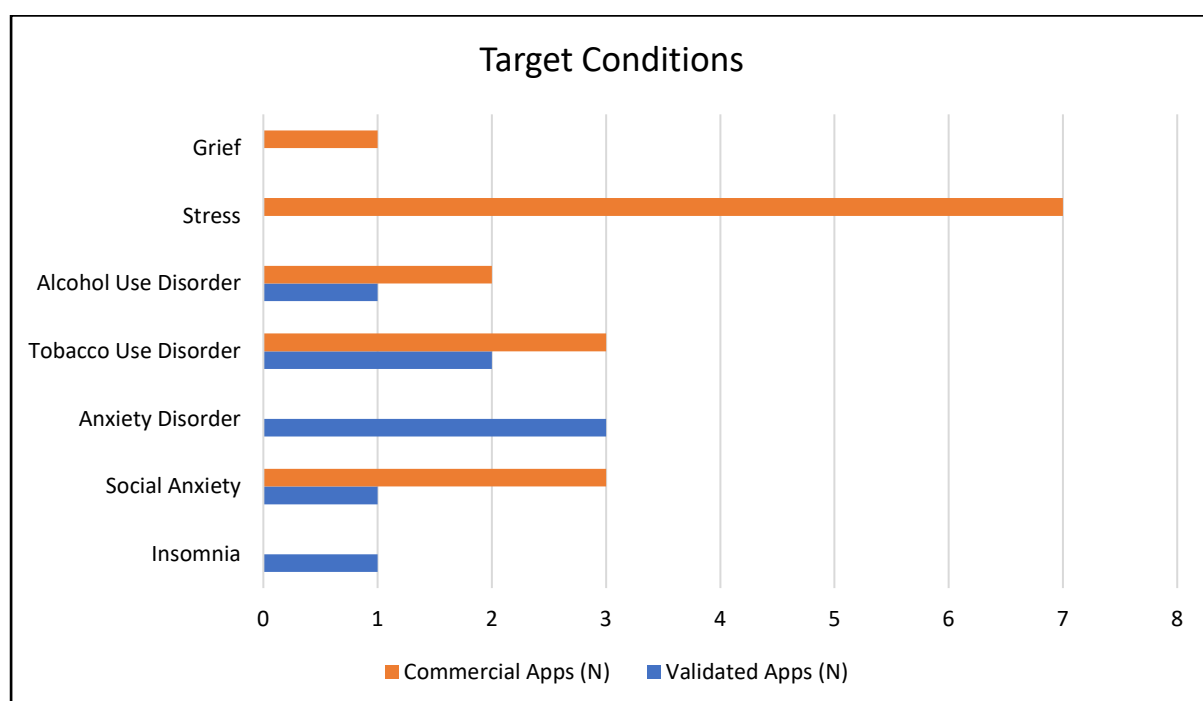
		the tobacco products						
Grief Relief App (Paid App: \$0.99)^	Grief Relief lets you choose positive images and words. The app uses cognitive bias modification, a form of therapy used by psychotherapists.	Attention Visual search	Grief	NA	50-100	2.6	Grief Relief Reference source attributed within application	14 th June 2017
Find the Happy Face (Free App)	The main task is to click on happy faces among the grid of faces. By focusing on the happy faces and keeping apart the non-happy ones, you will re-program your brain to focus on positive events in everyday life. All of this will help you with social anxiety and make you a more optimistic person.	Attention Visual search	Social Anxiety	NA	100-500	4.5	Maximiliano Aguirre No other reference sources.	27 th April 2017
Quit Smoking: Simple and Quick (Free App)	This Quit Smoking: the Simple and Quick app is based on the cognitive bias modification therapy (aka cbmt) which is proven to assist people in changing unhelpful habits and unhelpful mental patterns.	Attention Visual search	Tobacco use	NA	100-500	3.5	Cmbt4you No other reference sources.	5 th June 2014
Stay Sober, Stop Drinking (Also available as a standalone Apple App) (Free App)	The simple process of consciously and repeatedly selecting non-alcoholic drinks such as water or orange juice over alcoholic beverages, helps you to gradually develop a positive bias – a tendency to focus more on the positive information around you in everyday life.	Not based on conventional tools In the game play, the intention is to avoid hitting the alcohol products	Alcohol use	NA	100-500	NA	Optimum Design No other reference sources.	12 th January 2016
ChimpShop (Also available as a standalone Apple App) (Paid App: \$2.09)^	Developed by Scientists, ChimpShop contains psychological techniques to help make it easier for you to cut back (on drinking).	Not based on conventional tools In the game play, the intention is to grab	Alcohol use	NA	10-50	NA	Attention Retraining technologies Website attributed theory to work done by Professor Miles Cox	31 st July 2014

		the good stuff and avoid the bad						
Apple Apps								
Mood Mint – Boost Your Mood (Paid App: \$2.99)^	Mood Mint combines a variety of psychological techniques to help boost your mood and reduce stress, anxiety and depression.	Attention Visual search	Stress, Anxiety and Depression	Ability to customize images “Happy notes” appear during the bias modification session to provide bite-sized tips.	NA	NA	Jason Pegg No other reference sources.	1 st July 2015
Happytap Play (Free App)	In the game the user is tasked to "find the smile" in an array of faces with varying emotional expressions Stated that simple games could help provide positive distraction from everyday stress	Attention Visual search	Stress	Nil	NA	NA	Superego AS No other reference sources.	9 th February 2016

^Prices of apps are in Singapore dollars

Figure 3.3 provides a graphical overview of the target conditions for validated scientific apps and commercial apps. The published applications mainly targeted tobacco use disorder and anxiety use disorder, while most of the 17 commercially available apps targeted stress. Tobacco use disorder appeared to be a common disorder targeted by validated and commercial apps, with a total of 2 and 3 validated and commercial apps, respectively.

Figure 3.3 Overview of the Conditions Targeted by Scientific and Commercial applications



3.5 Discussion

The effectiveness of mHealth attention bias modification was reported in seven of eight previous trials. Of these eight trials, three involved evaluating mobile bias retraining in addictive disorders, specifically, alcohol and smoking disorders. All three trials involving individuals with substance use disorders reported positive findings, with a reduction in bias and in the absolute amount of substance use. This synthesised information helps justify the following work involving attention bias modification, tapping into mobile technology for delivery. Given that existing evaluations are limited

to alcohol and tobacco use disorders, it would be reasonable to investigate mobile attention bias modification in the other substance use disorders (opioid, cannabis, and stimulant use disorders). The evidence synthesis also demonstrated that nearly all the interventions relied on the visual probe task to modify attention bias, with most demonstrating effectiveness. Future interventions should therefore base their task paradigm on the visual probe task, although the stimulus images and stimulus presentation timings should be modified depending on the substance condition being targeted.

Of the eight evaluated apps, only one was commercially available. In determining the evidence base, the developers were contacted, but none could provide evidence regarding their app's scientific validation. Individuals are therefore highly likely to download other non-validated apps instead of validated ones after searching for attention or cognitive bias apps in the app stores. This review identified only one scientifically validated app; unfortunately, its download numbers were low and consequently ranked low in the stores, a similar finding to that of Haskins et al. who reviewed smoking cessation apps (172).

Our findings suggest a disconnect in how scientifically evaluated interventions are marketed and a disconnect between academics and developers. As evident from this review, most commercially available apps have been developed independently by companies, based on the references' attributions. While the developers of two of the apps (ChimpShop and AntiAnxiety) reported some form of collaboration with an academic institution, but only the ChimpShop evaluation was published in the literature. Clinicians and other healthcare professionals are rarely involved in app development (173). It is especially concerning that some of these commercial applications have included bias modification methods that are not based on evidence-based task paradigms. The varying bias modification methods included in some of the commercial applications suggest that developers may lack an understanding of the evidence base. Working together, clinicians and developer could better benefit the patient, with clinicians providing an evidence base and the developers the design and technology.

One of this study's major strengths was identifying scientifically validated and commercially available attention bias modification apps; however, there were several limitations with the methods used. We searched four databases; but other databases (such as Google Scholar) were not searched and might provide additional citations. The identification of apps was confined to the Apple and Google app stores, the two most widely used app stores; however, different apps might be available, such as progressive web apps. Systematically searching for progressive web apps was difficult, as there were no webstores that could be systematically searched using keywords. This review only included English-language apps, which might have excluded relevant apps on attention or cognitive biases that were not in English. Moreover, in this dynamic and expanding field the search may be immediately out of date as newer apps are constantly introduced into app store.

3.6 Implications for this dissertation

The results of this review confirm the potential for harnessing mobile technologies in bias modification for addictive disorders. Compared with the results for web-based interventions, mobile interventions appear to be more successful, with more studies reporting effectiveness. The results also demonstrated that, when this review was completed, no studies had yet examined mobile attention bias modification among individuals with other substance use disorders (opioid, cannabis, or stimulant use disorders), a research gap warranting further investigation. This study highlights the need for strong collaborations between academics and developers to ensure that resulting apps are built on evidence. This study's findings are a reminder to professionals working in the addiction field, to be cautious if recommending commercial applications to their patients as these applications are poorly evaluated.

The subsequent chapters of this thesis will begin to generate evidence for the development of a mobile attention bias modification intervention for Singaporean participants. This dissertation will explore how retention and engagement could be improved in interventions by including gamification elements (Review 3) and whether a mobile cognitive bias modification intervention would be feasible and acceptable for other highly prevalent substance use disorders (Study 1). If proven feasible and acceptable, this dissertation will then explore how a collaboration between academics,

developers and patients can conceptualise an evidence-based applications that meet patients' needs (Study 2).

Chapter 4 Gamified Cognitive Bias Modification Interventions

Chapter 4 reviews the effectiveness of gamified cognitive bias modification interventions, and to better understand gamification approaches that have been used. Sections 4.1 and 4.2 provide an overview of the concepts of serious games and gamification and how these methods have been applied in psychiatry. Section 4.3 overviews the application of gamification methods to cognitive bias interventions. Section 4.4 highlights the research gap and how the work undertaken in this chapter will bridge the gap. Section 4.5 describes a review of the published literature, examining the evidence for gamified cognitive bias modification interventions. Section 4.6 describes the content analyses of commercial gamified cognitive bias modification interventions in the app stores. Section 4.7 concludes the chapter by highlighting the implications of these studies.

4.1 Overview of Serious Games and Gamification

Advances in technology have transformed the delivery of psychological interventions in the recent years, and in parallel there has been an increased focus on using serious games and gamification technologies in healthcare interventions. Serious games refer to those created for non-recreational purposes, which when used in healthcare to improve health-related outcomes and provide health professionals with education through digital devices (174, 175). Serious games involving physical activity levels, nutrition, and stroke rehabilitation have been evaluated (176). The use of serious games has gained popularity due to their engaging nature, which increases the participants' intrinsic motivation. There are, however, challenges in using serious games, particularly relating to conceptualisation, development costs, and the need for dedicated consoles/equipment (176).

Given these challenges, researchers are considering alternative gamification strategies. Unlike a serious game, gamification refers to the application of certain game-design elements/ and features in a nongame context (177). Like serious games, these gaming elements render the intervention more enjoyable and engaging and enhance user motivation. Furthermore, the costs of development are lower. Common gamification techniques include digital rewards, avatars, competitions, social pressure, feedback, levels, achievement and ranks, leader boards and customisable environments (177).

These techniques have broad applicability to a spectrum of disorders and technological systems. It is proposed that including gaming elements could generate positive emotions, build better relationships, and create meaning and a sense of accomplishment (177).

4.2 Gamification for Psychiatry Interventions

Gamification technologies have been increasingly utilised in healthcare. A prior review by Sardi et al. reported that most interventions were applied in the context of chronic disease rehabilitation, increasing physical activity levels, and supporting mental health (176). Specifically for psychiatry, 10 studies using a serious game as an intervention have been reviewed (174). Lau et al. reported that serious games helped improve psychiatric symptoms, with an effect size of 0.55 (174). Other reviews have examined the effectiveness of gamification strategies. Lumsden et al. evaluated the evidence for gamification technologies as applied to cognitive assessment/training interventions and found that gamified tasks improved both short and long-term engagement in 33 studies (178).

4.3 Gamification and Cognitive Bias Modification Interventions

Cognitive bias modification interventions are repetitive and boring, and gamification has since been considered for these interventions (102). Boendermaker et al. examined several approaches for enhancing motivation and engagement (102). The first approach involved a serious game, the second involved a serious game with social networking functionality and the third involved a mobile app (102). For the first approach, the serious game included gaming mechanics, a backstory, and aesthetic features, while maintaining the main underlying paradigm elements (involving alcohol No-Go training) (102). In this serious game, the main character was a ninja mouse that walked along a hallway (102). The main character would pass by posters depicting images of beverages (which resembled the original alcohol No-Go training) (102). A cue would be presented in front of each poster (such as a slice of cheese or a cat), and the main character would have to collect as many preferred objects as possible (e.g., the cheese) while ignoring the harmful objects (e.g., the cat) (102).

For the second approach, in this variant with social networking functionality, the game (as described) was registered as an app on a social networking site (Facebook) (102).

Participants were assigned an account where they could post their scores and achievements. For the mobile version, the approach-avoidance task was adapted to an Android smartphone device (102). Participants were instructed to respond with a swipe gesture on their smartphone, swiping the stimuli either toward or away from themselves.

Boendermaker et al. reported no effects of the serious game approach on the overall bias score or drinking patterns (102). The gamified intervention was perceived as demanding and hard to use by the participants (102). However, social networking gamification elements did result in an immersive game that was more motivating to use. In a subsequent study, Boendermaker et al. specifically examined a gamified version of an attentional bias task (“evaluating the shots” game) amongst 96 undergraduate students with alcohol issues (103). The authors reported that gamification did not significantly reduce attentional biases, nor did it improve the motivation to use the task.

4.4 Research Gaps

The review by Boendermaker et al. provides a timely insight into the application of gamification strategies to cognitive bias modification interventions, but the review was not systematic, with no synthesis of evidence from published studies (102). No previous study has systematically evaluated the literature regarding gamified cognitive bias modification interventions or synthesised evidence of their effectiveness. Understanding their effectiveness determines if I should consider gamification strategies in the future conceptualisation of attention bias modification interventions. This review seeks to address the research question pertaining to the evidence base of published gamified applications in the literature.

Review 2 also highlighted commercially available applications that included gaming elements. Google Play Store has a larger repository of such applications (as indicated by the 15 apps from Google Play Store and two from Apple iTunes store). If the intent were to better understand gamification strategies in commercial applications, a search through Google Play Store might therefore result in better yields and coverage. For the reasons previously explained in Study 2, this search was not limited to addiction applications, as that would be too restrictive. A broad search was preferred as it

provides an understanding of the evidence and recognises gamification methods and strategies adopted.

The research objective was to examine the evidence base and gamification methods among commercially available gamified interventions. To this end, we conducted a review of gamified cognitive bias interventions in the literature, along with a content-analytical review of gamified commercial applications. The findings from each of these reviews will be discussed separately. Both these studies have been published (Appendix 6,7).

4.5 Review of Gamification Strategies in the Literature

4.5.1 Specific Aims of the Review

The primary aim was to review gamification in cognitive bias modification for psychiatric disorders. The secondary aim was to identify gamification elements used in cognitive bias modification interventions and evaluate the evidence for their effectiveness by assessing whether the gamified intervention changed biases or improved the secondary outcomes (e.g., improved anxiety/depressive scores, reduced the absolute amount of alcohol consumed) and whether there was any motivational improvement.

4.5.2 Search Strategy

To identify relevant articles, the following search terminologies were used: ('cognitive bias' OR 'attention bias' OR 'interpret* bias' OR 'approach bias' OR 'avoidance bias') AND ('training' OR 'modification' OR 'practice' OR 'therapy') AND ('gamification' OR 'game elements' OR 'game' OR 'gaming' OR 'game mechanics'). PubMed, MEDLINE, PsycINFO and Scopus databases were systematically searched for articles published after 2000 (before 2000, there were few computer-based interventions). When full-text access was not available, the original authors were contacted for their articles. All articles were searched from inception to April 2018.

4.5.3 Inclusion and Exclusion Criteria

Articles were included if they described a cognitive bias modification intervention in the form of a gamified task and included participants diagnosed with underlying psychopathological symptoms such as depression, anxiety and addiction. Articles were

excluded if they were opinion pieces, review articles or design documentation or described an intervention that used an existing commercial game. Only English-language articles were included.

4.5.4 Screening, Data Extraction, Sorting and Selection

All articles identified using the search strategy were downloaded and imported into a reference manager. The articles were screened based on their titles and abstracts by two authors independently. Full copies of the shortlisted articles were evaluated against the inclusion/exclusion criteria, with disagreements resolved by discussion with a third author.

The following data were extracted from relevant articles: (1) publication details (authors, study year and country where the study was conducted); (2) study design (observational or experimental); (3) sample size; (4) sample type (treatment-seeking or community); (5) sample demographics (mean age, gender); (6) psychopathological symptoms and methods for ascertaining psychiatric symptoms; (7) details of gamified cognitive bias modification interventions (gameplay mechanics and conventional cognitive bias modification interventions the gamified task was based on) and (8) primary outcomes and secondary outcomes (effectiveness of gamified cognitive bias modification interventions and any changes in psychiatric symptoms).

4.5.5 Data Integration and Synthesis

A qualitative synthesis of the evidence extracted from the articles was performed. Due to the heterogeneity of the reported outcomes, a meta-analytical synthesis was not considered appropriate.

4.6 Results

4.6.1 Identified Studies

The pre-defined search strategy identified 1008 citations from four bibliographic databases. After excluding duplicate articles, 970 records were screened, 962 of which were excluded for not being relevant to the topic of interest. Eight full-text articles were downloaded for further evaluation against the inclusion/exclusion criteria. Four citations were excluded for not fulfilling the inclusion criteria, leaving four articles for

the qualitative synthesis. Figure 4.1 provides an overview of the study selection process. Table 4.1 provides an overview of the selected studies' characteristics.

Figure 4.1 Overview of the Study Selection Process

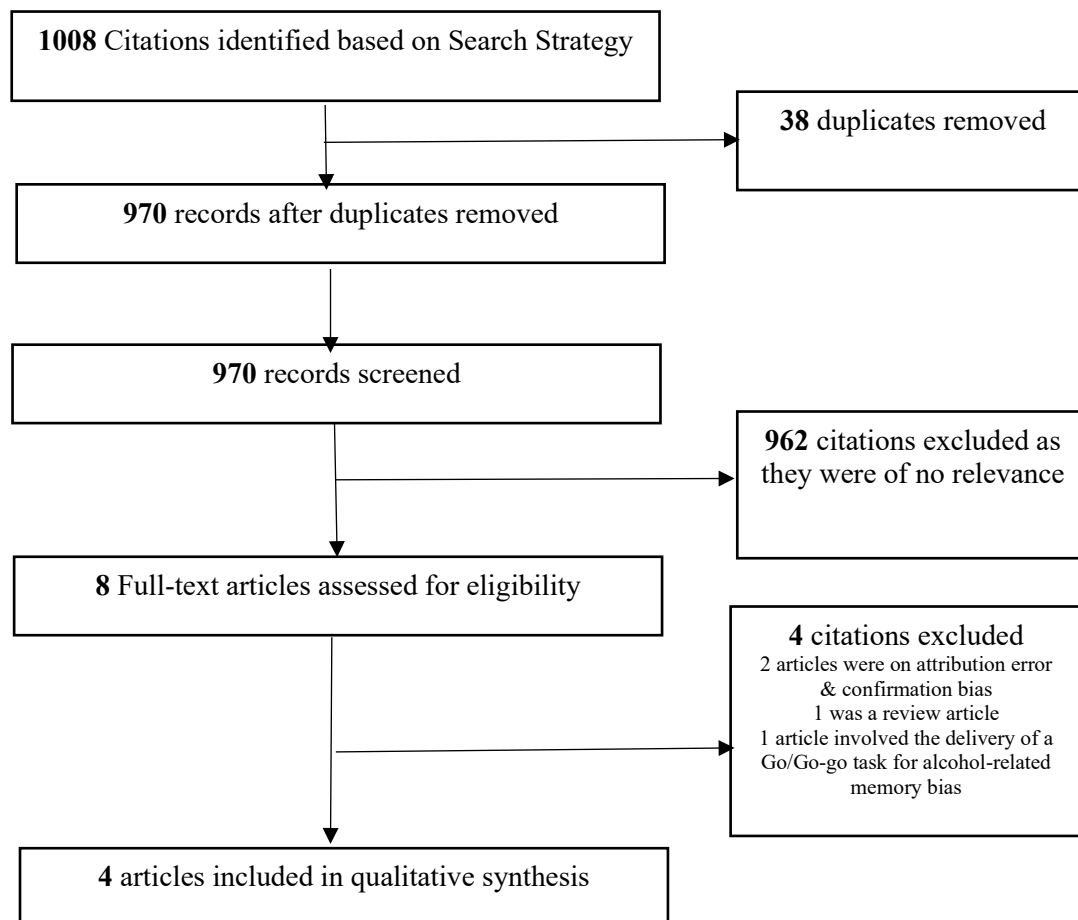


Table 4.1 Characteristics of the Identified Studies

Study & Country of Study	Study Design & Sample Size	Types of Sample	Demographics of Sample	Psycho-pathological symptoms	Details of Intervention	Primary and Secondary Outcomes
Dennis et al. (167) New York, United States of America	Randomised Controlled Study Total sample size =78 Long training condition: 38 participants ; 19 to Attention bias modification training (ABMT) and 19 to placebo training (PT) Short training condition: 40 participants; 2 excluded, leaving 18 to ABMT and 20 to PT	Adults recruited from an Introduction to Psychology Course at an urban University	Long training condition: mean age 22.3, 27 females, 11 males Short training condition: mean age 20.2, 28 females, 12 males	Anxiety symptoms Participants were recruited only if they scored more than 1 SD above the mean for college students on trait anxiety (using the State-Trait Anxiety Inventory).	Gamified mobile application was based on the dot-probe task. Gamification elements included animated characters, points and sound effects. In the game-play, two animated characters, one with an angry expression and another with a neutral/mildly positive expression would appear. Thereafter, both would disappear into a hole, with one causing a path of grass to rustle. Participants traced the path of grass. Feedback was provided after each trial: red jewel/low pitch sound for slow response, poor accuracy; purple jewel/medium pitch sound for moderate speed & accuracy; gold jewel/high-pitch sound for fast response & accuracy. A high pitch sound was played for errors made. Points were accumulated as the intervention progress. The short and long version of the app involved 25 and 45 minutes of training respectively. Mechanism of delivery: computer for assessment and iPod Touch (fourth generation) for training	Long-training resulted in reduced threat bias and difficulties with disengaging. Both the short and long training resulted in reductions in subjective and observed anxiety and stress.
Boendermaker et al. (103) Amsterdam, The Netherlands	Randomized Controlled Study Total sample size=96	Sample of undergraduate students recruited through the university laboratory's website	Mean age 21.2 years, (68/96) 71% were females Gamified visual probe task (VPT-G) group: mean age 21.0, 23/33 were females Regular visual probe task (VPT-R) group: mean age 21.3, 22/30 were females Placebo version of the regular visual probe task (VPT-	Alcohol Problems Participants were recruited if they consumed ≥ 5 standards glasses of alcohol on average per week for males; ≥ 4 for females Participants were assessed by means of the Timeline Follow back (TLFB), adapted version of the Alcohol Use Questionnaire (AUQ), and the Alcohol Use Disorders Identification Test (AUDIT)	Gamified mobile application was based on conventional visual probe task. The game elements included reward system, graphics, animations, and sound effects. The gamified intervention resembled that of a slot machine. Participants identified the position of the probe that replaced either the substance or neutral stimuli. Participants were rewarded for correct and fast responses (by means of time bonuses and special bonus trials) and new levels. Mechanism of delivery: Mobile Device	Decline in attention bias mainly in the regular visual probe training task. There was no decline in alcohol consumption after the training. Motivation to train decreased in all conditions. This implied that the training task did get boring over time. Participants in the game condition indicated a lower motivation to train as compared to other conditions.

			P_ group: mean age 21.4, 23 out of 33 females			
Dennis-Tiwary et al. (168) New York, United States	Randomized Study Total sample Size N=42	Adults recruited from an undergraduate research pool at an urban university in New York City, and through Craigslist	Mean age 20.6; 21/42 were females ABMT group: 11/19 were females PT group: 10/23 females	Anxiety symptoms State-Trait Anxiety Inventory was used to screen participants. Participants were recruited if they scored +1 standard deviation above the mean for college students on trait anxiety.	Similar app as Dennis TA et al. (2014)	A single session of gamified ABMT improved performance on anxiety-related stress task among females only.
Pieters et al. (180) Ghent, Belgium	Randomized Controlled Study Experiment 1: Total Sample= 58 Assigned to attend positive: 30 Assigned to attend negative: 20 Experiment 2: Total Sample= 86 Assigned to attend positive: 27 Assigned to attend negative: 29 Assessment-only group: 26	Undergraduate students	Experiment 1: Attend-positive group: mean age 23.9, 23/30 females Attend-negative group: mean age: 23.1, 25/28 females Experiment 2: Attend-positive group: mean age 21.2, 23/27 females Attend- negative group: mean age:21.2, 23/29 females Assessment-only group: mean age: 23.3, 21/26 females	Affective symptoms Assessed by the 30-item version of the Mood and Anxiety Symptoms Questionnaire (MASQ-D30), the Ruminative Response Scale (RRS),	Gamified application based on Intrinsically Motivating Playable Attentional Control Training (IMPACT). Intervention based on conventional visual attention task. Game elements included feedback, time points, difficulty levels and sounds. Faces (either smiling or disgust) continuously descend from top to bottom of the screen. Participants were to prevent faces from reaching the bottom of the screen by clicking on the faces twice. Participants in the attend-positive condition were required to clinic on happy faces and ignore disgusted faces; while participants in the attend-negative condition were asked to click on disgusted faces and ignore happy faces. Immediate feedback was provided through time points. The task consisted of 15 rounds of 1min each. In the attend-positive condition, 60% of the faces were smiling and 40% were disgusted. This was reversed for the attend-negative condition. Mechanism of delivery: computer in laboratory	No significant effect on measures of emotional attentional performance, or on self reported stress, anxiety and depression symptoms

4.6.2 Characteristics of Identified Studies

Two of the four studies identified involved participants with anxiety symptoms (167, 168). One involved participants with alcohol-related problems and one, participants with affective symptoms (103, 180). All studies were experimental, randomised controlled designs that recruited participants with mean ages of 20 to 30 years from universities. Two studies were conducted in the United States, one was conducted in Netherlands, and one was conducted in Belgium. None of the studies used a structured clinical interview to ascertain symptomatology or diagnosis, instead they relied on validated questionnaires (State-Trait Anxiety Inventory (167, 168), Mood and Anxiety Symptoms Questionnaire (180), and Alcohol Use Questionnaire and Alcohol Use Disorders Identification Test questionnaire (103)). Three studies based their gamified intervention on the visual probe task, and one based it on the attentional visual search task, as evident from the data in Table 4.1.

4.6.3 Gamification Elements Included in Interventions

Two studies used the same app for their intervention, a gamified attention bias modification app based on the conventional dot-probe task (167, 168). The gamification elements included animated characters, a scoring system, and sound effects (167, 168). Two animated characters would appear on the screen simultaneously and then disappear into a hole (167, 168). One character would cause a path of grass to rustle behind them. Users were asked to trace the path in the grass. Based on the author's description of the gamified intervention, four different sounds were played depending on accuracy and speed and appropriate rewards were given (167, 168). For slow and inaccurate responses, the lowest pitch sound would play, and a red jewel would be awarded. For moderately fast and accurate responses, a medium pitch sound would play, and a purple jewel awarded (167, 168). For fast and accurate responses, a high pitch sound would play, and a gold jewel awarded (167, 168). There was also a feedback sound for incorrect responses (167, 168). There were two variants of the gamified intervention: 25 minutes of training and 20 minutes of rest or 45 minutes of training with no rest (167, 168). Feedback and the points accumulated during the intervention were given immediately on completion.

Pieters et al. used a gamified app for cognitive bias modification for anxiety, based on the conventional visual attention task (180). The game required participants to tap on smiling faces, which comprised 60% of the faces (the remaining 40% consisted of disgruntled faces) (180). Once participants tapped on the smiling face, the face bounced up for a short distance and became untappable for 0.5 to 1 second (180). Participants were instructed to prevent the smiling faces from falling down the screen by tapping on them (180). Points were awarded to incentivise game play (180). A point was awarded for tapping the smiling face the first time, and 5 points were awarded if the same smiling face was tapped a second time (180). Users lost 3 points if the smiling face was not tapped and fell off the screen (180).

Boendermaker et al. used a slot game for attention bias modification, based on the conventional visual probe task (103). The gamified intervention included a reward system, graphics, animations, sound effects, time pressure, and levels. Their game resembled a slot machine with a coin-based reward system (103). Like the conventional task, participants were required to identify the probe that replaced the position of the alcohol or neutral image (103). Participants won bonuses for responding rapidly and gained access to new game levels.

Three studies (103, 167, 168) delivered the gamified cognitive bias modification intervention using a mobile device, whereas that by Pieters et al. (180) used a computer.

4.6.4 Reasons for Gamification

Two studies described the reasons for including gamification. Boendermaker et al.'s intervention included gaming elements to promote participant motivation to train via the intervention (103). The authors also explored if the inclusion of gaming elements increased the effectiveness of the conventional visual probe task (103). Dennis et al. similarly examined whether gamification changed the effects of the attention bias modification (168).

4.6.5 Primary and Secondary Outcomes Reported in the Literature

Of the four studies, two reported the cognitive bias modification intervention's gamified variant to be effective (167, 168). Dennis et al. reported that the long-training attention bias modification task reduced threat bias and the difficulties individuals had disengaging from the threat-related stimulus (167). There were also corresponding

reductions in the subjective and observed anxiety and stress. Similarly, the authors of the second paper reported that the single session of gamified attention bias modification was effective in improving the performance of the attention bias modification task (168), but significant results were only observed among women. Contrary to the findings of Dennis et al and Dennis-Tiwary et al, Pieters et al reported that their gamified intervention did not result in any reduction in attention biases or associated mood-related measures (167, 168, 180).

In the study involving participants with alcohol-related problems, the gamified variant of the cognitive bias modification task did not reduce attention bias and failed to achieve a decline in overall alcohol consumption (103). Importantly, the study by Boendermaker et al. was the only study investigating the effects of gamification and participant motivation in using the training task (103). The authors reported that motivation to train did not increase by adding gaming elements. In fact, participants assigned to receiving the gamified variant reported having lower motivation to continue the training task compared with participants assigned to other conditions.

4.7 Discussion of Findings

Of the four studies that evaluated gamified cognitive bias modification interventions, two included participants with anxiety symptoms, one included participants with affective symptoms, and one included participants with alcohol problems. The gamified interventions were based on the conventional visual probe task in three studies and on the attentional visual search task in one study. Gaming elements incorporated into the task included animations, sounds, feedback and a scoring system for response time and difficulty. Two publications discussed their rationales for gamification, one sought to determine whether gamification enhances motivation and one sought to determine whether the gamified attention bias modification was as effective as a conventional modification. Of the four identified studies, two reported their gamified intervention as effective. Of significance, these two studies used the same app and were from the same research group.

All identified studies based their gamified intervention on either the conventional visual probe task, or the attentional visual search task. In line with the recommended gamification techniques of Boendermaker et al, all four studies added gaming elements

to a conventional evidence-based training task (102). Adopting intrinsic integration makes tasks more engaging and might increase the inherent levels of motivation to continue training. Unfortunately, there was no evidence from this review that adopting intrinsic integration led to increased motivation to train, as only one study included motivation to train as an outcome measure, and in that study, there were no improvements (103).

The common gaming elements incorporated in the published gamified interventions included: animations, sound effects, point-scoring systems, time pressure, and levels. In their review, Hoffman et al. proposed a taxonomy of gamification strategies that could be applied to evaluate gamification strategies in apps (177). The authors used the taxonomy to evaluate stress management apps and found that feedback or performance-orientated strategies were frequently used in the 62 evaluated apps (177). Like the review of Hoffman et al (177), the current findings demonstrated that performance-orientated gamification strategies were used for some of the gamified apps (time pressure and levels in the Boendermaker et al.'s study (103)). Economic gamification strategies were more commonly used, with four studies reporting the use of a point system. Prior research highlighted the importance for designers to carefully consider the gamification techniques employed, depending on the app's nature and how gamification could affect user interaction (177). Thus, for cognitive bias modification interventions, incorporating feedback might be less feasible since feedback usually involves a comparison with a set standard or to the performance of other interventions. Considering the nature of the attention bias task, there are no set standards. Digital rewards such as points might be more tangible, both as extrinsic motivators and as surrogate indicators of user performance on tasks.

Overall, there is inconclusive evidence regarding the effectiveness of gamified cognitive bias interventions; only two of the four studies reported positive findings. Regardless, our review has several implications. Why gamification is effective in some studies and not others must be determined to help decide which gamification strategies should be adopted in an intervention. User perspectives of what makes an app engaging and which strategies result in short and long-term engagement are important considerations in designing gamified cognitive bias modification interventions. Although this review identified only four studies, Zhang et al. found that there were 17 commercial cognitive bias modification apps in the app stores (181). It might be helpful

to analyse the gamification features in commercial cognitive bias modification apps and determine whether certain gamification features are associated with higher download rates, as a surrogate measure of acceptability (undertaken in the next section).

4.8 Review of Gamification Strategies in Commercial Applications

4.8.1 Rationale and Objective of the Content Analysis Review

Understanding the common gamification approaches adopted in commercial applications, with broad public usage, is important, especially if researchers seek to co-create a new gamified cognitive bias modification intervention. This is because researchers need to be cognizant of gaming techniques that can make apps more appealing.

The main objective was to identify the gamification approaches adopted in commercial cognitive bias gaming applications. Such an analysis would also help determine whether commercial applications are evidence-based and whether their gamification approaches are based on interventions previously evaluated in the literature. This current review will help inform future studies involving gamification in cognitive bias modification applications.

4.9 Methods

4.9.1 Search Strategy

To identify commercial applications, a manual cross-sectional search was conducted from November 1 to 11 November 2017 on the Google Play Store. (163). The current review evaluated only the Google Play Store because the previous content analyses (Review 2) identified more applications in the Google Store than in the Apple Store. Previous content analyses have also examined only this store, given that the Android operating system currently holds the largest market share globally (94). Previous content analyses have also reported that similar applications are found in the Google Play and Apple stores (162,163). The search terms ‘Attention bias’ and ‘Cognitive bias’ were employed.

Given the expected diversity of attention or cognitive bias applications identified using these search terms (‘Attention bias’ and ‘Cognitive bias’), the description and

screenshots of each application were examined. We followed the approach used in Ubhi et al. in their comparative analysis of smoking cessation applications (182). In the initial screening, the decision to retain applications was made based on their description and screenshots, and only applications explicitly stating in their description that it was a gaming application were included. If free and paid versions of the same application were available, only the paid version was examined, given that the paid version was more likely to offer full functionality and access to the complete cognitive bias modification intervention (183). All identified applications were downloaded and further evaluated by two reviewers on an Android Device (Xiaomi Note 4) running on the Android 7.0 operating system.

The gamification technique's classification for the published applications and commercial applications was based on the six approaches described by Boendermaker et al. and the 17 gamification techniques described by Hoffman et al. (102, 177). Table 4.2 provides an overview of the gamification techniques described in the literature.

Table 4.2 Types of Gamification Techniques in Published Works

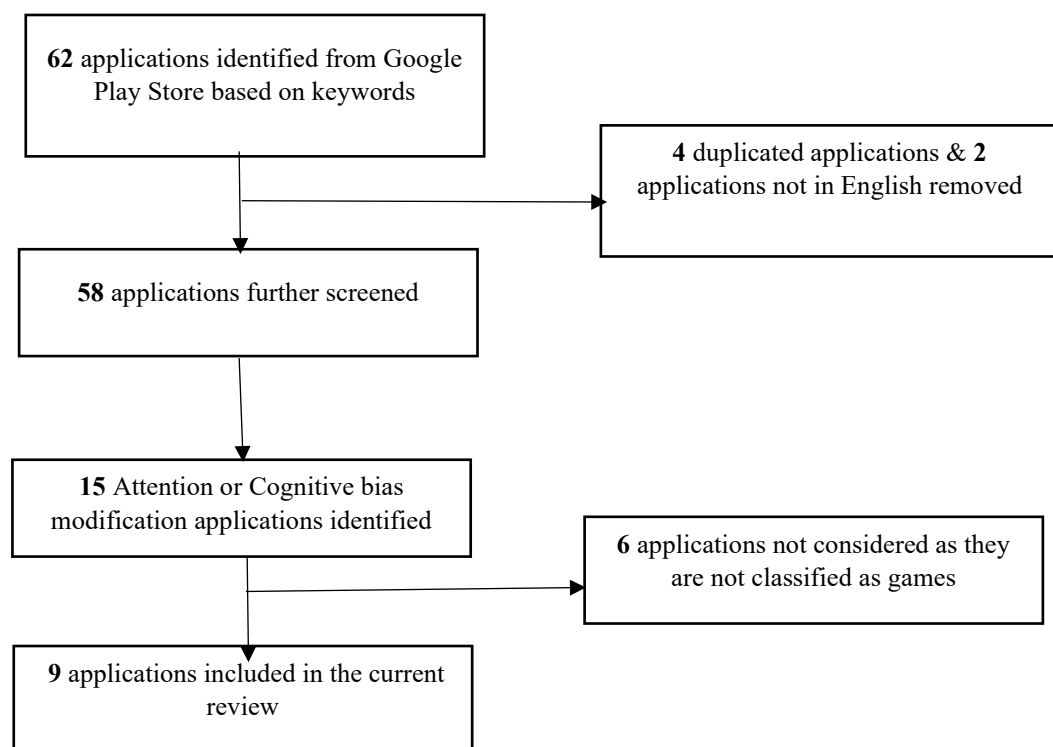
Studies	Gamification Techniques
Boendermaker et al. (102)	• Addition of gaming elements to the evidence-based training task: Inclusion of rewards systems such as motivating feedback, sounds or animations in the training task • Intrinsic integration with the evidence-based training task as a basis: Involves the transformation of the evidence-based task into a game • Intrinsic integration leaving the evidence-based task paradigm intact: Instead of using the evidence-based training paradigm as a basis, this involves the consideration of the theory behind the paradigm and using the theory as a basis to design the game • Adding a game shell around the original evidence-based task: Involves the addition of a full game shell incorporating the evidence-based task • Combining intrinsic integration with a game shell • Bias modification using OTS (off the shelf) entertainment games
Hoffman et al. (177)	• Economic Gamification Techniques • Marketplace and economics • Digital rewards • Real world prizes • Social Gamification Techniques • Avatars • Agents • Competitions • Teams • Parallel Communication systems • Social pressure • Performance-oriented Techniques • Feedback • Levels • Secondary game objectives • Ranks of achievement • Leader boards • Time pressure • Embedding-focused Techniques • Narrative context • 3-D Environment

After identifying the applications, we extracted the following information from each application, a) name; b) description; c) total downloads, d) total ratings, e) developer or author details and organisation affiliation and f) gamification approach. Two authors extracted the data and coded the applications based on the above taxonomy of gamification techniques. Any disagreements were resolved by discussion. Inter-rater reliability was assessed by the kappa statistic as follows: < 0.00, poor reliability; 0.00–0.20, slight reliability; 0.21–0.40, fair reliability; 0.41–0.60, moderate reliability; 0.61–0.80, substantial reliability and 0.81–1.00, perfect agreement.

4.9.2 Results

The keyword-based search identified 62 apps from Google Play Store. After excluding duplicates, 58 apps were further screened, and 15 apps were downloaded for further evaluation. Of these, six were excluded as they were not described as games, in their application description. Eventually, the current review included nine applications. Figure 4.2 shows the Google Store app selection flowchart.

Figure 4.2 Flowchart for selecting applications from the Google Play Store



Four of the nine identified applications did not indicate specific target conditions, but two applications were targeting alcohol use, two targeting smoking and one targeting grief. Applications like Happy Face, were highly downloaded, with 10000–50000 downloads. Most of the applications based their bias modification on attentional visual search tasks. Out of the nine, four applications, however, used a specific paradigm different from the conventional tasks being described and could therefore not be classified. Furthermore, four of the nine applications were paid applications. Table 4.3 provides an overview of the identified applications.

Table 4.3 Characteristics of the Identified applications

Application	Application Description (as extracted from store)	Condition Targeted & Cognitive Bias task integrated within game	Downloads	Application Ratings	Developer	Gamification approach
Spot Smile, brighten your day (Free Application)	The application is based on principles of cognitive bias medication. Marketed as a game and recommended to play the game at least once per day. The application helps to alter harmful thoughts patterns.	Stress Attentional Visual Search	5000-10000	4.6	Make Good Apps	Addition of gaming elements to the evidence-based training task Time pressure (Countdown timer)
Happytap (Paid Application)	The application is based on the principles of cognitive bias modification. Marketed as a game, in which the individual user is supposed to find a smile in the array of faces with varying emotional expressions.	Stress Attentional Visual Search	100-500	Nil	SuperEgo AS	Addition of gaming elements to the evidence-based training task Time pressure (Countdown timer) Feedback Leaderboard (best score) Digital rewards (points)
Bias Modification (Free Application)	The application is based on cognitive bias modification, which helps individuals to overcome the tendency to focus on negative stimuli. Marketed a game with match-three gameplay.	Specific condition not mentioned Cognitive Bias Modification for Interpretations	100-500	4.3	Tyske	Addition of gaming elements to the evidence-based training task Time pressure Feedback Digital rewards (points)
HappyFace (Free App)	Marketed as a game that has a basis on cognitive bias modification, and helps to reduce social anxiety, thus improving personal well-being. Users are encouraged to practice two to three minutes per day over a six weeks period.	Social Anxiety Attentional Visual Search	10000-50000	4.1	NA	Addition of gaming elements to the evidence-based training task Feedback Leaderboard (best score) Digital rewards (points)
Quitty (Paid App)	Marketed as a game that helps individuals to quit smoking, that is based on cognitive bias modification and hypnotic techniques.	Smoking Not based on any conventional cognitive bias modification paradigms	100-500	4.3	Playing for Health	No evidence of integration of any of the four approaches Digital rewards Feedback Levels Time pressure
Stop Smoking-Quit smoking	Marketed as a mobile runner game that helps individuals to quit smoking.	Smoking	1000-5000	4.4	Optimum Design	Intrinsic integration leaving evidence-based training paradigm intact

(Free App)	Game has basis on cognitive bias modification to help alter attentional biases	Not based on any conventional cognitive bias modification paradigms, but the game play scenario involves the participant controlling an avatar and avoiding smoking cues.				Digital rewards Feedback 3-D environment
Grief Relief App (Paid App)	Marketed as a game that helps to provide more positive thoughts and feelings, with basis on cognitive bias modification	Grief Attentional Visual Search	50-100	2.6	Grief Relief	Addition of gaming elements to the evidence-based training task Time pressure Digital Rewards Levels
Stay Sober, Stop Drinking (Free App)	Marketed as a mobile runner game that helps individuals to quit drinking. Game has basis on cognitive bias modification to help alter attentional biases	Alcohol Not based on any conventional cognitive bias modification paradigms but the game play scenario involves the participant controlling an avatar and avoiding alcohol cues.	100-500	NA	Optimum Design	Intrinsic integration leaving evidence-based training paradigm intact Digital rewards Feedback 3-D environment
ChimpShop (Paid App)	A game, which has basis on psychological principles and it helpful for individuals who are attempting to cut back on drinking	Alcohol Not based on any conventional cognitive bias modification paradigms, but the game play scenario involves the participant controlling an avatar and avoiding alcohol cues.	10-50	NA	Attention Retraining technologies	Intrinsic integration leaving evidence-based training paradigm intact Digital rewards Competition Feedback Leaderboards 3-D environment

The inter-rater reliability (Kappa) for the rating of the application was 0.74, equating to substantial inter-rater reliability. For gaming applications that were rated based on Boendermaker et al.'s proposed methods, three involved the use of intrinsic integration while leaving the evidence-based task intact (102). One application did not appear to make use of any of Boendermaker et al.'s proposed methods (102). Across the applications, a variety of different gamification techniques were utilised. Figure 4.3 summarises commercial applications' most common gamification techniques, based on both Boendermaker et al.'s and Hoffman et al.'s classification (102, 177). Based on Hoffman et al. taxonomy, the most common gamification strategies were those that provided digital rewards ($n = 8$) and feedback ($n = 7$) (177). Considering only the gamification techniques based on the Hoffman et al. classification, all applications included at least one gamification technique (177). The average number of techniques across all nine applications was 3.2. The number of techniques in a single application ranged from 1 to 5. Figure 4.3 presents a summary of the number of gamification strategies included.

Figure 4.3 Summary of Gamification Strategies

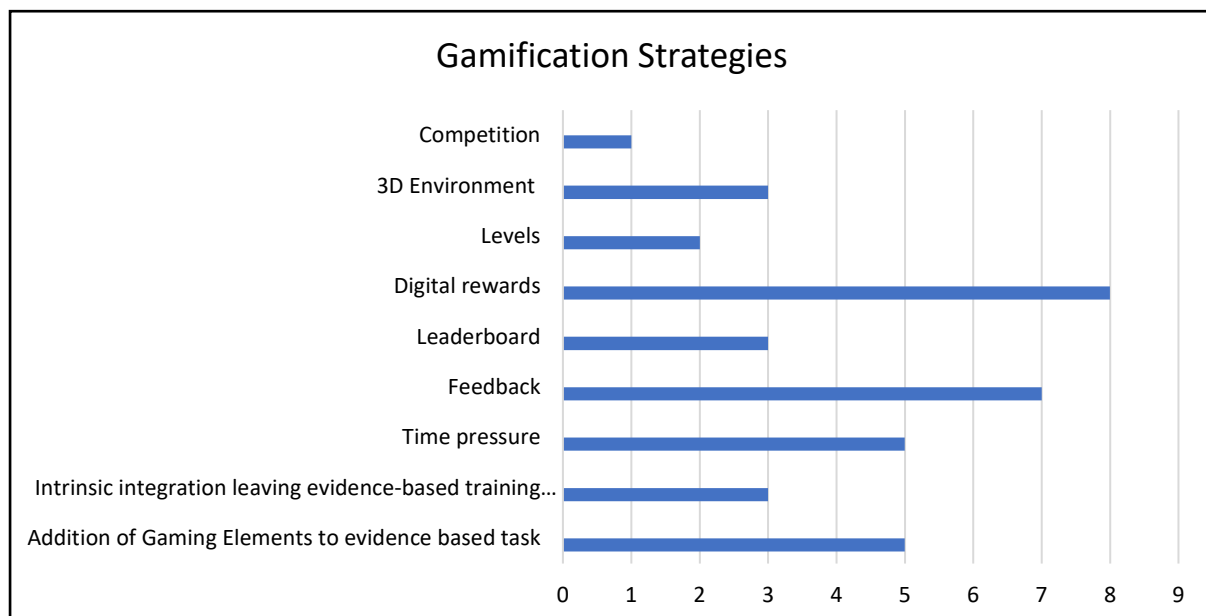


Table 4.4 provides an overview of the mean number of gamification techniques integrated within the application by total download rate. While calculating the mean

number of techniques per download category was limited by the absolute number of applications per category, most commercial applications included a mean of 3.5 gamification techniques and had a download count of 100–500. Feedback and time pressure were common techniques in the four apps that had a download range of 100–500. There were outliers, with a single application incorporating three gamification techniques and having a total download range of 10000–50000. The analysis also demonstrated that the inclusion of more gamification elements does not lead to an app being more often downloaded. There was a single application with five gamification techniques but downloads of only 10–50.

Table 4.4 Mean Number of Gamification Techniques Integrated by Download Rates

Download Rates	Mean Number of Gamification Techniques (Hoffman A et al., 2017's taxonomy)	Number of Apps taken into consideration
10000-50000	3	1
5000-10000	1	1
1000-5000	3	1
100-500	3.5	4
50-100	3	1
10-50	5	1

4.10 Discussion

The current review's main objective was to identify common gamification techniques adopted by commercial applications, the most common being the addition of gaming elements to an evidence-based task and intrinsic integration while leaving the evidence-based task intact. The addition of gaming elements to an evidence-based training task was the most common approach, which is expected, given that this is the most common first step in gamification and routinely involves adding game-like elements that seek extrinsic motivation, such as motivational feedback and points (102, 177). However, the addition of features that seek to motivate extrinsically has been criticised by prior studies, which have suggested that extrinsic motivation might eventually undermine intrinsic motivation for a task and might hinder performance.

The current review showed an average of 3.2 gamification techniques in the nine identified applications, which is much higher than that found by Hoffman et al. in their analysis of gamification techniques in stress-management applications, in which only

0.5 techniques were found across 62 applications (177). One of the reasons for this discrepancy might be the potential bias introduced due to the decision to evaluate only apps classified as games. Given that these apps were classified as games, there is a higher likelihood that they incorporate gaming elements. The analysis, based on Hoffman et al.'s taxonomy also revealed that the most common gamification techniques applied were that of digital rewards and the provision of feedback (177). Digital rewards, while not commonly used in stress-management applications (177), were typically used in other gamification applications, and offer extrinsic incentives to continue the intervention. Feedback is not just a gamification technique, because feedback can also encourage behavioural changes.

4.11 Implications for This Dissertation

The current reviews (both the literature and content analyses) have strengthened the evidence regarding gamification for cognitive bias modification, previously provided by Boendermaker et al.'s prior review (102). Despite the limited studies identified, the first review was important for several reasons. First, it demonstrated that researchers are considering gamification strategies to address the intrinsic problems of poor motivation and the highly repetitive nature of the interventions' tasks. Second, it demonstrated that most tasks had their gamified variants based on the conventional validated task. Third, it identified gamification strategies that made interventions more effective. These gaming elements included animations, sound effects, point-scoring systems, time pressure and levels. The content analysis review found several cognitive bias modification games, some of which appear to deviate from the original bias modification task paradigm. There are several implications for this doctoral work. First, in conceptualising future gamified research, we need to consider gaming elements/features that have made published interventions more effective. Second, future conceptualisations of gamified interventions should be based on a conventional interventional paradigm. These reviews will inform the subsequent co-design process, because it will be easier to demonstrate to participants what is meant by each of the gamification strategies by using screenshots from these applications.

4.12 Funding Application

These reviews were integral to my Games for Healthcare Innovation centre grant application, they provided evidence and justification for my research. The reviews form

the background and provide justification for proceeding with a co-design study (to help with the co-creation of a gamified application).

Chapter 5 Conceptualisation of an Evidence-based Mobile Attention Bias Intervention

Introduction

Chapter 5 introduces the preparatory work for a feasibility and acceptability study conducted on a new mobile-based attention bias modification intervention for inpatient participants at NAMS (Study 1). In preparing for this study, a review of the visual probe task paradigms was conducted. A multidisciplinary team then worked to conceptualise a new mobile attention bias modification intervention.

5.1 Overview of Visual Probe Paradigms Applied for Substance Use Disorders

As described in Chapter 1, the visual probe task is an indirect measure of attentional biases, which starts by presenting a fixation cross at the centre of a screen. A pair of images then appear simultaneously (58). To assess attentional biases in substance use disorders, the task presents two images, one a substance image and the other a neutral image (58). The two images are closely matched in terms of colours and complexity (58). The image pair remains on-screen momentarily before disappearing. A probe, usually in the form of an arrow or asterisk, appears in one of two places, either the in the position of the substance image's or in that of the neutral image (58). The probe then disappears, and the participants must indicate the probe's position as quickly as possible. Participants complete multiple repetitions of this task. In assessing baseline biases, 50% of the trials involved pairing the probe with the substance image, and the other 50% involved pairing it with the neutral image (58). Attention bias is present if the reaction time taken for participants to respond to probes replacing the substance image is faster than that of probes replacing the neutral image. For the modification and retraining of attention biases, the probe is repeatedly paired with the neutral image instead of with the substance image (58), thus allowing for the retraining of attentional biases.

To ensure the evidence base of the visual probe task included in the newly designed mobile attention bias modification intervention for opioid, cannabis and stimulant disorders, we examined the published research literature from 2017 and 2018. This study aimed to identify and compare the various task paradigms and methods for the

visual probe task used for highly prevalent disorders (opioid, cannabis and stimulant disorders) in Singapore and has since been published as ‘Variations in the Visual Probe Paradigm for Attention Bias Modification for Substance Use Disorder’ (Appendix 8) (184) and aimed to identify and compare the various task paradigms and methods for the visual probe task used for highly prevalent substance disorders (opioid, cannabis and stimulant disorders) in Singapore.

5.2 Methods

5.2.1 Identification of Relevant Studies

The current analysis was prepared using data from the Zhang et al.’s review, which identified 11 articles involving opioid use disorder, 16 involving stimulant use disorder and nine involving cannabis use disorders (125). Subsequently, data arising from Maclean et al.’s review was also considered, as it was an updated review that synthesised studies for opioid use disorders (151). This review included a total of 21 articles that previously examined attentional biases in opioid use individuals. An examination of the visual probe task paradigms was performed based on the studies identified in these two reviews.

5.2.2 Results

a. Opioid Use Disorders

Table 5.1 provides an overview of the characteristics of the visual probe task employed in studies involving opioid use disorders. From Zhang et al.’s and Maclean et al.’s publications, a total of nine articles were identified that described the use of the visual probe task for attention bias assessment or modification (125, 151). There was significant variability in the number of stimuli included in the identified articles, ranging from 12 to 44 picture pairs. The number of trials ranged from 64 to 512 trials (59, 187). Across the studies, there was significant variation in the Visual Probe Task paradigm. Most studies presented the fixation cross for 500 milliseconds (ms), except Frankland et al. (185) and Zhao et al. (66), who presented the fixation cross for 1000 ms. Several studies have presented the stimulus and neutral image set for both a short and long duration (58, 65). The short stimulus timing was typically 200 ms, and the long stimulus timing was 2000 ms, though, an exception being Frankland et al.’s (185) study where the images were presented for 500 and 1500 ms.

Table 5.1 Characteristics of the Visual Probe Task in Opioid Use Disorders

Study	Participants	Intervention Details	Nature of Stimulus Included	Details of Assessment Task	Outcomes
Charles et al. (59)	23 Opiate Users, 21 Healthy Controls	Dot Probe task for attention retraining in the lab Participants maintained on Buprenorphine and MMT	44 picture pairs Forty pairs, matched for visual complexity and composition, contained opiate-related items (spoons, needles, lighters, heroin-like substance). Remaining four pairs neutral images only	Fixation Cross Timing: 500ms Stimulus Pair Timing: Short (200ms) or Long (500ms) Probe: Arrow pointing upwards or downwards, remained on screen until participant responded Probe Timing: Not mentioned Inter-trial interval: 250-500ms SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 64 (assessment), 512 (Intervention) Total number of neutral trials: 16 Total number of practice trials: Not mentioned	No baseline difference in attention bias between patients and controls No significant effect of ABM on AB or substance cravings
Constantinou et al. (69)	16 opiate users in treatment, 16 ex-users, 16 healthy controls	Dot probe task for attention retraining in the lab. Participants maintained on methadone maintenance therapy	40 picture pairs 20 pairs – matched for visual complexity and composition, contained one opiate related picture and one non opiate related picture The other 20 neutral pairs	Fixation Cross Timing: Not mentioned Stimulus Pair Timing: Short (200ms) or Long (2000ms) Probe: Probe appeared on the side of the screen where one of the pictures have been previously Probe Timing: Not mentioned Inter-trial interval: Not mentioned SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 160 Total number of neutral trials: Not mentioned Total number of practice trials: Not mentioned	Greater attentional biases towards drug-related stimuli for current users, as compared to ex-users. Ex-users showed a bias away from drug-related stimuli in the stress condition and this correlated positively with their length of abstinence.
Frankland et al. (185)	19 opioid dependence, 20 healthy controls	Dot probe task for attention retraining in the lab. Participants maintained on partial MMT	14 drug-related images (images of drug paraphernalia, an unidentified addict appearing to cook up and inject heroin), 14 matched control pictures (items from a children's	Fixation Cross Timing: 1000ms Stimulus Pair Timing: 200, 500 and 1000ms Probe: Probe replaced the images. Participants to press one of the buttons as quickly as quickly as possible, without making mistakes, to indicate whether the probe appeared on the left- or right-hand side.	Opioid dependent group had a significant attentional bias for opioid related information presented at 200ms and 500ms. No attentional biases at 1500ms.

			building game, and a person building a model railway)	Probe Timing: Not mentioned Inter-trial interval: Not mentioned SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 164 Total number of neutral trials: 84 Total number of practice trials: 10	
Garland et al. (186)	32 opioid-dependent; 33 non opioid-dependent	Dot probe task for attentional retraining in the lab Participants maintained on partial buprenorphine and MMT	12 opioid images, included photos of pill (Oxycontin, Vicodin), pill bottles, crushed and powdered opioids for insufflation, and a syringe next to a vial of injectable morphine Neutral images included 12 photos from the International Affective Picture System, depicting household items	Fixation Cross Timing: 500ms Stimulus Pair Timing: 200 or 2000ms Probe: Target probe will replace the images after 50ms inter-stimulus interval Probe Timing: 100ms Inter-trial interval: Not mentioned SOA: 50ms Response Timing: Not mentioned Total number of critical trials: 64 Total number of neutral trials: 12 Total number of practice trials: Not mentioned	Opioid-dependent individuals had significant attention bias towards opioids cues presented for 200ms but not for cues presented for 2000ms.
Garland and Howard et al. (187)	High risk for misuse (n=28) Low risk for misuse (n=19)	Dot probe task for attentional retraining in the lab	12 opioid images, included photos of pill (Oxycontin, Vicodin), pill bottles, crushed and powdered opioids for insufflation, Neutral images included 12 photos from the International Affective Picture System, depicting household items	Fixation Cross Timing: 500ms Stimulus Pair Timing: 200 or 2000ms Probe: Target probe will replace the images after 50ms inter-stimulus interval Probe Timing: 100ms Inter-trial interval: Not mentioned SOA: 50ms Response Timing: Not mentioned Total number of critical trials: 64 Total number of neutral trials: 12 Total number of practice trials: Not mentioned	Biased initial attentional orienting to prescription opioid cues.
Garland et al. (188)	72 opioid misusers 26 opioids non misusers	Dot -probe task for attentional retraining in the lab	Pair of photos containing one emotionally salient image and one neutral image. Three blocks of cues (opioid-related, pain-related, and pleasure-related) Opioid-related cues included images of pills and bottles	Fixation Cross Timing: 500ms Stimulus Pair Timing: 200 or 2000ms Half of the trials presented at 200ms, half 2000ms. Probe: Target probe will replace the images after 50ms inter-stimulus interval Probe Timing: 100ms Inter-trial interval: Not mentioned SOA: 50ms	Opioid misusers exhibit attentional deficits during reward processing

			Pain-related cues included images of severe injuries, painful medical procedures, and human faces grimacing in pain. Natural reward cues included images of romantic couples and food. 36 Neutral images selected from IAPS.	Response Timing: Not mentioned Total number of critical trials: 64 Total number of neutral trials: 12 Total number of practice trials: Not mentioned	
Lubman et al. (119)	16 Methadone maintained addicts 16 age-matched controls	Pictorial Probe Detection task	Drug-related photographs (drug paraphernalia for example, needles, spoons and heroin wraps) Scenes of unidentified addict cooking up and injecting heroin. Control photographs – items from children building game, scenes showing an unidentified person building a model railway using various components from the set	Fixation Cross Timing: 1000ms Stimulus Pair Timing: 500ms Probe: After each pair of images, a dot probe will appear in the position of one of the pictures Participants are to press as quickly as possible, one of the two response buttons. Probe Timing: Not mentioned Inter-trial interval: Not mentioned SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 160 Total number of neutral trials: Not mentioned Total number of practice trials: 12	Attentional biases in opiate addicts to probe that replaced the drug pictures, rather than neutral images.
Wei et al. (189)	22 heroin addicts 22 Healthy Controls	Visual Probe Task	10 heroin images 10 natural scenery pictures	Fixation Cross Timing: 1000ms Stimulus Pair Timing: 500ms Probe: Appear in the location where one of the images disappear Probe Timing: 200ms Inter-trial interval: 1350ms SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 80 & 240 Total number of neutral trials: Not mentioned Total number of practice trials: 20	Heroin addicts have more rapid response when the dot located on the heroin-related picture as compared to the neutral picture.
Zhao et al. (66)	30 methadone-maintained outpatients, 38 healthy controls	Visual Probe task	Drug neutral picture pairs & neutral-neutral picture pairs. 20 pictures of substance-related scenes and 20 similar pictures matched with same	Fixation Cross Timing: 1000ms Stimulus Pair Timing: 2000ms Probe: Probe then displayed in one of the positions of the pictures	Heroin group reacted faster to probes associated with substance-related pictures than neutral pictures More initial fixations

			layout but lacking substance-related cues. 20 pairs of pictures matched with similar neutral scenes of daily life.	Probe remained until the participant responded by clicking the left or right button of mouse Probe Timing: Not mentioned Inter-trial interval: 200ms SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 120 Total number of neutral trials: Not mentioned Total number of practice trials: 16	Maintained longer initial fixation durations towards substance-related pictures

Footnotes:

Fixation cross timing: Duration of time for the presentation of fixation cross. Stimulus pair timing: Duration of time of presentation of set of images. Probe: Duration of time in which probe appears for. Inter-trial interval: Duration of time between each trial. Response time: duration of time for participants to indicate a response. Stimulus onset asynchrony: Duration of time between the presentation of one set of stimuli to the next stimuli

While all of the studies were based on the visual probe task, there were variations in the structure of the task. Some studies included an interstimulus interval before probe presentation (186-188). The time the probe remained on the screen until the participant also responded varied (59,66,69). Some studies also included an inter-trial interval, but there was variation in the interval's timing (from 250 to 2000 ms). Three studies (66, 119, 185) have included practice trials. Figure 5.1 provides a tabular representation of the visual probe task details that were reported in each of the identified studies for opioid use disorder. The response timings were always described, but details of other five characteristics were not presented universally.

Figure 5.1 Representation of the details of the visual probe task that were reported in each of the identified studies for opioid use disorder (n=8)

Study	Fixation Cross Timing	Stimulus Timing	Probe Timing	Inter-trial Interval	Stimulus-Onset Asynchrony	Response timing
Charles et al. (2015)						
Constantinou et al. (2010)						
Frankland et al. (2016)						
Garland et al. (2013)						
Garland and Howard et al. (2014)						
Garland et al. (2015)						
Lubman et al. (2000)						
Zhao et al. (2017)						
Wei et al. (2016)						

Footnotes: *Green Highlights: Reported in Study, Red Highlights: Not reported. Figure extracted from published paper.

b. Cannabis Use Disorders

Table 5.2 focuses on the characteristics of the visual probe task employed in studies involving cannabis use disorders. A total of three articles from Zhang et al.'s prior review was included, as they have reported the use of the Visual Probe Task (125). Field et al. included words instead of pictorial stimuli for the stimulus (128). In terms of the Visual Probe Task, two studies presented the fixation cross for 500 ms, whereas Field et al. presented it for 1000 ms (74, 124, 132). There were once again variations in

the timings for the stimulus cues, with two studies presenting the stimulus cue for 500 ms, whereas that of Field et al. presented it for 2000 ms (74, 124, 132). In terms of probe presentation, two studies presented the probe until a response was made (124, 132). In Vujanovic et al.'s study, they presented the probe for only 125 or 250 ms and they also included an inter-trial interval across all the studies, which ranged from 1000 to 1500 ms (132). In terms of the number of trials, it ranged between 72 and 96 (132). All studies reviewed included practice trials for participants. Figure 5.2 provides a tabular representation of the Visual Probe Task details that were reported in each of the identified studies for cannabis use disorder.

Table 5.2 Characteristics of the Visual Probe Task in Cannabis Use Disorder

Study	Participants	Intervention Details	Nature of Stimulus Included	Details of Assessment Task	Outcomes
Field et al. (128)	17 regular cannabis users 16 non-users	Visual Probe task	Cannabis-related words, Environment-related words, pleasant words, unpleasant words	Fixation Cross Timing: 500ms Stimulus Pair Timing: 500ms Probe: Immediately after the offset of the words, small dot probe was presented in the position of one of the words, until the participant gave a manual response. Probe Timing: Not mentioned Inter-trial interval: 1000ms SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 64 Total number of neutral trials: 32 Total number of practice trials: 12	High levels of craving associated with significant attention bias for cannabis-related words
Field et al. (74)	23 regular cannabis users 23 non-user controls	Visual Probe task with concurrent eye movement monitoring	18 cannabis related photograph Depicting a scene relating to cannabis use Control photograph (did not contain cannabis related content)	Fixation Cross Timing: 1000ms Stimulus Pair Timing: 2000ms Probe: After picture offset, small visual probe (an arrow which is pointed up or down) was presented on the left or right of the screen Respond to the probe as quickly as possible Probe Timing: Not mentioned Inter-trial interval: 500ms SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 72 Total number of neutral trials: Not mentioned Total number of practice trials: 10	Regular users had biases to maintain gaze on cannabis cues, faster approach responses to cannabis cues
Vujanovic et al. (132)	12 adults with cannabis use disorder, 13 controls	Visual Probe task	6 cannabis pictures – cannabis related stimuli 6 neutral pictures matched in size, colour and context	Fixation Cross Timing: 500ms Stimulus Pair Timing: 500ms Probe: Probe stimulus removed, picture (cue) remained on screen 1500ms Probe Timing: 125 or 250ms Inter-trial interval: 1500ms SOA: Not mentioned Response Timing: 1500ms Total number of critical trials: 96 Total number of neutral trials: Not mentioned Total number of practice trials: 12	Cannabis use group showed greater attentional biases to cannabis cues at the 125ms probe time

Figure 5.2 Representation of the details of the visual probe task reported in each of the identified studies for cannabis use disorder ($n = 3$)

Study	Fixation Cross Timing	Stimulus Timing	Probe Timing	Inter-trial Interval	Stimulus-Onset Asynchrony	Response timing
Field et al. (2004)						
Field et al. (2006)						
Vujanovic et al. (2016)						

Footnotes: *Green Highlights: Reported in Study, Red Highlights: Not reported.
Figure extracted from published paper.

c. Stimulant Use Disorders

Table 5.3 provides an overview of the characteristics of the visual probe task employed in the studies involving stimulant use disorders (cocaine use disorders). Four articles from Zhang et al.'s prior review was included (125). While all the studies were based on the visual probe task, their paradigms varied. Some studies included 10 sets of images, while others included up to 20 sets of images (105, 121,140). The number of trials needed to be undertaken varied from 80 to 240. Two studies included practice trials (105, 140). Three out of the four studies reported that they presented a fixation cross for 500 ms. In terms of stimulus timings, they were presented for 500 ms in three studies (105, 121, 140) and a short (200 ms) and long (500 ms) interval in Mayer et al.'s study (105). In all the studies, the probe appeared up until a response was made. Only two of the four identified studies allowed for an inter-trial interval (105, 121). There was variation in the inter-trial interval, as it ranged from 500 to 1500 ms. Figure 5.3 provides a graphical representation of the visual probe task details reported in each of the identified studies for stimulant use disorder.

Table 5.3 Characteristics of the Visual Probe Task used in Stimulant Use Disorders

Study	Participants	Intervention Details	Nature of Stimulus Included	Details of Assessment Task	Outcomes
Montgomery et al. (121)	32 regular cocaine users 40 nonusers	Visual Probe and Modified Stroop task	10 pairs of images, one cocaine-related image depicting cocaine, cocaine paraphernalia, or close up of an individual using cocaine. Matched with a neutral image, perceptually similar to cocaine image as possible, but did not have cocaine content	Fixation Cross Timing: 500ms Stimulus Pair Timing: 500ms Probe: Visual probe (an arrow pointing up or down) presented in the location previously occupied by one of the pictures Required to rapidly identify the orientation of the arrow probe by pressing the appropriate arrow on the keyboard Probe Timing: Not mentioned Inter-trial interval: 500ms SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 80 Total number of neutral trials: Not mentioned Total number of practice trials: 10	Cocaine participants who received alcohol had increased attentional biases for cocaine pictures.
Tull et al. (138)	30 cocaine dependent patients with PTSD; 30 cocaine dependent without PTSD	Visual Probe task	20 Cocaine-related images (crack rocks, powder cocaine, crack pipes) and 40 images of furniture	Fixation Cross Timing: 500ms Stimulus Pair Timing: 500ms Probe: Dot probe appeared in the left or right position, remaining until the participant responded Indicate where the dot appeared by pressing one of the two response keys. Probe Timing: Not mentioned Inter-trial interval: 250ms SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 240 Total number of neutral trials: Not mentioned Total number of practice trials: 5	PTSD participants have had greater attentional biases towards the location of cocaine imagery than non-PTSD participants
Bardeen et al. (140)	22 cocaine dependent patients with borderline personality disorders; 36	Visual probe task	20 cocaine-related pictures (crack pipes, crack rocks), 40 pictures of furniture.	Fixation Cross Timing: 500ms Stimulus Pair Timing: 500ms Probe: Dot appeared on the screen replacing one of the two pictures.	Greater bias for attending to cocaine stimuli among male cocaine dependent patients with or without borderline personality

	cocaine dependent patients without borderline personality disorder			Press a button on the computer keyboard that corresponded to the relative position of the dot on the screen Probe Timing: Not mentioned Inter-trial interval: Not mentioned SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 240 Total number of neutral trials: Not mentioned Total number of practice trials: 5	disorder, when presented with a trauma script intervention
Mayer et al. (105)	37 participants randomly assigned to ABMT or control therapy	Visual Probe task	Cocaine and neutral stimulus were equivalent in size and visual angle, generally matched for colour and content	Fixation Cross Timing: Not mentioned Stimulus Pair Timing: Stimulus pairs presented for 200ms (speed detection trials) or 500 (difficulty to disengage trials). Probe: Stimulus replaced by a probe (arrow) Probe Timing: Not mentioned Inter-trial interval: 1000 or 1500ms SOA: Not mentioned Response Timing: 1500ms Total number of critical trials: 240 Total number of neutral trials: Not mentioned Total number of practice trials: 5	Attention bias modification was not more effective than control at reducing attentional biases

Figure 5.3 Graphical representation of the details of the visual probe task reported in each of the studies for stimulant use disorder

Study	Fixation Cross Timing	Stimulus Timing	Probe Timing	Inter-trial Interval	Stimulus-Onset Asynchrony	Response timing
Montgomery et al. (2010)						
Tull et al. (2011)						
Bardeen et al. (2013)						
Mayer et al. (2016)						

Footnotes: *Green Highlights: Reported in Study, Red Highlights: Not reported. Figure extracted from published paper.

5.3 Implications of Findings from Doctoral Work

Although this study highlighted the varied task parameters for the visual probe paradigm, there were some notable common elements. Most of the studies involving opioid use disorders presented the fixation cross for 500 ms and presented the set of stimulus images for both short and long stimulus durations. In contrast, the studies involving cannabis use or stimulant use disorders, presented the stimulus pair for 500 ms. Collectively, across all the substance disorders, 500 ms was a common timing used for stimulus presentation. Most of the studies utilizing these timings have provided positive findings for attentional biases, except for Charles et al. (for opioid use disorder) and Mayer et al. (for stimulant use disorder) (59, 105). For studies involving cannabis use disorders, short stimulus intervals ranged between 125 and 500 ms. For studies involving stimulant use disorder, the short stimulus intervals ranged from 200 ms to 500ms, though one study (Mayer et al.) classified 500 ms as a long stimulus interval (105). It has been suggested by previous research that a short stimulus interval allows for the assessment of enhanced vigilance for a particular stimulus, whereas long stimulus intervals measure that of delayed disengagement of attention. Short stimulus intervals thus assess for covert shifts of attention (i.e., the changes in the focus of attention that took place without eye movements) (19). In contrast, longer stimulus intervals assess for overt orienting of attention (i.e., the eye movements that took place) (190). Thus, depending on the presentation times of the stimulus, the dot-probe task assesses for different aspects of the attentional process.

The findings from this study have implications for further research. Although there are differences in the structure of the task parameters, the insights gathered from tasks used for opioid use disorders revealed that researchers need to consider the types of attentional processes they wish to measure (whether initial orientation or delayed disengagement) and determine if stimulus need to be presented at two separate timing intervals. It might be worthwhile to consider this, to better capture all the attentional processes. Before this study, there remained no understanding of the common timing intervals used for stimulus presentation across opioid, cannabis and stimulant disorders. This review has managed to identify some of the common timings, that will be useful for researchers who are intending to implement a common research platform that targets all these disorders. Moreover, this review also highlighted the range of trials used for both the attention bias assessment and modification interventions, between that of 160 to 240 trials. This range will be valuable for future conceptualisation of mobile interventions, but it is also important to balance the number of repeated trials against participants' fatigue if they were to undertake too many repeats.

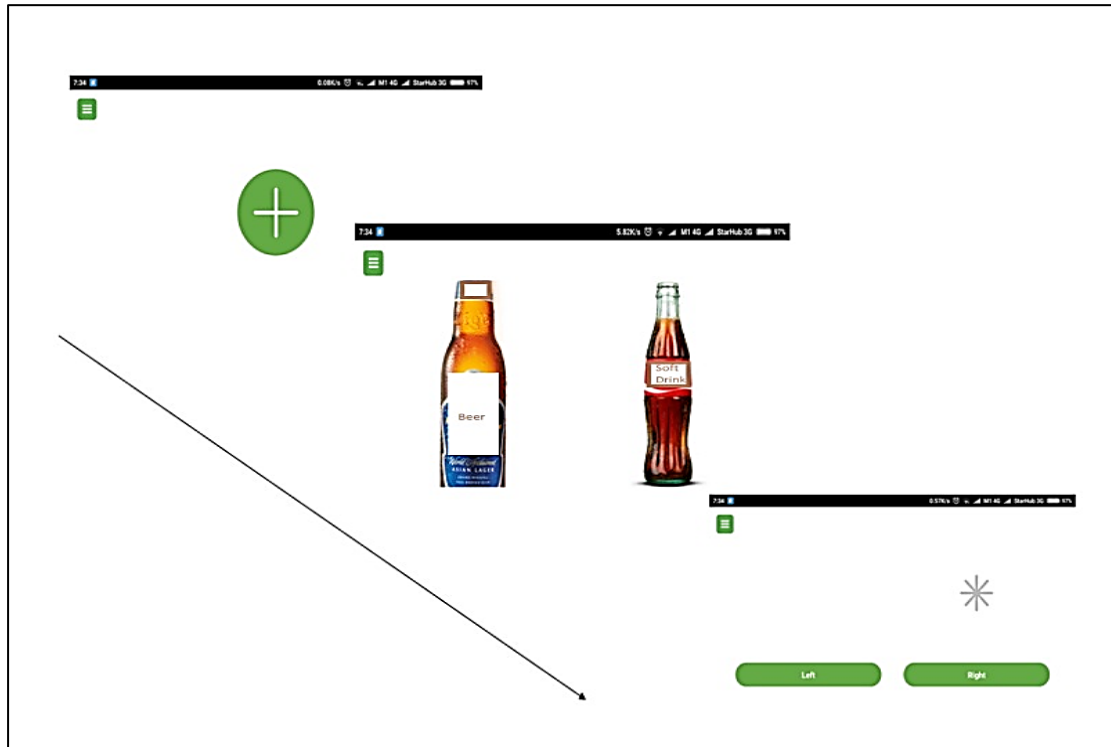
In the subsequent section, we will describe how this new knowledge has guided the conceptualization of a mobile attention bias modification intervention, that would be evaluated by means of a feasibility and acceptability study.

5.4 Design and Conceptualisation of a Mobile Attention Bias Modification Intervention

A multidisciplinary team conceptualised the mobile attention bias modification intervention, considering the evidence synthesised to date regarding the visual probe task paradigms. The team comprised two psychiatrists specialising in addiction psychiatry, a psychologist with prior expertise in attentional bias modification for alcohol disorders and a software engineer. To support the mobile app, it was decided to use a server that would enable real-time customisation of the algorithm underlying the tasks and for collecting the participants' reaction times. The server would also enable researchers to programme and control specific sets of images presented in the mobile app. Figure 5.4 presents an overview of the proposed platform for this new, mobile-based attention bias modification intervention for substance use disorders. This conceptualisation has been published as the 'Mobile Phone Cognitive Bias

Modification Research Platform for Substance Use Disorders: Protocol for a Feasibility Study in JMIR Research Protocols (Appendix 9) (191).

Figure 5.4 An overview of the progress of the assessment task for alcohol use disorders.



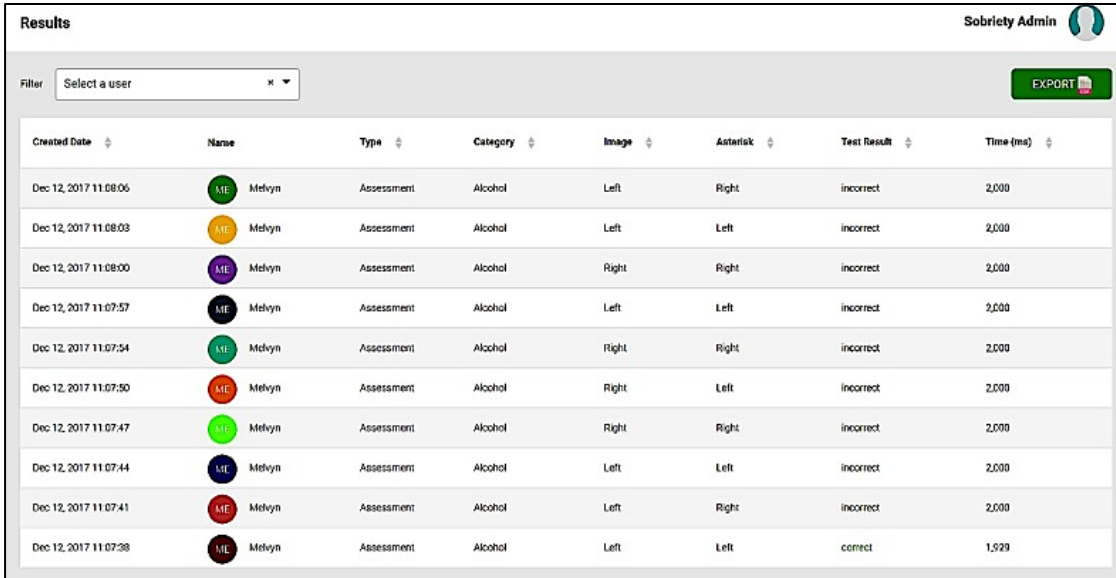
Footnote: The quality of this figure is limited by the resolution of the screenshots obtained from the mobile application.

The mobile app featured the conventional visual probe task and included two types of tasks: assessment and bias modification. For the assessment task, a fixation cross appeared at the centre of the screen for 500 ms. A set of stimuli were then presented (with one stimulus image being substance-related and the other neutral). The presentation time was set at 500 ms, the common presentation timing across opioid, cannabis and stimulant disorders. A probe was then presented at the previous position of either the substance image or neutral image (50% probability for either position). Participants were allowed a maximum of 2000 ms to indicate a response and had a total of 200 trials to complete. The decision to include 200 trials was to ensure an even distribution between the pairings of stimulus images with the probe, and in consideration that most previously studies have included a range of between 160-240 trials. Individuals with attentional biases were likely to respond faster when the probe

replaced the drug image. For the bias retraining/modification task, participants engaged in the same paradigm (as described above), with the exception that the probe would always replace the neutral stimulus to retrain one's attention away from the drug stimuli.

The platform described above offers a common interface for all substance use disorders, implying that participants with different substance disorders would be presented with the same graphic user interface. However, the stimulus images would be based on their substance of abuse. The server will collect the reaction time data and other essential variables when using reaction times to determine the presence of attentional biases. These variables include the probe position, the positions of the substance-related stimuli and the correctness of the response. Figure 5.5 provides an overview of the sample dataset collected by the server, which was also programmed with a specific algorithm to enable the control of the probe frequencies, replacing the substance stimuli (50% or 100%). The research platform also allows researchers to vary the number of repetitions of a particular set of images. Figure 5.6 provides an overview of how the server can control these parameters.

Figure 5.5 Overview of reaction-time data collated by the server



Created Date	Name	Type	Category	Image	Asterisk	Test Result	Time (ms)
Dec 12, 2017 11:08:06	Melvyn	Assessment	Alcohol	Left	Right	incorrect	2,000
Dec 12, 2017 11:08:03	Melvyn	Assessment	Alcohol	Left	Left	incorrect	2,000
Dec 12, 2017 11:08:00	Melvyn	Assessment	Alcohol	Right	Right	incorrect	2,000
Dec 12, 2017 11:07:57	Melvyn	Assessment	Alcohol	Left	Left	incorrect	2,000
Dec 12, 2017 11:07:54	Melvyn	Assessment	Alcohol	Right	Right	incorrect	2,000
Dec 12, 2017 11:07:50	Melvyn	Assessment	Alcohol	Right	Left	incorrect	2,000
Dec 12, 2017 11:07:47	Melvyn	Assessment	Alcohol	Right	Right	incorrect	2,000
Dec 12, 2017 11:07:44	Melvyn	Assessment	Alcohol	Left	Left	incorrect	2,000
Dec 12, 2017 11:07:41	Melvyn	Assessment	Alcohol	Left	Right	incorrect	2,000
Dec 12, 2017 11:07:38	Melvyn	Assessment	Alcohol	Left	Left	correct	1,929

Footnote: The quality of this figure is limited by the resolution of the screenshots obtained from the server.

Figure 5.6 Overview of server control parameters

Setting		Sobriety	
Plus transition duration (ms)	500	Asterisk display left (%)	50
Display photo (ms)	500	Right	50
Reaction (ms)	2000	Repeat Limit	1
SAVE			

Footnote: The quality of this figure is limited by the resolution of the screenshots obtained from the server.

The attention bias modification app was developed using open-source, cross-platform gaming software, React Native (192). Integrating an open-source approach would ensure that the intervention was compatible with and could be used across various platforms without inter-platform differences. Participants could therefore undertake the task on their mobile devices and a computer. This gaming platform also allows for the future incorporation of gamification elements (101). The platform is versatile and allows for scaling and modification of the entire program for use in other disorders, drastically reducing the time and costs associated with development, while ensuring that the timings of the conventional paradigms are retained. Regarding the stimulus set used, the images for alcohol and substances are either images of the drug/substance itself or drug equipment. Most alcohol images are freely available via the Internet. The drug images were obtained from the United States Drug Enforcement Agency image library and the CNB website. The neutral images were those from the Internet that were matched in complexity to the substance images, usually images of household items or food products. There was a total of 10 image sets for alcohol, heroin, and cannabis use disorders, and eight image sets for stimulant use disorders.

5.5 Conclusions

The insights gained and the application developed will be tested in Study 1, the feasibility and acceptability study.

Chapter 6 Determining the Feasibility and Acceptability of Mobile Attention Bias Intervention

Introduction

The work presented in Chapter 5 lays the groundwork for Study 1 (Feasibility and Acceptability study), which is discussed in this chapter. A protocol was created, and the study was conducted between May 2018 and September 2019. The study findings and the relevant analyses are presented. This chapter concludes by discussing the main findings and how this study provides evidence for the subsequent studies.

6.1 Importance of Preliminary Work

Study 1 was conducted according to the recommendation of the National Institute for Health Research (NIHR) for conducting feasibility and pilot studies before randomised trials (193). NIHR states that conducting a feasibility study is important because it examines factors related to the participants' willingness to be randomised or recruited, the number of eligible participants, the proposed outcome measures' characteristics, the follow-up and response rates, the data availability and the time needed for the data collection and analysis (193). It is evident from the published literature that most evaluations and mobile interventions concerning attention bias modification are focused on alcohol and tobacco use disorders. While attention bias and bias modification among individuals with opioid, cannabis and stimulant disorders have been explored, examinations have been largely limited to assessing biases, with few studies evaluating bias modification. To date, there has been no exploration of such interventions in an Asian cohort or in Singapore.

It is important to distinguish between a feasibility study and a pilot study (194, 195). While the former addresses whether a study can be performed, the latter is a miniature version of the main study that tests whether all components of the main study work together (194, 195). A pilot study's main objective is to determine whether the main study processes (e.g., recruitment, randomisation, treatment, and follow-up processes) can proceed smoothly. A pilot study examines a primary outcome measure, while a feasibility study does not. Pilot and feasibility studies help plan the definitive

randomised trial (194, 195). Prior research has shown how the absence of prior evaluative work (feasibility and pilot studies) has led to unsuccessful randomised trials, with negative results and no significant findings (188). Given that these trials typically require significant funding, failure due to poor preparation/planning wastes public resources (196).

6.2 Theoretical Models and Guiding Framework

The conceptualisation of this feasibility and acceptability study was based on the framework proposed by Bowen et al. and Glasgow's Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) framework (197, 198). Bowen et al. proposed guidelines for designing and evaluating feasibility studies (197). Feasibility studies are crucial for determining whether the planned intervention should proceed for further effectiveness testing. In our case, a feasibility study is justified, given the small number of prior evaluations of mobile attention bias modification interventions and the lack of examination of this type of intervention among treatment-seeking Asian participants. The authors proposed eight areas that feasibility studies should focus on: acceptability, demand, implementation, practicality, adaptation, integration, expansion, and limited-efficacy testing (197). Table 6.1 lists these areas and the potential outcomes that the feasibility study could analyse.

Table 6.1 Area of Focus of Feasibility Study based on Bowen et al.'s criteria (197)

Area of Focus	What the feasibility study aims to do.	Potential Outcome of Interest
Acceptability	To determine how receptive participants are towards the new intervention	Perceived perceptions towards the new intervention Engagement, Ease of Use, Interactiveness, Motivation to continue training/using the application
Demand	To determine if the participants would utilize the new intervention	Expressed interest in participation. Actual usage of the intervention
Implementation	To what extent can the new intervention be successfully delivered to the intended participants	Recruitment rates Adherence rates Attrition rates Factors affecting the uptake of the intervention

Practicality	To determine if the planned intervention could be conducted using existing resources	Additional resources that participants need in order to complete the new intervention The cost associated with new resources Impact on existing treatment programs
Adaptation	To determine whether the new intervention could be applied to a different substance-using population	The ability of the intervention to be applied to different substance use disorder
Integration	Can the new intervention fit into the existing model of care	Ability to conduct the intervention whilst participants undergo conventional care Any adaptation needed to be made so that patients could continue receiving conventional care Any potential disruptions
Expansion	Could the new intervention be expanded into a new program or service	Could this new intervention be an adjunctive treatment to conventional counselling and psychotherapies that patients are receiving?
Limited efficacy	Would this new intervention show evidence of effectiveness	Could this new intervention result in any reduction in attentional biases amongst individuals following intervention? What is the average magnitude of change?

A limitation of Bowen's criteria was that they did not address the issues relating to the external validity of interventional studies (197). Green et al. indicated that most trials have been conducted in controlled environments to determine their effectiveness, which allows researchers to conclude whether their intervention is effective, leading to causal inferences, but this also limits the external validity and generalisability of the results (199). Researchers are therefore advised to consider testing their intervention in real-world situations. The RE-AIM criteria were proposed to ensure that outcomes from feasibility studies are realistic and can be achieved in real-world settings (200). Given these recommendations, the RE-AIM criteria was the basis for further refinement of the proposed outcomes of the feasibility study. Table 6.2 lists the main RE-AIM criteria and potential outcome measures and tools for outcome assessments.

Table 6.2 Conceptualisation of the Feasibility Study based on RE-AIM Criteria (200)

Dimension	Outcome Measures	Assessment Tools
Feasibility	Percentage of Participants who are eligible. Participation rates Retention Rates Attrition Rates	Descriptive Statistics of recruitment rate, participation rates, retention rates, attrition rates
Reach	The proportion of participants screened at baseline before recruitment	Computed as: Total number of participants recruited over the total number of participants invited
Effectiveness	Change in Attentional Bias Changes in confidence levels in managing the addiction problem	Comparison of magnitude change in Attentional bias following all completed interventions against baseline. Qualitative questionnaire
Adoption	Number of participants who completed all the planned interventions	Descriptive statistics
Implementation	Limitations of existing intervention and challenges associated with using the intervention	A perspective questionnaire focusing on assessing ease of use, interactiveness, engagement, motivation to continue training
Maintenance	Not considered as part of this feasibility study	Not considered as the objective was to test the intervention during the duration that participants are enrolled in the inpatient program

Bowen's criteria and RE-AIM criteria helped develop realistic outcomes measurable through our feasibility study and that shaped the study design (197, 201). The next section presents the objectives and methods of the feasibility and acceptability study, followed by its findings. The study protocol was submitted to the National Healthcare Group Domain Specific Research Board (DSRB) and was approved on the 2nd of May 2018 (DSRB ethics approval number: 2018/00316). The protocol was also published as 'A Smartphone Attention Bias Intervention for Individuals with Addictive Disorders: Protocol for a Feasibility Study' in the Journal JMIR Research Protocol (Appendix 12) (202).

Given that this feasibility study will shape the design and conduct of the pilot and subsequent definitive randomised trial, we subsequently considered the Avery et al. framework for the criteria of progressing pilot studies to randomised trials (203). The recommendations of the Avery et al. framework included the following: 1) a traffic light system of green (go), amber (amend) and red (stop) to determine progression, 2) an assessment of intervention adherence, cross-over and outcome event rates to determine if there is sufficient data to guide progression and 3) determining whether the pilot sites are representative of the main study site (203). Herbert et al. recently examined the progression criteria in trials with an internal pilot and reported that 89.7% of their reviewed studies had stated a clear criterion for the pilot study progression to the full randomised trial (204). Among these studies, the mean proportion of the sample to be recruited in an internal pilot was 18.5% (range 2.3%–50%), and the length of recruitment for an internal pilot was 9.4 months (range 3–30 months).

6.3 Objectives and Methods of the Feasibility and Acceptability Study

This study's primary aim was to determine the feasibility of a mobile attention bias modification intervention for treatment-seeking individuals with addictive disorders at an inpatient addiction facility. Feasibility was determined by the number of recruited participants, participants' adherence to the planned interventions until discharge, completion of planned interventions and the mobile application's ability to detect changes in attentional biases. The secondary aim was to determine the intervention's acceptability to patient participants.

6.4 Methods

6.4.1 Study Setting and Study Design

The target population comprised individuals admitted for inpatient medication-assisted detoxification and rehabilitation (total duration of 14 days, with 7 days in detoxification and 7 days in rehabilitation) at the National Addictions Management Service (NAMS), Institute of Mental Health, Singapore. At NAMS, treatment is entirely voluntarily, allowing participants to self-discharge at any time. The NAMS inpatient unit has approximately 22 beds, most of which are occupied by patients undergoing detoxification. The design was a feasibility study, with recruitment through convenience sampling.

6.4.2 Recruitment and Sample Size

Participants were recruited upon completion of their inpatient detoxification treatment (7 days) and at the start of day 1 of their rehabilitation treatment. Potential participants were identified by their primary psychiatrist, provided with further information by the study team, and given time to consider participation. Those who agreed to participate completed an informed consent form, which was signed in the presence of an impartial witness, according to the regulations of the Human and Biomedical Act. Given that the study was designed to assess feasibility and acceptability, power computation was not performed. Given the diversity of disorders, the minimum recruitment target was 30 participants, and the maximum was 34. A sample size of 30 was decided, considering Bell et al.'s recommendations following their audit of sample sizes for pilot and feasibility trials (205).

6.4.3 Inclusion and Exclusion Criteria

Patients included in the study were aged 21 to 65 years; diagnosed with a primary psychiatric disorder of alcohol, opioid, cannabis or stimulants; diagnosed with polysubstance dependence, with alcohol, opioid, cannabis or stimulants as the main substance of use; able to read and write English; and able to use a smartphone or tablet device.

Patients were excluded if they had a history of cognitive impairment, dementia, seizures, withdrawal seizures, migraines triggered by flashing lights, or moderate to severe comorbid psychiatric disorders based on clinical assessment. Participants with alcohol and drug use disorders were considered, given that they are highly prevalent disorders in Singapore and represent most patients admitted electively into the treatment programme.

6.4.4 Measures

Baseline demographic and clinical information was collected from the participants, including nationality, gender, marital status, race, religion, educational level, housing conditions, treatment history, chronic diseases (psychiatric and physical disorders) current psychiatric medications and current substance use, consumption method, quantity consumed and frequency. Participants also completed a modified Addiction

Severity Index (ASI)-Lite, Severity of Drug Dependence Scale (SDS), and the Short Form (SF-12) questionnaires.

The ASI-Lite collected information for the following domains: drug and alcohol use, medical, employment/school, legal, family, social and psychiatric (206). The modified version retained only drug and alcohol use questions. Participants were asked about their alcohol and substance use in the past month and over the course of their lives. Participants were asked whether they had used alcohol, nicotine, heroin, amphetamine-type stimulants, cannabis, other opioids, benzodiazepines and other sedatives, barbiturates, ketamine, cocaine, inhalants, hallucinogens, and new psychoactive substances. The SDS comprised five items, all of which are explicitly concerned with the psychological components of dependence (207). A previous study reported that the total severity score was highly positively correlated with dependence severity, as measured by the Diagnostic and Statistical Manual of Mental Disorders-IV. SF-12 has been widely used in assessing the self-reported quality of life and covers only eight health domains from the original SF-36 but has demonstrated good content and criterion validity with no evidence of systematic biases (208).

Given that the questions are relevant to the next planned co-design study, I employed the following self-constructed questionnaire for the perception questionnaire:

1. Prior to using the app, how confident were you in managing your addiction problems? (rated on a 5-point Likert Scale)
2. How easy was it to use the app? (rated on a 5-point Likert scale and participants were asked to provide verbatim comments)
3. How interactive was the app? (rated on a 5-point Likert scale and participants were asked to provide verbatim comments)
4. Do you feel motivated to continue using the app? (rated on a 5-point Likert scale and participants were asked to provide verbatim comments)
5. Do the images in the app remind you of your substance use? (rated on a 5-point Likert scale)

6. After using the app, how confident are you in managing your addiction problem?
(rated on a 5-point Likert scale)

A self-constructed questionnaire was utilized, as the questions asked are of relevance to the next planned study, that of a co-design study.

6.4.5 Details of the Intervention

After enrolment, participants completed a visual analogue scale (VAS) for craving before and after completing each session. Study team members familiar with the app provided a 15-minute briefing before commencing the assessment and intervention. Participants were provided tablets for the mobile attention bias modification intervention.

On day 1, participants completed a baseline attention bias assessment task and an attention bias modification task. They then rested for 15 minutes before completing a reassessment of their attention bias. On subsequent days (days 2–7) of their rehabilitation, they completed the attention bias modification task and were allowed 10 minutes of rest before retaking the attention bias assessment task. Participants had to complete the VAS for craving before and after completing each bias modification task. Participants who completed three sessions were asked to complete a questionnaire about their perceptions of the app. Participants were expected to undertake the intervention each day of their rehabilitation stay, except on weekends and public holidays. Participants could undertake the intervention up to five times.

The parameters of the visual probe task for the attention bias assessment are described in Chapter 5. The presented images were of drugs, individuals using substances or paraphernalia for administering drugs. Participants were presented with stimuli specific to their drug addiction. The images were sourced from the Internet, the United States Drug Enforcement Agency (DEA) website, and the Singapore Central Narcotics Bureau website. For each substance disorder, there were 10 images, which were repeated 20 times. The neutral image, openly sourced from the Internet, was similar in colour and complexity to the substance images.

For the intervention or bias modification task, participants had to choose the same task as that described. However, an asterisk replaced the position of the neutral image 100% of the time, enabling retraining of attentional bias. Participants were instructed to

complete 200 trials, with the task parameters similar to those of the bias assessment task (i.e., presenting the fixation cross for 500 milliseconds, presenting the stimulus images for 500 milliseconds, with 2 seconds to indicate a response). This study examined attentional biases at baseline and after completing each intervention to determine whether the intervention changed biases.

Table 6.3 provides an overview of the measures and interventions participants needed to complete across the intervention period.

Measures	Aim	Day of Rehabilitation Stay				
		1	2	3	4	5
Baseline demographic and clinical information questionnaire	Baseline characteristic of participants	X				
Addiction Severity Index	Details about Substance Use	X				
Severity of Substance Dependence Questionnaire	Assessment of Severity of Psychological Dependence	X				
Short-Form 12	Baseline Health Status	X				
Attention bias assessment task	Measurement of baseline biases	X	X	X	X	X
Attention bias modification task	Retraining of attentional biases	X	X	X	X	X
Visual analogue scale for craving	Assessment of cravings	X	X	X	X	X
Perspective questionnaire	Acceptability of Intervention			X		

Participants undertook a maximum of 5 sessions, considering that the study was not conducted on weekends and that the maximum duration of the rehabilitation stay was one week. The attention bias assessment task was completed twice on the first day; one to assess for baseline biases and the other to assess for the changes in biases following the intervention.

6.4.6 Outcomes

Feasibility, the primary outcome, was operationalised as the number of participants recruited (recruitment rate) and their intervention adherence (adherence rate). The inpatient programme is voluntary. Participants could therefore leave at any treatment stage (detoxification or rehabilitation). NAMS statistics show that approximately 17%–25% of patients progress from detoxification treatment to rehabilitation treatment.

Based on this statistic, the target recruitment rate was set at 25% of those who were in their rehabilitation phase. The adherence rate was set at 60%, considering that approximately half of those in the rehabilitation phase would complete the entire programme. Other feasibility aspects were the number of intervention sessions that participants completed and whether the mobile app could determine the changes in attentional biases.

Acceptability, the secondary outcome, was measured with a self-constructed perspective questionnaire to elicit information for the subsequent co-design study. Generic validated questionnaires, such as the Mobile Application Rating Scale (Stoyanov et al.), were not employed because the team sought to obtain participants' perspectives on specific aspects of the app (such as the stimulus images) (209). The study was deemed acceptable if participants were willing to use the app daily; if ease of use, interactivity, motivation, and reality (questions 2–5) were rated positively (either 'very' or 'extremely' on the 5-point Likert scale) by at least 30% of the participants; and if at least 30% perceived a change in their confidence level after having undergone three intervention task sessions (questions 1 and 6). The app was also deemed acceptable by the absence of any severe adverse events (such as intense cravings leading to premature discharge from the inpatient programme).

6.4.7 Data Management and Monitoring

All participants were allocated a subject number upon recruitment. No participant-related identifiers were recorded on the hardcopy forms, which were stored in secure, locked cabinets in a restricted area. The app's electronic data were automatically synchronised to a secured, password-protected cloud database. The principal investigator performed a monthly backed up of the electronic data records onto a local, secured computer. The principal investigator and research assistants assumed responsibility for coding the data from the hardcopy forms. An independent co-investigator routinely checked the data entry for reliability and quality. All records will be kept securely for at least 6 years after the completion of the study.

6.4.8 Statistical Analyses

Collected data was analysed using SPSS (version 22. IBM Corp, Armonk, NY) (210). Baseline demographic information was summarised using descriptive statistics, including means and standard deviations (SD). The presence of attentional biases was

determined based on the mean reaction times for responding to the probes' position when replacing the drug or neutral image. The formula to calculate the attentional biases was $(\sum T_1/n_1) - (\sum T_0/n_0)$, where T_1 refers to the time for the probes that replaced the neutral images, n_1 refers to the number of trials for the probes that replaced the neutral images, T_0 refers to the time for the probes that replaced the substance images, and N_0 refers to the number of trials for the probes that replaced the substance images.

6.4.9 Qualitative Analysis of Acceptability Data

The participants' perspective and feedback were collected through the perspective questions. Two independent researchers coded their verbatim, handwritten comments using NVivo Version 12.0 (211). Similar codes were grouped together and further analysed to identify higher-order themes.

6.4.10 Ethical Approval and Funding

This study was approved by the National Healthcare Group's Domain Specific Research Board (reference number: 2018/00316) on May 2, 2018. NAMS provided an inconvenience fee for participants of (\$30 each for 30 participants).

6.5 Results

The study results have been published in an article entitled 'A Smartphone Attention Bias App for Individuals with Addictive Disorders: Feasibility and Acceptability Study' in the Journal of Medical Internet Research (JMIR) MHealth UHealth (Appendix 11) (212).

6.5.1 Primary Outcome: Feasibility of Recruitment and Adherence Rates

Of the 40 individuals invited to participate, 10 declined, yielding a recruitment rate of 75%. Of the recruited participants, 6 were diagnosed with alcohol dependence, 17 with opioid dependence; 2 with cannabis dependence; and 5 with stimulant dependence. Eleven of the 30 participants failed to complete all planned interventions, resulting in a 63% adherence rate. The mean number of completed sessions was 3.8 (range, 0–5). Ten participants discontinued due to a desire to be prematurely discharged from the ward, and another participant withdrew after the initial intervention because they were unable to keep pace (i.e. keep up with the speed of the trials). Table 6.4 lists the baseline demographics of the 30 participants.

Table 6.4: Participants' baseline demographic characteristics (n = 30)

Demographic Characteristics	Substance Disorder			
	Alcohol Dependence (n=6)	Opioid Dependence (n=17)	Cannabis Dependence (n=2)	Stimulant Dependence (n=5)
Mean age (years)	43.7 (SD = 11.64)	47.9 (SD = 11.8)	58.0 (SD = 1.4)	37.6 (SD = 7.0)
Nationality				
- Singaporean	4 (66.7%)	16 (94.1%)	2 (100%)	5 (100%)
- Others	2 (33.3%)	1 (5.9%)	0	0
Gender				
- Male	4 (66.7%)	15 (88.2%)	2 (100%)	5 (100%)
- Female	2 (33.3%)	2 (11.8%)	0 (0%)	0 (0%)
Race				
- Chinese	2 (33.3%)	2 (13.3%)	0 (0%)	3 (60.0%)
- Malay	1 (16.7%)	11 (64.7%)	0 (0%)	0 (0%)
- Indian	3 (50.0%)	3 (17.6%)	1 (50.0%)	2 (40.0%)
- Others	0 (0%)	1 (5.9%)	1 (50.0%)	0 (0%)
Religion				
- Christianity	2 (33.3%)	4 (23.5%)	0 (0%)	2 (40%)
- Hinduism	1 (16.7%)	0 (0%)	0 (0%)	2 (40%)
- Muslim	2 (33.3%)	12 (70.6%)	2 (100%)	0 (0%)
- Others	1 (16.7%)	1 (5.9%)	0 (0%)	1 (20%)
Education				
- Primary education	2 (33.3%)	3 (17.6%)	1 (50.0%)	1 (20.0%)
- Secondary education	2 (33.3%)	11 (64.7%)	1 (50.0%)	2 (40.0%)
- Junior College/ Polytechnic/Technical Studies	1 (16.7%)	3 (17.6%)	0 (0%)	1 (20.0%)
- Undergraduate studies	1 (16.7%)	0 (0%)	0 (0%)	1 (20.0%)
Employment				
- Unemployed	6 (100%)	12 (70.6%)	1 (50.00%)	4 (80.0%)
- Part-time employment	0 (0%)	1 (5.9%)	1 (50.0%)	1 (20.0%)
- Full-time employment	0 (0%)	4 (23.5%)	0 (0%)	0 (0%)
Housing				
- Homeless	1 (16.7%)	3 (17.6%)	0 (0%)	2 (40.0%)
- 1 Room	3 (50.0%)	5 (29.4%)	0 (0%)	0 (0%)
- 2 Rooms	0 (0%)	2 (11.8%)	0 (0%)	0 (0%)
- 3 Rooms	1 (16.7%)	1 (5.9%)	0 (0%)	1 (20%)
- 4 Rooms	1 (16.7%)	3 (17.6%)	1 (50.0%)	2 (40.0%)
- 5 Rooms	0 (0%)	2 (11.8%)	0 (0%)	0 (0%)
- Others	0 (0%)	1 (5.9%)	1 (50.0%)	0 (0%)
Other Chronic Diseases				
- Presence	3 (50.0%)	7 (41.2%)	1 (50.0%)	1 (20.0%)
Psychiatric Disorders				
- Presence	1 (16.7%)	0 (0%)	0 (0%)	2 (40%)

Severity of Substance Dependence Mean Scores	11.2 (SD = 1.9)	11.7 (SD = 2.2)	9.0 (SD = 5.7)	8.8 (SD = 4.5)
SF-12 Scores				
- Physical Health Composite Mean Scores	40.5 (SD = 24.5)	54.7 (SD = 21.6)	82.0 (SD = 15.6)	70.2 (SD = 21.2)
- Mental Health Composite Mean Scores	29.3 (SD = 11.1)	41.0 (SD = 17.3)	52.0 (SD = 0)	39.2 (SD = 24.3)
- Total Mean Scores	33.7 (SD = 9.2)	46.5 (SD = 16.3)	64.5 (SD = 6.4)	51.4 (SD = 15.2)

The mean age of the participants with alcohol, opioid, stimulant, and cannabis dependence was 43.7 (SD, 11.6), 47.9 (SD, 11.8), 37.6 (SD, 7.0) and 58.0 (SD, 1.4) years, respectively. Most of the participants were Singaporean (90%), and male (86%). 53% had a secondary school education, 76% were unemployed and 20% reported being homeless. Furthermore, 50% of the participants with alcohol dependence and 50% of those with cannabis dependence had comorbidities, and 60% with stimulant dependence had an underlying psychiatric disorder. Participants with alcohol dependence had a mean score of 11.2 (SD, 1.9) on the severity of substance dependence questionnaire; those with opioid, stimulant and cannabis dependence had mean scores of 11.7 (SD, 2.2), 9.0 (SD, 5.7) and 8.8 (SD, 4.5) respectively. These scores confirm that the participants had a psychological dependence on the substances they were using. The physical and mental health composite scores were lower for alcohol use disorders than for the other disorders.

6.5.2 Primary Outcome: Identification of Baseline Biases and Changes in Biases

Table 6.5 provides the mean attention bias scores across the attention bias modification trials. Based on the protocol, participants were expected to complete 5 training sessions. However, not all participants completed all 5 sessions, due to a public holiday during their stay. Of the 30 participants, 14 had positive attentional biases at baseline, and 16 had no underlying baseline attentional biases. For those with baseline attentional biases, there was a general decrease in the attention bias scores from baseline to the end of the planned intervention trials. Across all participants, the changes in attentional bias scores ranged from -129.6 to 409.4 (with the negative change indicative of an increase in bias following bias modification). The overall mean change in attentional biases was 21.3 (SD: 98.6).

Table 6.5: Mean Attention Bias Scores for each participant across the trials

		Baseline		Post 1st		Post 2nd		Post 3rd		Post 4th		Post 5th		Overall Change in AB
Participant	Drug	AB	Task Ratio (Neutral: Drug)	AB	Task Ratio (Neutral: Drug)	AB	Task Ratio (Neutral: Drug)	AB	Task Ratio (Neutral: Drug)	AB	Task Ratio (Neutral: Drug)	AB	Task Ratio (Neutral: Drug)	
1	Stimulants	30.3	96:100	70.6	99:101	36.3	98:102	9.3	98:102	-23.6	96:98	13.3	99:99	17.0
2*	Stimulants	-22.4	103:97	-23.4	97:103	-11.7	95:105							10.7 (increased)
3	Stimulants	6.7	100:100	-3.6	98:101	-28.9	99:99	-11.3	100:99	4.1	100:99	-7.3	100:99	14.0
4^^	Opioid	32.1	96:93	28.7	99:100	12.2	99:100	31.2	100:99	20.1	100:99			12.0
5^^	Alcohol	91.2	97:98	-23.3	100:99	-37.4	100:99	-5.3	99:100	-33.2	99:100			124.4
6^^	Opioid	98.9	28:116	33.4	60:46	14.5	71:66	-9.7	88:86	-31.5	86:84			130.4
7	Stimulants	-30.5	100:100	-13.5	100:99	-23.4	98:99	-27.7	100:99	-28.2	98:99	-7.6	96:99	22.9 (Increased)
8*	Opioids	58.7	36:56	85.1	40:57									26.4 (Increased)
9*	Opioids	25.8	97:97	13.5	96:98									12.3
10	Cannabis	-9.9	97:99	-20.7	60:40	-54.6	93:90	-14.1	96:95	-22.9	99:100	-48.4	100:99	38.5
11	Opioids	-30.9	33:66	2.4	97:97	-15.4	99:99	-7.4	97:99	14.2	99:99	7.3	98:99	38.2 (Increased)
12*	Opioids	0.7	99:97	34.8	100:99	-15.3	98:99	-52.4	100:98					53.1
13	Alcohol^	-20.9	99:98	-12.3	100:98					-75.8	90:92	-48.6	99:100	27.7
14*	Alcohol	397.7	26:94	44.2	97:98	45.3	99:99	-32.0	98:100	-11.7	99:100			409.4
15	Cannabis	-7.7	100:96	-40.5	100:99	8.6	99:100	-33.6	99:99	-31.8	99:100	-50.3	100:99	42.6
16*	Opioids	-27.4	93:96											NA
17	Opioids	-42.5	49:49	-64.8	75:71	63.4	63:61	8.9	73:78	-15.5	78:82	26.7	96:92	69.2 (Increased)
18	Opioids	27.9	92:92	-17.8	99:96	3.2	100:99	-22.6	97:97	-104.6	99:99	-9.2	97:95	37.1

19*	Opioids	3.8	99:96	35.1	99:98	13.7	99:98	32.4	100:98					28.6 (Increased)
20	Opioids	10.1	99:98	9.4	100:98	105.2	99:98	54.1	100:99	-1.7	100:99	20.3	99:100	10.2 (Increased)
21	Alcohol	224.5	79:54	61.5	98:97	73.3	99:100	176.7	94:97	130.3	98:100	107.0	99:97	117.4
22	Opioids	-52.9	100:99	10.9	99:100	5.6	98:98	39.1	99:99	36.5	98:100	76.6	99:100	129.6 (Increased)
23	Opioids	-36.4	96:97	18.0	95:96	45.0	98:97	74.8	97:97	35.9	94:96	41.3	100:97	77.7 (Increased)
24	Opioids	-16.9	97:97	45.2	99:98	1.49	100:99	3.8	99:100	33.9	99:100			50.8 (Increased)
26*	Opioids	-77.1	84:79	-82.5	92:91									5.4
27	Stimulants	-15.2	100:100	-11.6	98:100	10.1	98:100	-27.0	99:97	-25.7	100:98	-1.6	98:100	13.6 (Increased)
28	Alcohol	-33.3	99:100	-29.4	99:98	-48.3	99:100	-10.9	99:100	-15.6	99:100	-11.6	100:99	21.8 (Increased)
29*	Alcohol	-41.4	98:100	-18.0	99:99	20.6	99:99	28.2	99:100					69.6 (Increased)
30	Opioids	1.3	96:94	38.6	98:93	7.9	98:95	11.5	98:91	13.0	98:98	-8.9	99:98	10.2
31	Opioids	-38.4	88:62	-282.7	96:33	-166.4	96:3	-190.1	97:3					151.6

Footnotes: ^Due to a technical issue, participant 13 was not administered an assessment task following the 2nd intervention, and the participant took another intervention task instead. Attentional bias assessment was performed only after the 4th session. ^^ There was a holiday during and hence the maximum number of sessions completed was 4.

*Participants who did not complete the study as they left the voluntary program

6.5.3 Secondary Outcome: Acceptability of the Intervention

Twenty two of the 30 participants (73%) completed the perspective questionnaires. All sampled participants rated the application to be at least very easy (10/22 participants) or extremely easy (11/22 participants) to use, with one participant describing it as “like a primary school application” (Participant 1). Participants also commented on the adequacy of the provided instructions (“easy to follow instructions and exercise” (Participant 3); “first of all you give me instructions how to press” (Participant 22)). Other participants felt that the application was easy to use due to the simplicity of the task (“no need to take time to think, just look at the photos and press either one of them” (Participant 6); “just to follow the asterisk *star” (Participant 15); “just need to follow the stars” (Participant 24). Participants commented on the ease of responding to the task (“only 2 options – left or right that’s why it is easy” (Participant 4)); “just press only” (Participant 10). Participants also felt that a diverse group of participants could undertake the task (“but both young and old adults would be able to” (Participant 7); “very simple and easy to be administered to subjects at almost any level of intelligence and age” (Participant 3).

Eight participants reported the app as being extremely interactive, 9 felt it was very interactive and 5 considered it moderately interactive. Participants commented that the application was “like playing the game” (Participant 4), and that the application “becomes more engaging” (Participant 3) over time.

Regarding motivation, there were a range of views. 8 participants reported being extremely motivated, 4 participants very motivated, 5 participants moderately motivated, 4 participants slightly motivated and 1 participant not at all motivated. Participants who were motivated shared that the application helped them “pass time” (participant 1), and that it was “just like playing game” (Participant 4). Other participants were motivated as they felt that the application “makes me feel better” (Participant 21), and that the application could “help me with my treatment” (Participant 29). Some participants who have indicated that they were motivated in using, did highlight possible reason, such as “continually using daily will become repetitive and boring” (Participant 3); “It is a repetitive task and some may find it boring to continue using it, unlike a game which really interacts with the user” (Participant 5);

and “If I concentrate, if I do this all the way, boring” (Participant 10). The participant who was not at all motivated commented that they found that the application “doesn’t help with my addiction problem” (Participant 22).

There was a range of responses to whether the images reminded participants of their drug use, with 5 indicating ‘very’, 4 indicating ‘moderately’, 3 indicating ‘slightly’ and 10 indicating ‘not at all’. Regarding participants’ confidence in managing their underlying addiction problem, 12 (54%) reported no change in their confidence level after using the app, 10 reported a change in their confidence level and 8 reported a positive change.

All participants were invited to provide additional feedback. Feedback was related to the need to concentrate on the task, “put your mind on it, follow the star, it would not go wrong” (Participant 14); “must be alert” (Participant 23), “it requires your full attention because the switch between the image and the asterisk is very fast so I have to be really focused” (Participant 5).

6.6 Discussion of Findings

The results demonstrate the study’s feasibility regarding participation and adherence. A modest recruitment rate was necessary, considering the number of patients enrolled in the rehabilitation programme and how patients could voluntarily discharge themselves from the programme. Lower participation rates were expected, given that individuals with a history of withdrawal seizures or diagnosed seizures and individuals with moderate to severe psychiatric conditions (as assessed clinically) were excluded. The acceptance rates in this study were higher, potentially due to the diversity of substance use disorders considered and because most of the participants who sought help had opioid dependence and no prior history of withdrawal seizures, which are not common in opioid withdrawal. Despite the nature of our programme, the adherence rate was not affected. Another objective of the feasibility study was to determine whether participants adhered to the intervention and whether the mobile attention bias modification intervention could assess and modify attentional biases. Most participants have had adhered to undertaking the intervention daily; uncompleted sessions were mainly attributed to participants’ premature discharge or public holidays. The mobile

intervention could assess the baseline biases and determine trends in attentional biases over time.

Acceptability was defined as willingness to use the application daily, if at least 30% of the participants positively rated the ease of use, interactivity and motivation and perceived a change in their confidence in managing their addictive disorders after performing 3 intervention tasks. The participants were amenable to using the app daily, except for those who left the ward prematurely and hence did not complete the planned interventions, all of whom left prematurely for reasons unrelated to the study. There were no adverse outcomes reported during the study. All participants rated the application as very easy or extremely easy to use, which exceeded our projection of 30%. Seventy-seven percent of the participants rated the application as very interactive, and 54% reported being very or extremely motivated in using the application, which exceeded our projection of 30%. Of the participants, 36% reported improved confidence in managing their addictive disorders, which was consistent with the projections.

In the qualitative feedback, 10 participants reported that the images did not remind them of their substance use. The images used in the app might have differed from those of the substances they had used and therefore failed to capture their attention, which is consistent with Field et al., who reported that a key factor leading to the visual probe task's poor reliability is the nature of the stimuli (61). Field et al. highlighted the importance of customising the stimuli, postulating that relevant and identifiable stimuli increases baseline attentional bias scores and provides evidence of greater change in the magnitude of attentional biases (61). Most of the images in the mobile app were extracted from the Internet, via the DEA media library. Some images were extracted from the CNB website. The included images might not approximate the participants' experience and might be unrealistic. For opioids, the app shows images of oxycodone and morphine pills; in Singapore, however, these drugs are not commonly abused. Similarly, the app showed images of spice (synthetic cannabis) for the cannabis image set, which is not commonly abused locally.

6.7 Research Implications

Several implications for research design arise from this study. Firstly, the presence of individuals without attentional biases at baseline warrants further statistical analyses; to compare those with and without baseline biases and this is explored in the next section. After comparing the recruitment rates to those reported by Herbert et al., the rates in this study indicate that a future pilot study could be undertaken (204). The qualitative feedback from the acceptability section suggests that I should involve patients in improving the app to provide image personalisation and other functionality in the app. Participatory research methods involving focus groups and co-design workshops were subsequently included in Study 2. Through participatory design, the existing app could be enhanced by involving patients and healthcare professionals in a joint co-design to create an app that is more feasible, acceptable, and able to detect and modify biases in opioid, cannabis, stimulant, and alcohol use disorders. The results might also be affected by the images included in the app. The next iteration of this intervention is designed to allow participants to first rate the images' relevance before embarking on the actual intervention.

6.8 Further Exploration of Negative Baseline Biases

Fourteen of the 30 participants recruited in the feasibility study had positive attentional biases at baseline; the remaining 16 had no underlying attentional biases. Table 6.6 provides an overview of the baseline demographics of those with and without baseline biases. The mean age of those with positive baseline attention bias and those with no attention bias was 46.3 and 45.8 years, respectively. There was no difference in the number of individuals with alcohol use disorders who presented with and without baseline bias. Of the participants with opioid use disorders, the number with positive baseline bias exceeded that of those with negative baseline bias by 1. All participants with cannabis use disorder had negative baseline bias. Of those with stimulant use disorder, 3 had negative baseline bias, as compared with two with positive baseline bias. Most of the participants were Singaporean, and more women had negative baseline bias than men (8% vs. 7.1%). Notably, 14.3% of the participants with positive baseline bias had an undergraduate educational level. Most were unemployed (71.4% and 81.3%, respectively). Physical disorders were more common (43.8%) among those

with negative baseline attention bias. The mean scores for substance dependence severity were comparable (10.93 and 10.31, respectively).

Table 6.6: Baseline demographic characteristics (n=30)

Demographic Characteristics	Positive Baseline Attention Bias (n=14)	Negative Baseline Attention Bias (n=16)
Mean age (years)	46.3 (SD = 12.7)	45.8 (SD = 10.7)
Substance Use		
- Alcohol	3 (21.4)	3 (18.8)
- Opioids	9 (64.3)	8 (50.0)
- Cannabis	0	2 (12.5)
- Stimulants	2 (14.3)	3 (18.8)
Nationality		
- Singaporean	12 (85.7)	15 (93.8)
- Others	2 (14.3)	1 (6.3)
Gender		
- Male	13 (92.9)	13 (81.3)
- Female	1 (7.1)	3 (18.8)
Race		
- Chinese	4 (28.6)	3 (18.8)
- Malay	6 (42.9)	7 (37.5)
- Indian	3 (21.4)	6 (37.5)
- Others	1 (7.1)	1 (6.3)
Education		
- Primary education	4 (28.6)	3 (18.8)
- Secondary education	7 (50.0)	9 (56.3)
- Junior College/ Polytechnic/Technical Studies	1 (7.7)	4 (25.0)
- Undergraduate studies	2 (14.3)	0
Employment		
- Unemployed	10 (71.4)	13 (81.3)
- Part-time employment	1 (7.7)	2 (12.5)
- Full-time employment	3 (21.4)	1 (6.3)
Housing		
- Homeless	4 (28.6)	2 (12.5)
- 1 Room	4 (28.6)	4 (25.0)
- 2 Rooms	2 (14.3)	0
- 3 Rooms	1 (7.1)	2 (12.5)
- 4 Rooms	0	7 (43.8)
- 5 Rooms	2 (14.3)	0
- Others	1 (7.1)	1 (6.3)
Psychiatric Disorders		
- Presence	2 (14.3)	1 (6.3)

Physical Disorders - Presence	4 (28.6)	7 (43.8)
Severity of Substance Dependence Mean Scores	10.93 (3.33)	10.31 (3.281)

Table 6.7 provides an overview of the participants with and without baseline attentional bias and their reported drug use, recorded on the modified ASI-Lite questionnaire. Most participants started their substance abuse at a young age and most reported daily use prior to admission. The group with positive baseline attention bias appeared to have experimented with more substances, compared with those in the group without baseline attention bias.

Table 6.7 Substance Use History of Participants

Positive Baseline Attention Biases							
Participant	Age	Baseline Bias	Current Drug	Drug History	Age of Onset	Age of Problematic use	Frequency prior to admission
Abm001	46	30.3	Stimulants	Polysubstance (9)	45	45	Daily (1-2 grams once per day)
Abm003	35	6.7	Stimulants	Polysubstance (7)	31	31	Daily (0.5 grams once per day)
Abm004	46	32.1	Opioids	Polysubstance (12)	14	17	Daily (30-40mls, 1-2 times each day)
Abm005	26	91.2	Alcohol	Alcohol (1)	20	21	Daily (750mls, 2-3 times per day)
Abm006	64	98.9	Opioids	Polysubstance (11)	20	22	Daily (2 Straws)
Abm008	60	58.7	Opioids	Polysubstance (4)	13	13	Daily (1 Straw, 2 times daily)
Abm009	28	25.8	Opioids	Polysubstance (5)	17	19	Daily (1.5 straw, 6 times daily)
Abm012	28	0.7	Opioids	Polysubstance (5)	18	25	Daily (5 tablets, 5 times daily)
Abm014	61	397.7	Alcohol	Polysubstance (5)	13	27	Daily (3 tall cans, 2 times daily)
Abm018	54	27.9	Opioids	Polysubstance (5)	34	34	*Patient did not fill up
Abm019	57	3.8	Opioids	Polysubstance (3)	40	40	Daily (90mls, once per day)

Abm020	45	10.1	Opioids	Polysubstance (4)	23	23	Daily (1 straw, 3 times daily)
Abm021	50	224.5	Alcohol	Alcohol & Tobacco (2)	15	50	Daily (8 cans once daily)
Anm030	48	1.3	Opioids	Polysubstance (3)	16	16	Daily (4 Straws, 4 times daily)
Negative Baseline Attention Biases							
Abm002	44	-22.4	Stimulants	Polysubstance (4)	38	40	Daily (Unknown quantity, 6 times daily)
Abm007	32	-30.5	Stimulants	Polysubstance (3)	29	30	Daily (0.3 grams, 5 times daily)
Abm010	59	-9.9	Cannabis	Polysubstance (5)	59	59	Daily (2 joints once per day)
Abm011	50	-30.9	Opioids	Polysubstance (3)	24	24	Daily (4 straws, 4 times per day)
Abm013	42	-20.9	Alcohol	Alcohol and Tobacco (2)	18	18	Daily (3-4 bottles, 3 times per day)
Abm015	57	-7.7	Cannabis	Polysubstance (7)	57	57	Daily (1 joint 20 times per day)
Abm016	47	-27.4	Opioids	Polysubstance (6)	17	17	Daily (1 joint 6-7 times)
Abm017	63	-42.5	Opioids	Polysubstance (4)	16	17	Daily (1/2 straw 3 times per day)
Abm022	43	-52.9	Opioids	Polysubstance (6)	16	17	Daily (2 straws, 2 times per day)
Abm023	54	-36.4	Opioids	Polysubstance (6)	15	16	Daily (3 straws, 10 times per day)
Abm024	46	-16.9	Opioids	Tobacco & Heroin (2)	17	21	Daily (7 straws, 4 times per day)
Abm026	57	-77.1	Opioids	Tobacco & Heroin (2)	17	28	Daily (1 straw, 2 times per day)
Abm027	31	-15.2	Stimulants	Polysubstance (9)	17	25	Daily (0.3grams throughout the day)
Abm028	44	-33.3	Alcohol	Alcohol and Tobacco (2)	17	28	Daily (750mls, 16-18 times per day)

Abm029	39	-41.4	Alcohol	Polysubstance (3)	14	30	Daily (9-10 cans, 9 times per day)
Abm031	25	-38.4	Opioids	Polysubstance (8)	20	20	Daily (1 straw, 2 times per day)

6.9 Discussion of Findings Relating to Negative Baseline Bias

Four factors accounting for the absence of baseline bias were abstinence, images in the mobile app, stimulus timings and participants' clinical characteristics.

Firstly, the absence of baseline bias might be due to our participants having undergone treatment and being abstinent for at least 7 days before study recruitment. This abstinence period might have reduced their baseline attentional bias. To achieve abstinence, participants were monitored for withdrawal symptoms; drugs to alleviate their withdrawal symptoms were prescribed. The medication-assisted detoxification could have been highly effective in ameliorating attentional bias among these participants. In their review, Zhang et al. stated that dopaminergic and serotonergic agents (such as antipsychotics and antidepressants) might reduce attention bias in the acute phase (56). Some of these medications might have been taken to relieve psychotic or affective symptoms during the withdrawal phase. Ethics approval had not been granted to extract information from the patients' medical records, and therefore the association between prescribed medications and baseline bias could not be determined (56).

Secondly, the nature of the images/stimuli used in our application may have contributed to a null finding at the baseline assessment. The images might have been inadequate or unrealistic representations of the drugs the participants were familiar with and therefore failed to capture their attention. The importance of personalising the stimulus images has been discussed earlier (61). Many of the app's images were taken from the DEA media library, due to its large repository of substance images. Fewer images came from the CNB website. As highlighted above, a co-design workshop is an excellent forum for exploring this issue.

Thirdly, the experimental procedure employed in the current study could have affected the detection of baseline biases, as could the duration the images were presented. In this study, the stimulus presentation time was 500 milliseconds, given that most studies

(Chapter 5) have indicated a cue stimulus of 500 milliseconds. The presentation of the stimulus for 500 milliseconds primarily assessed the presence of an initial orientation bias. Attentional biases due to delayed disengagement of attentional processes might therefore go undetected. Other studies have used short and long stimulus intervals presenting stimuli for as short as 200 milliseconds and as long as 2 seconds (69, 185, 186, 187). This study's findings highlight the importance of reconsidering stimulus timings for pilot and definitive randomised trials, to ensure better accuracy in detecting attentional bias (i.e., capturing the initial orientation and delayed disengagement processes).

Lastly, the absence of baseline bias might be the result of the participants' clinical characteristics. Prior studies have suggested that abstainers might demonstrate an attention bias away from alcohol-related stimuli (69). In Noel's study (213), abstainers did not have an attentional bias when viewing substance-related stimuli for 500 to 1250ms. Abstainers might tend to avoid triggering stimuli, similar to individuals with anxiety disorders (214). Abstinence is but one clinical factor that might account for the absence of baseline bias. Due to the limited sample size, I was unable to examine other possible demographics and clinical factors that might have affected baseline bias; future research should consider this issue.

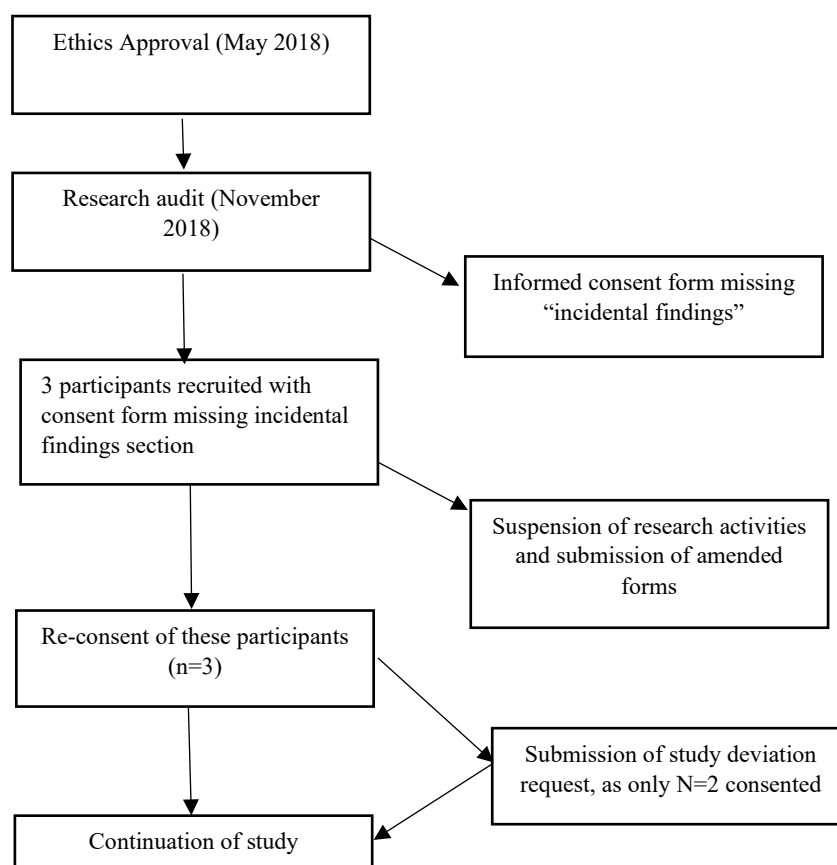
6.10 Ethical Challenges

This study was planned to be completed within a year, with the first six months for recruitment. Unfortunately, the study was extended for several reasons, including the regulatory changes to the governing ethics due to the introduction of the Human Biomedical Research Act (HBRA).

In the initial application approved in May 2018, the study was identified as a human biomedical research study that adhered to the guidelines of having witnesses during the informed consent process. In an audit conducted in early November 2018, however, the approved informed consent form was found to be noncompliant because it lacked a statement on "incidental findings". Recruitment stopped while amendments were submitted to the DSRB, justifying the reason for not mentioning incidental findings in the study protocol and revised informed consent form. Unfortunately, 3 participants

were recruited after November 1, 2018 (prior to the aforementioned audit), when the HBRA regulations were entirely in place. An informed consent document that did not contain the necessary declaration on incidental findings was used. A non-compliance report to be submitted to the DSRB was therefore required, which entailed suspending recruitment until the DSRB provided further directions. No further actions were necessary following the DSRB investigation. However, consent needed to be reacquired from the three enrolled participants who used the noncompliant informed consent form. The study team obtained consent from only 2 participants. A further amendment was submitted to allow us to disregard the data from the participant who could not be enrolled as per the guidelines and to recruit a new participant. The study protocol was amended in terms of the maximum and minimum number of participants. Figure 6.6 provides a flowchart summarising the critical events following the study's ethical approval.

Figure 6.1 Flowchart summarising the critical events following ethical approval of the study.



Consequently, recruitment was completed in early 2019. Changes in the HBRA regulations and the lack of clarity regarding the regulations resulted in a delay in the study completion.

6.11 Implications of the Research

Several essential research implications are arising from this study. First, the study has demonstrated the feasibility and acceptability of a mobile attention bias intervention amongst inpatient participants. The recruitment methods were feasible, and participants adhered to the planned interventions. The qualitative feedback demonstrated the participants' willingness to use this intervention. The study's findings will help design methods for the pilot and definitive randomised trials.

The acceptability study revealed motivational issues in using the app and the relevance of the stimulus sets. Future research should examine whether gamification strategies can increase motivation to use a particular application. The participants reported that they did not identify with certain images. Participatory action research methods should therefore be applied to personalise the images and determine appropriate gamification strategies. The next study (Study 2) therefore explores the use of co-design methods in conceptualising a novel intervention that addresses the limitations of current methods and meets the needs of patients and healthcare professionals.

This feasibility study highlighted the greater practicality of developing and evaluating such an intervention in the NAMS setting among opioid users who are more frequently admitted to inpatient units. MacLean et al. reviewed attentional bias among individuals with opioid use disorder; their findings are consistent with our feasibility study. The authors reported robust evidence for attentional bias, even among individuals on methadone maintenance (151). Opioid substitution therapy is not available in Singapore, and therefore psychological interventions become even more important for these individuals with opioid use disorders. Study 3 (Pilot Study) examines this pertinent topic.

Chapter 7 Co-design Study

Chapter 7 begins with an overview of participatory design research and its application to psychiatry. Section 7.3 highlights the potential for applying participatory research methods in attention bias modification research. The co-design study was conducted after completing the feasibility and acceptability study (Study 1), it was undertaken to refine the previously tested conventional mobile attention bias modification intervention. Chapter 7 concludes with a discussion of the main study findings and implications for future research.

7.1 Participatory Design Research: Overview

Participatory action research was first introduced by Kurt Lewin, and then the experiential learning and inquiry communities to researchers in the 1960s and early 1970s (215). According to Green et al., participatory action research refers to a process of “systematic inquiry, with the participation of those affected by the problem being studied, for education and action or effecting social change (216).” Participatory design research is typically qualitative and involves key players (such as patients) in the research process, given that their inclusion increases the relevance of the research and increase the findings’ acceptability (216). In the past decade, there has been increased focus on using these research methodologies (216). A 2008 review by Munn-Giddings et al. examined the uptake and design of participatory design research conducted in nursing in 2000–2005, indicating that at least 38% of identified published research studies included such methodologies. Of these, 13% were clinical studies (108). Their review demonstrated that such research methodologies have been utilised. Munn-Giddings et al. also reported a diversity of the research methods utilised (108). Their review showed that most of these studies included only practitioners instead of other healthcare professionals and patients, which is particularly concerning, because it implies that the opinions and perspectives of the latter might be ignored.

Applying participatory research methods therefore involves collaborating with the relevant players in exploring the following aspects of research: developing and defining core research questions; conducting research; and collecting and disseminating data and findings (217). Such methods have been increasingly applied to psychiatry and mental health research. In psychiatry, the conventional methodologies are community-based

participatory research, participatory action research, participatory design, and user-centred design (217). Participatory action and community research are similar; both methods involve key participants or community members to create changes either at the individual, group, or community level (218). Participatory design research involves iterative design cycles with participants (218). The user-centred design approach is usually driven by researchers or designers. In this approach, the participants' input is sought, which helps shape the researchers' plan for the eventual research design (218). In recent years, technological solutions, such as eHealth and mHealth, have been widely used in psychiatry because they help reduce geographical barriers, increase accessibility, and reduce expenditures for various interventions (90,92). E-Health refers to electronic health and includes web-based and Internet-based interventions (90). M-Health refers to mobile health and includes smartphone-based interventions, mainly in the form of smartphone applications (92).

Participatory methodologies have been increasingly used to aid the development and refinement of various web and mobile-based interventions. Ospina-Pinillos et al. utilized participatory design research methodologies involving young individuals aged 16-25 years and youth health professionals to facilitate the development of a web-based mental health clinic (111). Such a web-based mental health clinic will help provide young people with timely access to mental health care.

7.2 Application of Participatory Design Research in Psychiatry

Participatory design research methods have been considered for mental health/psychiatry research. Table 7.1 provides an overview of studies that included participatory research methods in these settings. While there are variations in the participatory action research methods across studies, the most common methods involved designing or co-creating workshops and focus groups. Studies have provided differing rationales for including participatory design research methods. Not all identified studies detailed the methodology for analysing the data collected. O'Connor et al. considered a qualitative exploratory case study design involving focus groups to elucidate the potential barriers faced by participants, which helped ensure that the developed application was more effective (110). Owens et al. highlighted the importance of including participatory design research methods in their study, given that it ensured that text messages delivered to individuals with self-harm tendencies were

safe and personalised. (220). Both Whitehouse et al. and Wilier et al. suggested that adopting participatory design approaches would improve the uptake of interventions (222, 223).

Table 7.1 Studies that included participatory research methods in psychiatry

Studies	Participants	Psychiatric Condition	Participatory Design Research (PDR) Method & Method of Analysis	Rationale for inclusion of Participatory Design Research Methods	Main Findings/Results	Key Limitations (Specific for Methods)
Gordon et al. (219)	Core group of participants (n = 17), which is made up of: - Patients with history of depression in pregnancy (n = 4) - Prenatal providers (n = 2) - Social workers/care managers (n = 2) - Mental health specialists (n = 2) - Clinic administrator (n = 1) - Support staff (n = 3) - Research staff (n = 2) - Programmer (n = 1)	Perinatal Depression	Iterative participatory design strategy: - Meeting occurred monthly in a waiting area of the prenatal centre immediately following the regular workday and lasted 2 h. - Meetings were focused on generating ideas and providing feedback on brief pilot studies. Meetings facilitated by the research team and involved brainstorming, problem-solving, role-playing, and feedback on content. Method of Analysis: - Rapid cycle iterative approach. - At each of the meetings, progress was reviewed, feedback was provided, the pilot software was tested, and it helped to guide the specific recommendations for the next steps. - Live-action videography was used. - Animated guides were produced by means of a commercial software.	Aim to develop e-health tools geared to the particular support needs of low-income, ethnic/racial minority women at risk of perinatal mental disorders (PMD).	3 Applications were developed, the MyGamePlan suicide prevention mobile app for iPhone, a tablet-based screening tool for PMD and a patient decision aid (PtDA) for supporting treatment decisions for depression in pregnancy by women and their clinicians.	Multistakeholder participatory design groups take time to establish.
O'Connor et al. (110)	Total number of participants (n = 16); in-depth focus group (n = 10) and interviews (n = 6). Participants included that of dementia patient-carer dyads, an occupational therapist, a project manager and a software engineer.	Dementia	Qualitative exploratory case study design: - In-depth focus (n = 10) and interview (n = 6) with people involved in the co-design was conducted. Method of analysis: -Data was analyzed thematically using the framework approach.	To explore the barriers experienced by all participants during the co-design of the My House of Memories application, to ensure that the future production of mobile technology is more effective.	The study highlighted the lack of digital literacy knowledge and skills among people with dementia and their carers. Inaccurate perceptions of how people with dementia or carers would use mobile technology. Individuals in the later stages of dementia struggled to take part in the workshops and compromises also had to be made to the design and functionality of the mobile app.	Not mentioned

Studies	Participants	Psychiatric Condition	Participatory Design Research (PDR) Method & Method of Analysis	Rationale for inclusion of Participatory Design Research Methods	Main Findings/Results	Key Limitations (Specific for Methods)
Ospina-Pinillos et al. (111)	18 young participants & 10 youth health professionals participated in stage 1. The group included 4 psychologists, 2 occupational therapists, 1 medical student, 1 general practitioner, 1 social worker and 1 Aboriginal youth worker. 9 young people and youth health professionals in Stage 2. The young health professionals included 3 psychologists and 1 occupational therapist. 6 people participated in Stage 3. This also included 1 clinical psychologist, 1 psychology student and 4 young people.	Not specified For the creation of a web-based mental health clinic	Four Participatory Design Workshops held Each workshop was followed by a knowledge translation session. At the end of the cycle, the alpha prototype was built with one round of one-on-one end user consultation sessions conducted. PD Workshop (Phase 1): Transition of knowledge and idea generated during workshops to produce mock-ups of webpages Phase 2: Rapid prototyping with one-on-one consultations with end users Phase 2: Rapid prototyping and user acceptance testing Methods of Analysis: Not specified	To help develop a Mental Health eClinic to improve timely access to, and better quality, mental health care for young people	Helped in revealing the importance of five key components for the Mental Health eClinic: a welcoming home page with a visible triage system; a comprehensive physical and mental health assessment; a detailed dashboard of results; a booking and a video visit system; and the generation of a personalized well-being plan that includes links to evidence-based, and health professional-recommended, apps and etools.	Nothing specific to PDR
Owens et al. (220)	Eight mental health service users and one carer. Three liaison psychiatry team members.	Self-Harm	6 participatory workshops First workshop: Full day, designed to introduce people to the project, enable the various stakeholders to understand and feel comfortable with one another. Time was spend exploring the meaning and functions of self-harm and attitudes towards prevention. Acceptability and merits of text messaging were discussed. Methods of Analysis: -	Involving potential recipients at the design stage may be particularly important when the intervention is intended to bring about behavioural, as opposed to biochemical, change. This study reports on the challenge of working with a group of people with	Service users rejected both the idea of a generic, one-size fits all approach and that of audience segmentation. Text messages could be safe and effective only if individualized.	Workshop participants were not involved in every aspect of decision making. Difficulties in keeping the same group of participants due to their fluctuations in the mental state. Researchers need to keep restating

Studies	Participants	Psychiatric Condition	Participatory Design Research (PDR) Method & Method of Analysis	Rationale for inclusion of Participatory Design Research Methods	Main Findings/Results	Key Limitations (Specific for Methods)
			Principal task in Workshop 1: Generate a catalogue of potential messages that could be market tested. -Workshop 2: Focus group, with additional participants with histories of self-harm. Purpose: validating and rating the messages generated in Workshop 1 -Workshop 3: Retest of a selection of messages, followed by a free-ranging discussion -Workshop 4,5,6 involved stimulating, evaluating and refining the intervention.	relevant lived experience to develop a text-messaging intervention to reduce repetition of self-harm.		the aims of the project and re-establishing consensus at each workshop. The iterative nature of the participatory process meant that plans had to be revised in response to the findings from each session.
Peters et al. (221)	Male workers, invited to participate via email announcements in 2 male-dominated organizations in Australia. Total of 60 workers, Mean age 47 years old, 97% of the participants reported the use of a mobile phone	Not specified General Mental Health Well-being of Males in the Workplace	Participatory Design Workshop Activity-based workshop, 2.5 h each, were carried out with groups of participants (minimum of 5 and maximum of 17 participants in each group). Activities included individual reflection, collaborative ideation, and paper prototyping. Data collated included participant-generated artefacts from each of the activities, collection of feature ideas on sticky notes, field notes and audio recording of each workshop. Methods of Analysis: Theoretical thematic analysis	To address the difficulties in engaging men with mental health support by presenting qualitative results of their perceptions, preferences and ideas related to mental health technologies and providing an example of how a research-based app for mental health could be designed.	Workers do have a set of features, languages and style preferences that they feel would be essential in any future mental health app. Perceived stigma against the term “mental health” with terms like “mental fitness” being preferred. Range of specific features including mood tracking, self-assessment and “mood boost” tools were highly valued in addition to characteristics such as brevity, minimal on-screen text and a solutions-orientated approach.	Self-selection bias – those who volunteered for the study are likely to represent those who were more willing to discuss mental health issues.
Whitehouse, et al. (222)	A design student from Emily Carr University of Art and Design (ECUAD) undertook the initial co-creative research and subsequent preliminary development of TickiT with youth from the	Not specified Mental health issues in Youth	Total of three 2-h co-creation sessions First group co-creation session – youths brainstormed about the concept of psychosocial screening, to determine strategies that could be followed to align their ideas with those of health professionals. Focus groups were set up to discuss youth perceptions of content and	To improve the uptake of psychosocial screening among youths	This study described the early developments of the TickiT eHealth platform that was initially designed to engage the patient, enhance the relationship between patient and provider and improve efficiency. Youths gave an overall positive response regarding the concept of the tool. Some were concerned about	Lack of support for long-term research collaborations between industry and academic institutions. Industry timelines are inconsistent

Studies	Participants	Psychiatric Condition	Participatory Design Research (PDR) Method & Method of Analysis	Rationale for inclusion of Participatory Design Research Methods	Main Findings/Results	Key Limitations (Specific for Methods)
	Youth Advisory Committee (12–20 years old, n = 8) Subsequent co-creation sessions were held with adolescents in a high school (n = 16) and a 1st year design class at ECUAD (n = 24).		language from the questionnaire. Subsequent sessions youths were provided with paper PDF copies of version of questions reflecting revisions suggested from their previous feedback sessions. These were presented on colour templates with icons for responses. Youths were asked to interact with the interface, provide comments on the copies and discuss their feelings about the User interface. Methods of Analysis: - Not specified		privacy. Suggestions regarding specific design constructs. Identified problems with the text, simplified questions. Concerns raised with technical issues.	with academic timelines.
Wiljer et al. (223)	65 post-secondary students	Not specified. Creation of a mental health platform	Co-creation involved student development teams, hosting a hackathon, conducting focus group and evidence-based workshops and student advisory groups. Key components of the co-design workshop: Student driven development teams; Crowd-sourcing/data workshops; Hackathon; Knowledge transition and engagement strategies. Methods of Analysis: - Not specified	Co-design could strengthen youth buy-in, increased the efficacy, usability and sustainability of the intervention, generate innovative and creative design concepts and foster youth empowerment, skill and capacity building.	This project has demonstrated the benefits and challenges of co-creation in the development of a crowd-sourcing platform for students seeking support for their mental health.	Some challenges in maintaining individual engagement.

It is evident that participatory design research has been increasingly adopted in psychiatry to inform the conceptualisation process and increase the uptake, acceptability and usability of the research product. These articles highlight the importance of such research methodologies to conceptualise new web or mobile-based interventions. Such methods have been applied to a selected few psychiatric disorder.

7.3 Application of PDR for Attention Bias Modification Research

Review 2 (Review of mobile cognitive bias modification interventions) highlighted the disconnect between academics and developers, given the small number of commercially available, scientifically validated applications and the many unvalidated commercial applications. Review 3 described how gamification strategies have helped mitigate the lack of motivation to train, although there have been few studies on this topic.

None of the existing interventions for cognitive bias modification have been conceptualised by considering the patients' perspectives. The administration of a mobile attention bias intervention (Study 1) has demonstrated that there are issues regarding motivation to continue training. Only 54% of the participants in the feasibility study reported being extremely motivated to continue undertaking the intervention daily. The sampled participants (ten out of the 30 participants recruited in the feasibility and acceptability study) did not perceive the included images as resembling the drugs they used. Participatory and design research methods could improve the conceptualised mobile attention bias modification intervention.

7.4 Co-designing an Attention Bias Modification App

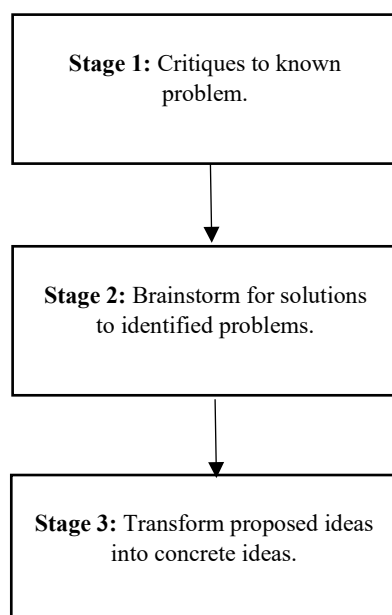
Given these considerations as aforementioned in Section 7.3, a co-design study was conceptualized and conducted from March to July 2019. A protocol was written defining the study methods, and the co-design study has been published.

7.5 Consideration of Methods for the Co-design Study

This study used the principles of participatory action research, a model of research that uses “systematic inquiry, with the participation of those affected by the problem being studied, for education and action or effecting social change (224).” There are several

participatory action research models, including Software Technology for Evolutionary Participatory Systems Development, MUST (Danish acronym for theories and methods of initial analysis and design activities) and Cooperative Experimental System Developmental Approach (224). The use-oriented design was chosen because it relates to a real-life problem, understanding practice, identifying needs and wishes, describing requirements, concretising and materialising, and finally, testing and evaluation (224). This approach was also selected because it is explorative and allows for negotiation and collaboration on the design before a stepwise refinement through sketching and prototyping and is therefore the most appropriate for addressing the current research question. The goal of this study was the co-design and co-development of a new gamified novel attention bias modification intervention. “Future Workshops” are part of the use-oriented design approach and are optimal for the generation of new and innovative ideas. A future workshop typically involves three key phases (225). In the first, individuals are asked for their critiques to a known problem. In the second, individuals are asked to brainstorm on positive and even impossible solutions to this problem. In the third, participants are asked to transform their proposed ideas into concrete and achievable goals (226). **Figure 7.1** summarises the steps involved in a future workshop.

Figure 7.1 Framework of the Future Workshop.



7.6 Specific Aims of the Co-design Study

This study aimed to involve patients and healthcare professionals in designing a gamified mobile attention bias modification intervention. The following four questions were to be addressed based on the perspectives of the health professionals and patients:

1) What are the participant's perspectives on the mobile attention bias modification intervention? 2) What features of a mobile attention bias modification intervention would a participant expect to help minimise attrition from the task and increase intrinsic and extrinsic motivation in completing the intervention? 3) Would gamification help enhance the existing mobile bias intervention task (i.e., increase the magnitude of bias change, increase motivation, and reduce rates of attrition)? and 4) What gaming elements are preferred?

7.7 Specific Methods of the Co-design Study

7.7.1 Study Settings and Recruitment

Participants were recruited from the largest addiction treatment centre in Singapore, which specialises in both substance and behavioural addictions. The healthcare professionals recruited were addiction psychiatrists and addiction counsellors. Ten healthcare professionals and patients were recruited for each group for equal representation. Patients at various recovery stages were invited to participate to ensure that the collected perspectives would be unbiased. Following the Human Biomedical Research Guidelines, informed consent was obtained from all participants.

7.7.2 Participants

Patients were included if 21–65 years of age, diagnosed with a primary psychiatric disorder (alcohol, opioid, cannabis, or stimulant use disorder), were able to speak and write in English and knew how to use a smartphone device. Patients were excluded if they had significant psychiatric comorbidity (moderate to severe depressive disorder, anxiety disorder, psychotic disorder), were non-English-speaking or had cognitive impairment or intellectual disability. The inclusion criteria were identical to those of our prior feasibility study (212) and representative of the demographics and clinical characteristics of the patients admitted for treatment in our programme.

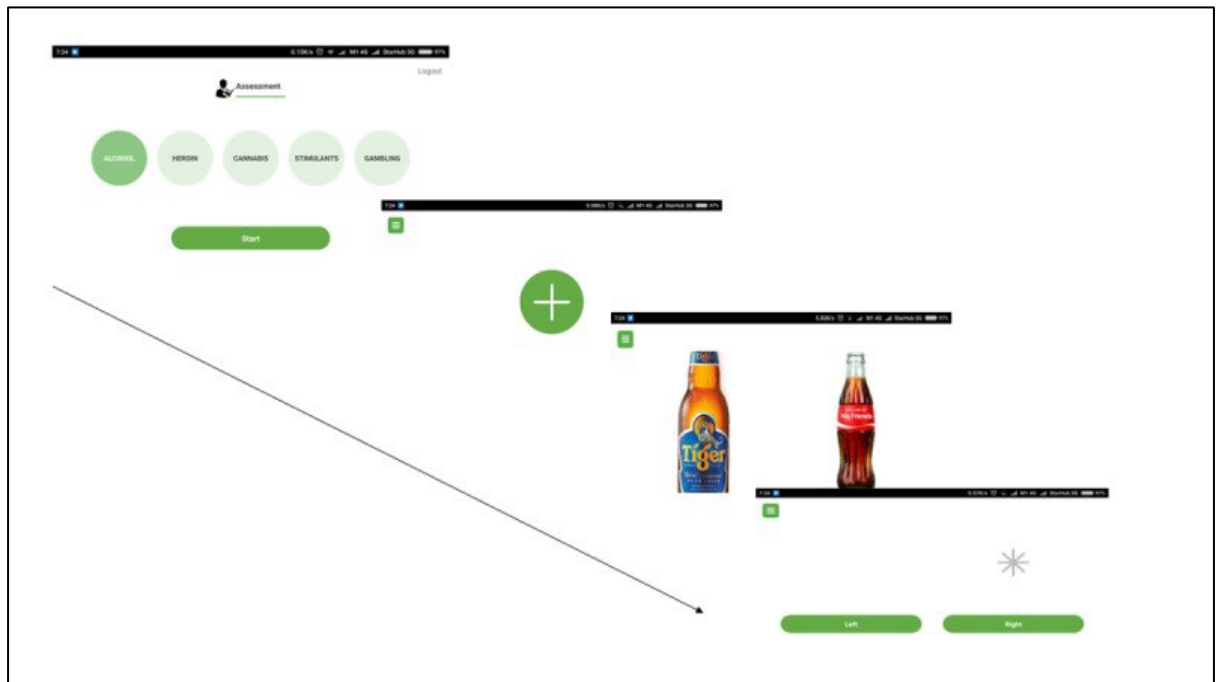
The healthcare professionals included in the study had to be currently working in an addiction unit and actively involved in treating addictive disorders, with a minimum of 2 years of experience working with addictive disorders.

7.7.3 Workshop Procedures

All participants completed a questionnaire before participating in the co-design workshop. The questionnaires asked about the participants' demographics and clinical characteristics. I, as the principal investigator, facilitated all three workshops.

- a. Phase 1 – Critique of existing smartphone-based mobile attention bias modification intervention

In the first phase of the co-design workshop, individuals critiqued the existing smartphone-based attention bias modification intervention. The existing attention bias modification intervention was based on a prior protocol (202). In the mobile app, participants could select the intervention specific for their substance of abuse. In the assessment task, participants were presented with a central fixation cross. After the cross disappeared, a neutral stimulus and a nonneutral stimulus were presented simultaneously. A probe then replaced either stimulus, and the individuals had to indicate the probe's position within a predetermined time. In the assessment task, the probe would replace either stimulus with equal probability. In the intervention task, the probe would replace the nondrug stimulus every time. Figure 7.2 provides an overview of the nature of the assessment and intervention tasks.

Figure 7.2 Overview of the Nature of the Assessment and Intervention Tasks

Participants were introduced to the project's rationale and study objectives and were shown a presentation of the attention bias modification app. They used the app on the tablet devices to undertake the attention bias assessment and modification intervention. Participants were asked to provide their thoughts narratively and identify limitations. The following questions were posed: 1) Having seen and used the app, what are your thoughts about it? 2) What are some of the app's limitations?

b. Phase 2 – Identification of solutions to limitations previously identified

In phase 2, participants were asked to brainstorm solutions to their critiques and features that could be added to the mobile app. The questions were as follows: 1) What additional features do you think could be added? 2) Why would these features be helpful? Participants were encouraged to write down their ideas on sticky notes, which were then collected by the study team and discussed among the whole group.

One of the objectives was to determine whether gamification could address the limitations of the app. Participants were shown screenshots of commercial attention bias apps, which included gamification elements (e.g. digital rewards, avatars,

competition, feedback, leader boards, time pressures and 3D environments). To ensure everyone understood gamification techniques, the facilitator provided an overview of techniques summarised in the literature (Table 7.2). Participants were shown gaming strategies adopted in commercial apps and approaches used for apps in other disciplines and were asked to consider appropriate strategies for the current intervention.

Table 7.2: Overview of Gamification Approaches (Hoffman et al. (177))

Gaming Approach	Description
Economic gamification techniques a. Marketplace and economies b. Digital rewards c. Real world prizes	Providing gamers with a virtual currency that allows them to deal in game These include badges, game currency, game points, virtual goods and powers or abilities Provides gamers with options to exchange in-game credits for real-world prizes such as vouchers or other forms of goods and services
Social gamification techniques a. Avatar b. Agent c. Competition d. Teams e. Parallel communication systems f. Social Pressure	Allows individuals to choose a virtual character to represent oneself A virtual character that help guides or provides instructions to user Allow individuals to compete with other players or with each other Game that involves several individual players, allowing them to interact and form relationships Allows individuals to communicate with one another Ability of game to pressurize individuals to perform in certain task, so that he or she will be invited to subsequent events.
Performance-orientated a. Feedback b. Levels c. Secondary game objectives d. Ranks of achievement e. Leader boards f. Time pressure	Spoken, visual or auditory feedback about user's performance Information on the stage of a game one has attained Secondary goals that reward the player upon completion Measurement of character development Allows for comparisons with other players Pre-determined time limits for task completion
Embedding-focused a. Narrative Context b. 3-D environment	A storyboard or stories that guide the development of the character 3-D models of objects that parallel the real world

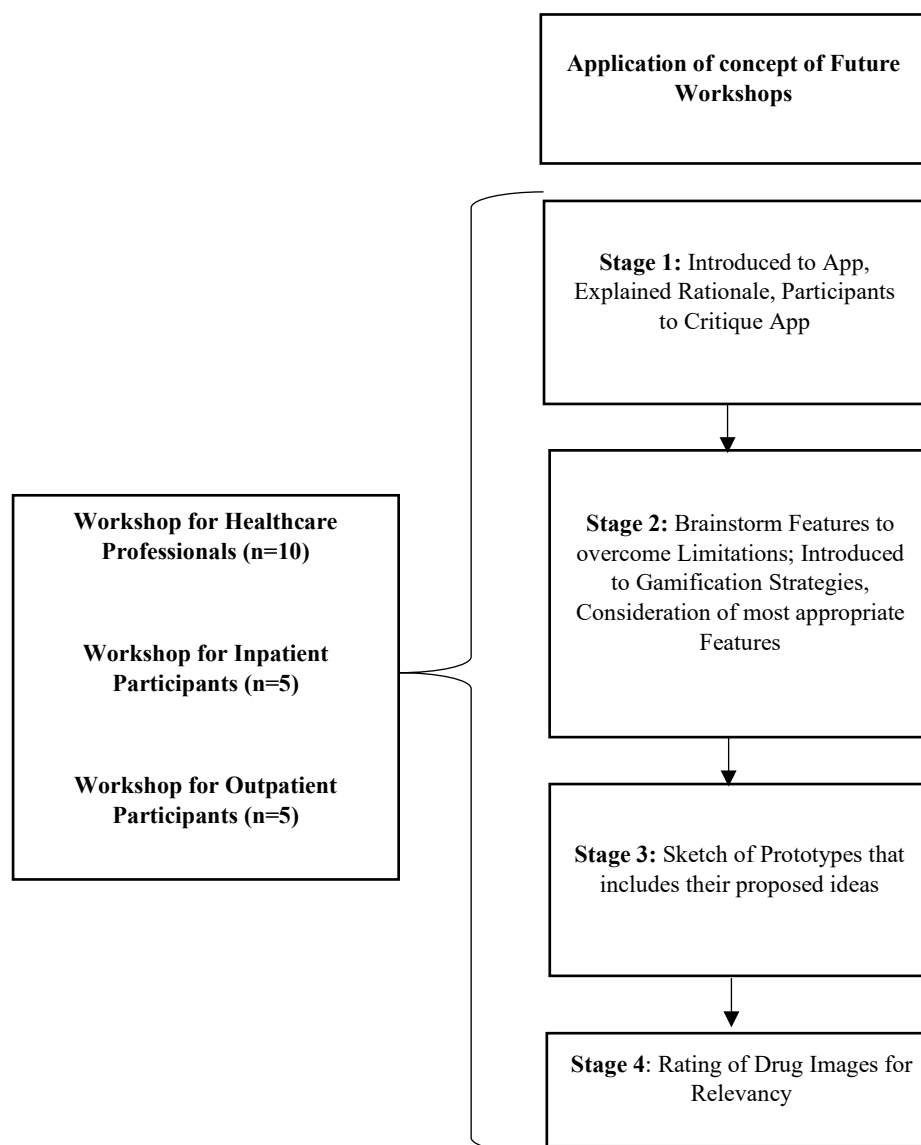
Participants were asked to discuss their perspectives on the gamification ideas described above and then individually select their top three gamification techniques they felt were most appropriate for implementation in the app.

c. Phase 3 – Conceptualisation of a Prototype & Rating of Stimulus Images

In the last stage of the workshop, participants were divided into smaller groups of two to five to develop frame-by-frame sketches of a prototype app that incorporated their proposed solutions. Participants sketched freely on paper using a variety of writing instruments and were told to include the original task, which they could modify. All groups were given 15 minutes to work on the task.

Before completing the workshop, participants were shown a set of substance images that have since been incorporated into the app. Participants were assigned to rate the images' relevance for individuals with addictive disorders, using a Likert scale (1 to 10, where 1 is not relevant and 10 is extremely relevant). Participants were asked to share their opinions with the workshop facilitator. Figure 7.3 provides an overview of the flow of the workshops.

Figure 7.3 Flowchart of the workshop.



7.7.4 Ethical Approval

The study obtained ethical approval from the National Healthcare Group's Domain Specific Research Board (ethics approval number 2018/01363).

7.7.5 Data Analyses

Descriptive statistical analysis was performed using SPSS (version 24; IBM Corp, Armonk, New York) (210) for the quantitative data collected from the questionnaire. The workshops were audio-recorded and transcribed verbatim by the principal investigator and independently by a private transcription service (WayWithWords) (227). The principal investigator then listened repeatedly to the workshop's audio recordings and developed a coding frame. To ensure the frame's reliability, two authors reviewed the transcripts and discussed the frame, thereby ensuring adherence to the intercoder consensus process (228). Disagreements were resolved through discussion with another author. The identified codes were categorised and then reorganised into themes. NVivo (version 12.0; QSR International, Melbourne, Australia) (211) was used to facilitate the analysis. Two independent study team members (a psychologist and another psychiatrist) reviewed the prototype sketches and identified the common elements.

7.8 Results

All three workshops were successfully conducted and completed by July 2019 and included 20 participants (10 healthcare professionals, 5 inpatients and 5 outpatients; mean age of 47.3, 44.4 and 43.2 years, respectively). The mean addiction duration was 12.7 years. One inpatient had an alcohol use disorder, and the remaining four had a substance use diagnosis. All outpatients had used alcohol and illicit substances.

Themes were identified from each workshop phase. Table 7.3 presents the participants' comments verbatim. In phase 1, the healthcare professionals identified issues with the design, visual probe trials and images. Both patient groups identified issues with the visual probe trials and images. The outpatients highlighted issues with the intervention design, safety and administration.

Table 7.3: Themes relating to Limitations of Existing Application

Themes	Healthcare Professionals (n=10)	Inpatient Participants (n=5)	Outpatient Participants (n=5)
Design of Application	“Buttons were too small” making them “easy to miss” (Participant 2) “Press a few times, will add on to the reaction time” (Participant 1) “There is no try out to understand how it works.” (Participant 3 & 5)	No mention	“More instructions”(Participant 2) “When I got things clear, I focus on star” (Participant 5) “No design or anything” (Participant 1) buttons to be “bigger” (Participant 1) “Joystick interface” to indicate a response (Participant 2)
Visual Probe Tasks	“Too many repetitions” (Participant 2) the task was “so fast” (Participant 3 & 5). “Distinguish the frame from one another “looking at the asterisk” (Participant 1) “Focusing on the asterisk only.” (Participant 3 & 7) “Pictures were so fast, after a while, I stopped paying attention and just look for the asterisk” (Participant 8)	“Were too fast” (Participants 3, 5 & 7) “My mind cannot catch up, fingers cannot catch up” (participant 5) “Repetition is the same” (Participant 5) Task is “too tedious” (Participant 3)	The trial was “too long” (Participant 1 & 4) “Too fast” and “quick” (Participant 2, 4 & 5) “I never even have a chance to see” (Participant 1) “Too fast. My mind was to aim for the star. The pictures I was not interested.” (Participant 4)” “It is too fast that we don’t really see the picture” (Participant 3)
Images included in Visual Probe Task	“Image colour does not stick out” (Participant 3) “Non-white background will enhance the focus of the images” (Participant 2)	The “colour is dull” and that the images are repetitive (Participant 1) “I see the same image for 30 times or more” (Participant 1)	“Keep seeing the same pictures” (Participant 3) “Very boring, put more pictures” (Participant 1) “Maybe more picture, very repetitive. I keep on seeing the same pictures over and over again” (Participant 2) “It comes in pairs. It always weed and chocolate cake. You can figure out” (Participant 2)
Safety of Administering Application	No mention	No mention	“Triggering. Like I think just keep seeing pictures of drug of choice” (Participant 2) “Early recovery is triggering. For myself, if I am in detox, might trigger me.” (Participant 5)

In phase 2, the healthcare professionals suggested improvements to the stimuli, the response mechanism, and the presentation of scores. The inpatients recommended adding new functionality to the design and enhancements to the images and task. The outpatients recommended improvements to the design, including images and presentation of results. Gaming was the aspect with the greatest difference between the healthcare professionals and patients, with the former suggesting integrating gamification elements. In contrast, all but one of the inpatients opposed including

gaming elements. The outpatients perceived the inclusion of gaming elements as appropriate only if the gamified app was intended for abstaining individuals. Table 7.4 lists the themes related to the solutions addressing the limitations of an existing app. Table 7.5 summarises the participants' comments regarding the inclusion of gamification elements.

Table 7.4: Themes relating to Solutions addressing Limitations of Existing Application

Themes	Healthcare Professionals (n=10)	Inpatient Participants (n=5)	Outpatient Participants (n=5)
Images included in Visual Probe Task	"As much as possible, it should be similar as possible. The two pictures should be of the same quality and same size" (Participant 2) "How come the tiger bottle is so big and the cola bottle so small? Obviously, my eyes will zoom to the big one. I am attracted to the obvious. It just shines out" (Participant 5)	"Something associated with alcoholism. Clubbing, coffee shop, anything associated with alcoholism" (Participant 1) Images with substances in different "environment" (Participant 3) "Can include like family members. Drinking with family members" (Participant 2) "Images personalized, can identify with" (Participant 3)	"Higher intensity" of images" instead of just 2 pictures (Participant 1)
Design of application	"Is it possible to press on the picture instead of right/left. Pictures are bigger than the right/left button" (Participant 10) "Maybe instead of buttons, they could tap anywhere on the half of the screen. That would make it easier rather than to aim on the button. This will also help to mitigate the older folks who have difficulties to move on to the button" (Participant 2)	"Colours" for the asterisk (Participant 1) and for the buttons to be "round or bigger" (Participant 1)	"When press down on the star, right or correct, some positive words or pictures, smiling. Would be more interesting" (Participant 4) "If they hit the correct one, maybe there is a nice emoji. Wrong, maybe a crying emoji" (Participant 3)
Scoring Functionality	Scoring was "very complicated" and that the scoring appealed only to "investigators or clinicians" (Participant 1)	No mention	"When they finish the game, can have instant results, instead of having to scroll down" (Participant 3)
Other possible Functionalities	No mention	"What are the diseases you are going through if you have alcoholism? More information of what alcohol does to you in the short term and long term" (Participant 2)	No mention
Visual Probe Trial	No mention	"Just 3 seconds interval" (Participant 1) "You can request for 5-10 seconds interval delay" (Participant 1)	"Do it from slow, all the way to fast" (Participant 3)
Consideration of Gaming Elements	No mention	No mention	"Show the fastest speed and slowest speech in the result, make it like a game" (Participant 1)

			“Maybe you could have a board (1 st , 2 nd , 3 rd)”(Participant 3)

Table 7.5: Themes relating to Gamification Elements for existing application

Themes	Healthcare Professionals (n=10)	Inpatient Participants (n=5)	Outpatient Participants (n=5)
Performance-oriented gaming elements	“Lowest cost way of doing this app that will make users want to continue using it.” (Participant 2) “The feedback that you are doing better is kind of helpful for them” (Participant 9) “In between giving feedback about their performance; three times you press the correct thing, you are on a roll” (Participant 4) “As it motivates you to go into higher grades, either as an individual or as a group” (Participant 6) “Motivate them to continue playing the application” (Participant 11) “Bronze to silver to gold medals” (Participant 2) “Some achievement in the form of badges would help” (Participant 7) “Track their progress” “aware of the questions remaining” (Participant 8)	“Leader-board”, social gaming elements “Having connect with Facebook would allow you to see who else has participated” and “Levels” in the game (Participant1)	“Results” of his or her performance (Participant 2) Time-pressure, levels and leaderboard were also chosen, as it allows for “competition” (Participant 2) “When you see the leaderboard, maybe I am here. I can do better to go up” (Participant 3)
Rewards (Digital / Real World) based gaming elements	“Entice them to continue to play” (Participant 4)	No mention	“Can change for vouchers (Participant 1)” “Like voucher, exchange coffee. Get something realistic” (Participant 4)
Context (Storyboard)	“Motivating” (Participant 7) “Map out the real-life experiences”, this giving “a reason in doing the exercises” (Participant 6) “more realistic and engaging (Participant 9)	No mention	No mention
Against Gamification	None mention	“Childish” (Participant 3) making the application to be more catered for “Kids” (Participant 1) “All these are game right? Part of games right? All these are addiction already” (Participant 2) “As a gamer, I could relate to Number 2, this is gaming addiction” (Participant 1)	“If I am using, I would not play game. When you are into drugs, you are in no mood to play games” (Participant 4) “When you are heavily using, you cannot be bothered by this. Especially when you are high” (Participant 5)

In phase 3, each of the six groups sketched out a prototype. The two healthcare professional groups recommended including training tasks. Regarding the visual probe task paradigm, the healthcare professionals suggested lengthening the initial trial interval to 1 second, with a gradual reduction to 500 milliseconds over time. The healthcare professionals also suggested including gamification elements, such as scores and progress bars, to provide feedback and progress reports. The inpatients suggested that the stimulus be either animated or personalised to their substance of use. Both participant groups also recommended that the task start with a lengthened trial interval, which would then shorten progressively as the intervention progressed. For example, the interval could start at 800 milliseconds for the first 20–30 sets of images and then decrease to 600 milliseconds for the next set. Participants indicated that this would make them more comfortable with the task and allow them sufficient time to focus on the stimulus. Both patient groups also recommended providing explicit instructions. The participants also suggested using larger buttons to facilitate their task responses.

Figure 7.4 provides an overview of an example of a sketch by a group of participants. Appendix 12 contains the images of the sketches by each of the individual teams. Table 7.6 presents the selected verbatim comments of all groups of participants regarding their sketched prototype.

Figure 7.4 An example of a sketch

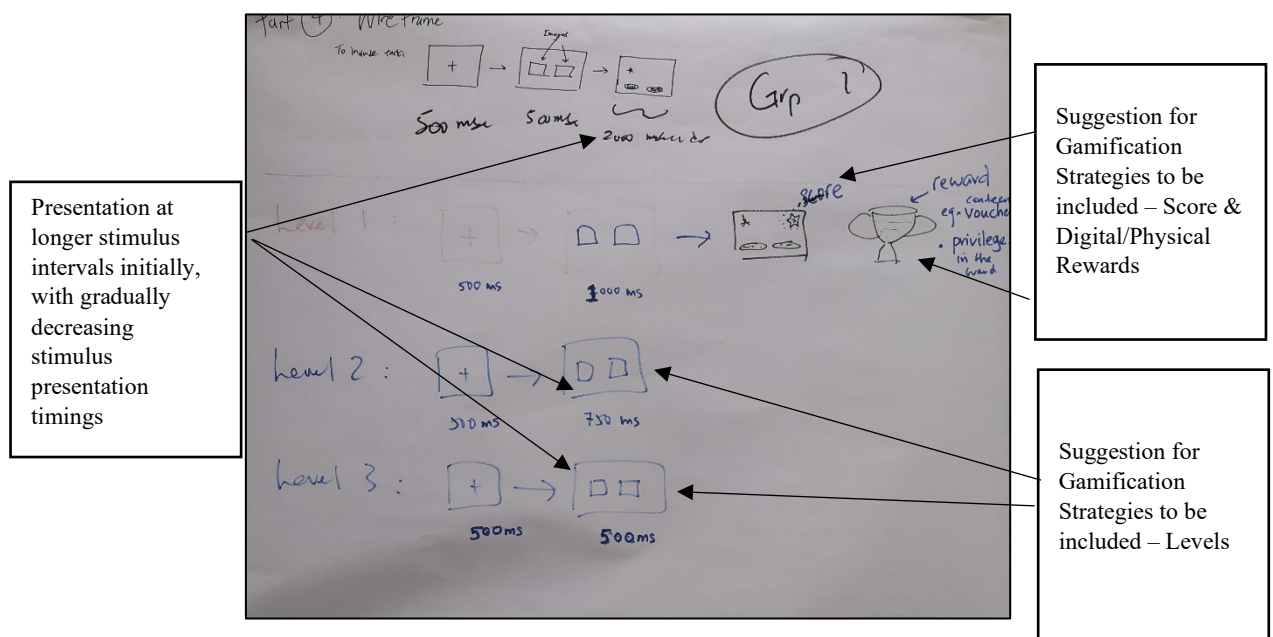


Table 7.6: Participants' comments on their newly conceptualized prototypes

Participants	Selected Verbatim Comments
HealthCare Professionals (Group 1)	"We think that there should be a few levels of difficulties. It is like a training phase. The assessment time becomes shorter and shorter. The time becomes shorter and shorter. We think there should be a score. Encourage the person to hit a higher score. The rewards we were thinking about.. Vouchers or privileges on the ward"
HealthCare Professionals (Group 2)	"First thing would be instructions." "Second part. There would be some motivation. You are doing good." "After the training is done, task score. And the progress bar. How many percent completed." "The pictures. We thought of different modalities. Not just the pictures. Sometimes virtual ones." "Need a trial of how to do it"
Inpatient Participants (Group 1)	"Instead of using a cross, you can put a money sign." "After you focus on a while, you could have different images." "Secondly, instead of money, you could put a photo. A photo of your family After you focus on the photo for a while, you drift off to an animated picture." "Ask the user to type"
Inpatient Participants (Group 2)	"Family. Picture This is the family picture, wife and children picture Drugs and alcohol Which one you want to choose." "Instead of someone else drinking, can be someone I know drinking."
Outpatient Participants (Group 1)	"The first square is the instruction manual. The second one is a prompt for ready. Then straight away go to the cross with 2 pictures. The last one is the start. And end with results. Maybe it starts off with a bit slower and then progress to fast" "Maybe the first 20-30 pictures 0.8 seconds, then the next 0.6 seconds. Moderately decrease the speed instead of diving right in"
Outpatient Participants (Group 2)	"Introduction. The second column slightly slower than the tablet. 0.7-0.8 seconds. This one is 2 seconds. 1 seconds. Then you can random got different picture. Not only just come up star only. Can come up star with drug"

Before the end of the workshop, participants were shown images used in the existing app. The healthcare and patient participants suggested including more images relevant to the local context and images of commonly used drug paraphernalia. **Table 7.7** provides a summary of the participants' comments in accordance with the drug categories. **Table 7.8** summarises the mean scores for each picture included in the application. The low scores indicate that some images do not resemble relevant items.

Table 7.7: Suggestions of Participants for Images included in Application.

Image Category	Healthcare Professionals (n=10)	Inpatient Participants (n=5)	Outpatient Participants (n=5)
Alcohol	“Picture more relevant to the local context, for example, picture from coffee shop” (Participant 6) Not to focus on the “brands” of the alcohol (Participant 6)	“Hard liquor” was missing (Participant 1,2)	No need to include the “brand” of the alcohol (Participant 4) “More kind of hard liquor, such as whisky” (Participant 4)
Cannabis	“Some of the pictures were not familiar” (Participant 2)	A “barrel and aluminium foil” would be good (Participant 3) “Bottles” might not be so relevant, as they are synthetic cannabinoids (Participant 1)	“The bong is not the right bong” (Participant 2)
Heroin	“Straws” “pictures of the barrel and thin foils” (Participant 5) “Someone chasing the dragon, or someone using the main line” are the most relevant and triggering (Participant 3)	“The one with needle” (Participant 4)	“Syringe” image was perceived to be “very triggering” (Participant 1) “Nothing catches my eye except for this needle thing” (Participant 3) Pills “oxycodone” was not used locally (“Singapore people don’t abuse”). (Participant 1)
Stimulants	The images of the stimulant crystals might not be so relevant, as the crystals available locally are “of different quality” (Participant 2)	“Pure image of ICE” (Participant 1)	“Don’t look like ICE at all” (Participant 4)

Table 7.8 Mean Scores for the included pictures within the application

Substances	Image 1	Image 2	Image 3	Image 4	Image 5	Image 6	Image 7	Image 8	Image 9	Image 10
Alcohol	7.375	5.5	5.375	8.75	7.75	8	8.75	8.375	8.625	8.25
Heroin	2.5	5.25	5.375	4.375	4.5	9.125	6	6.75	4.375	4.125
Cannabis	6	5.25	7.375	8.5	8.5	8.125	5.125	2.375	5.375	4.75
Stimulant	7.125	9	7	6	4.825	7.25	6.375	7.142	-	-

7.9 Challenges

One of the main challenges was not being allowed to have the healthcare professionals and patients in the same workshop. The regulatory ethics body was concerned that the patients would be unable to share their perspectives freely if in the same room as the healthcare professionals. Separate workshops were therefore conducted for healthcare professionals and for patients.

An introductory briefing explaining the nature of the visual probe task paradigm, was given at the beginning of the workshop, but explaining the concept to the patients was challenging. Participatory action and design research could potentially be used in

designing the co-design workshop. It would have been preferable if an independent facilitator were present. Funding constraints prevented inviting an external facilitator and the principal investigator (myself) had to be the facilitator for the workshop, which might have affected what participants shared (in that, they might not be as forthcoming and as ready to share). It would have been preferable if an independent facilitator were present. There were also challenges in recruiting inpatients, and some participants were difficult to engage with, as they were still in withdrawal. Identifying a common timing for the outpatients was also challenging.

Conducting Reviews 2 and 3 was a timely and resource efficient way to identify research gaps in the mobile delivery and gamification of attention bias modification interventions. After identifying these gaps, I submitted a proposal to the Games for Health Innovation Centre (ALVE) grant body. Although competitive, \$10,000 was eventually secured for two studies (the co-design and pilot study). Due to the time required for the reviews, the feasibility study's conduct and the application for funding, this co-design study could be conducted only in early 2019 or the second year of my PhD programme. The conduct of the feasibility study prior to the co-design study was crucial because it helped to determine whether participants were willing to use a mobile attention bias modification intervention in the inpatient unit. The co-design study helped refine the conceptualisation of the mobile intervention. This limitation resulted in the delayed progression of the PhD, as other planned studies depended on the co-design study results.

7.10 New Knowledge and Findings

This co-design study highlighted several user preferences. The first was that the stimulus' presentation was too fast. Based on our prior review, I chose 500 milliseconds as the stimulus timing because it was the time commonly used among various substance disorders (184). The current findings indicated that participants preferred a slightly longer initial stimulus presentation interval and shorter stimulus intervals in subsequent interventions. Based on these workshop findings and those of our previous review, future research should consider presenting stimulus images at two intervals (short and long) (184) to measure attentional bias more reliably. The short interval captures the initial orientation, while the long interval captures delayed disengagement. Our

participants preferred having more time at the start of the intervention for them to focus on the images. Future research should therefore explore the impact of gradually decreasing stimulus intervals (i.e., over time, more trials would be presented for a short stimulus duration instead of a long stimulus duration). It is possible that the focus of bias modification at the start is the modification of one's delayed disengagement processes; as the interventions progress, the modification target evolves to the initial orientation.

The second important issue highlighted in the workshops was the lack of relevancy and personalisation of stimulus images. In future research, it might be worthwhile to have participants work through the stimulus set and identify relevant images and words. I adopted this approach in our co-design study (by providing comments for the included images and scoring the images), which was integral to the next step involving the evaluation of the co-designed app. The need for personalised images was previously suggested by Field et al. who reported that the poor reliability of the visual probe task could be improved if the image sets were personalised (61). Interestingly, in a recent study by Jones et al., however, reliability and internal consistency did not improve after personalisation (229). Unfortunately, this study remains limited by the fact that the investigators (not the participants) chose the stimulus images (229). Future research should reconsider personalising the stimulus on bias modification by allowing participants to rate and choose appropriate images and provide input regarding the images to be included.

The third issue was the differences in perspectives of the healthcare professionals and patients regarding the inclusion of gamification strategies, which would have been less of an issue if both groups had been evaluated in the same workshop. In our study, the healthcare professionals perceived that including gaming elements was beneficial, whereas the patients were cautious. It is more important to consider the patients' perspectives because they are the eventual users. In this study, the patients acknowledged that some gaming elements could be considered. The common gaming elements endorsed by both the patients and healthcare professionals were performance-oriented gaming elements, such as feedback, levels, and rewards. These elements were,

to some extent, similar to gaming elements (animations, sounds, feedback and a scoring system) that effective in our previous review. Future research should consider integrating these elements and exploring whether these elements would render bias modification more effective.

Lastly, the patients raised safety concerns regarding administering such an application, especially to individuals in early stages of recovery. These concerns contrast with published studies, which recruited participants undergoing detoxification for participation in bias modification interventions (52, 104). Manning et al. reported that it was advantageous to have participants perform bias modification in their detoxification phase of treatment. Such an approach could capitalise on the neural recovery stage (52). None of these studies reported dropouts due to relapse of the underlying addiction. Nevertheless, it is important to consider the patients' feedback, which might imply that future research should consider recruiting participants who have completed their detoxification and are in the rehabilitation phase. These individuals should perhaps first undergo the intervention in the confines of a controlled environment.

7.11 Conclusions

The user preferences identified by means of this co-design study will help to guide the conceptualisation of the application that would be tested in Study 3 (pilot randomised trial).

Chapter 8 Pilot Study

Introduction

This chapter begins with an overview of the rationale for Study 3 and the reasons for selecting individuals with opioid use disorders for the newly conceptualised intervention. Section 8.2 describes the protocol for Study 3, a pilot study examining the co-designed attention bias modification intervention. Section 8.3 provides an overview of the co-design results. Section 8.4 describes the challenges faced while conducting the study during the COVID-19 pandemic. The chapter concludes with a discussion of the research implications of the results.

8.1 Reasons for Targeting Individuals with Opioid Use Disorders

The first part of this dissertation focused on individuals with substance use disorders, namely those with opioid, cannabis, and stimulant use disorders. Based on the results of our feasibility and acceptability study, more individuals with opioid use disorders remained in rehabilitation than those with other substance disorders (such as alcohol, cannabis and stimulant disorders). Of the 30 participants, 17 were diagnosed with opioid use disorder, 9 of whom successfully modified their baseline biases. It therefore seemed reasonable to restrict the inclusion criteria to individuals with opioid use disorders, which are highly prevalent both globally and locally. According to recent World Health Organisation statistics, of the 269 million individuals who used drugs at least once in 2018, 58 million took opioids, prompting the World Health Organisation to declare a global epidemic of opioid abuse (230). While conventional opioids such as heroin are routinely abused, the abuse of prescription opioids, such as tramadol, oxycodone, and fentanyl, has recently increased (231, 232). Drug formulations have been changed to mitigate this increased abuse. The annual statistics released by the CNB show that heroin was one of the top three commonly abused substances in 2017 and 2018 in Singapore (15,16). With the influx of novel psychoactive substances, however, heroin was not one of the top three abused drugs in 2019, although the abuse of opioids such as heroin has always been a problem in Singapore. Teo et al. reported that the opioid problem started in 1977, with approximately 2000 arrests (based on the initial data) (233). Unfortunately, there have been no large-scale studies in Singapore regarding the changing trends in opioid abuse.

As highlighted in the introductory chapter, generally treatment for opioid use disorders includes pharmacological and psychological approaches. Singapore, however, relies largely on psychological therapy due to the unavailability of opioid substitution therapy. Individuals presenting for treatment at NAMS are typically given only symptomatic withdrawal medication to help them cope with the withdrawal symptoms associated with opioid use cessation. Psychosocial rehabilitation is critical in treating opioid disorders in Singapore, to help individuals not only cope with their cravings but also maintain abstinence.

The two reviews described in this thesis (Review 1) provided evidence for attentional biases among individuals with opioid use disorders. Other researchers, such as Maclean et al., have investigated attentional biases among opioid users and found that attentional biases persist despite highly efficacious pharmacological treatment (opioid substitution therapy) (151). Given the limitations of existing conventional psychotherapies such as cognitive behavioural therapy and motivational interviewing (in that they focus only on targeting the executive processes), the studies demonstrating cognitive deficits among individuals with addictive disorders and the justification for cognitive remediation using attentional bias modification, there is a pressing need to investigate attentional bias modification, especially among individuals with opioid use disorders.

To date, only my prior study (Study 1) has explored the possibility of attention bias modification in an Asian cohort of substance users (201). The study was also the first to demonstrate the feasibility and acceptability of a mobile bias intervention. From our feasibility and acceptability study, it is evident that there are more individuals with opioid use disorders who remained in rehabilitation treatment, compared with other substance disorders, such as those of alcohol, cannabis and stimulants. Of the 30 participants, 17 were diagnosed with opioid use disorder and 9 successfully modified their biases. Further evaluative studies (pilot and definitive randomised trial) to determine the intervention's effectiveness are warranted. As described in Chapter 6, the co-design study overcame the main limitations of the conventional intervention: repetitiveness and diminished motivation to train with time (90, 124). However, whether a co-designed app is more effective than a conventional intervention in reducing attentional biases has not been explored.

8.2 Objectives of this Pilot Study

The pilot randomised trial's objective was to determine the viability of the intended processes involved in the definitive study (i.e. the recruitment of participants with opioid use disorder, the randomisation process into two separate intervention arms, and the administration of the intervention). The pilot study's purpose was distinct and differed from that of the actual definitive randomised trial in that it sought to test the process for the definitive trial. A pilot study is critical for identifying and eliminating problems that might affect the definitive trial's eventual success. Prior research has highlighted that as much as 85% of research investment is wasted due to poorly designed and implemented trials (236). Previously identified issues that render a trial poor include a lack of a systematic literature review and inadequate concealment of treatment allocation (236). The protocol for this pilot study has been published as "Gamified M-Health Attention Bias Modification Intervention for Individuals with Opioid Use Disorder: Protocol for a Pilot Randomised Study" (Appendix 13).

8.3 Methods

8.3.1 Study Design and Setting

The study was designed as a non-blinded randomised controlled trial. Participants were allocated to take the conventional attention bias modification task or the newly designed co-designed task. Simple randomisation was performed using a computer spreadsheet. The study was conducted in the inpatient unit at NAMS. The trial's design was non-blinded, given that participants allocated to the various groups would be aware of their treatment allocation. It was not possible to blind the study team, because they recruited the participants and administered the interventions.

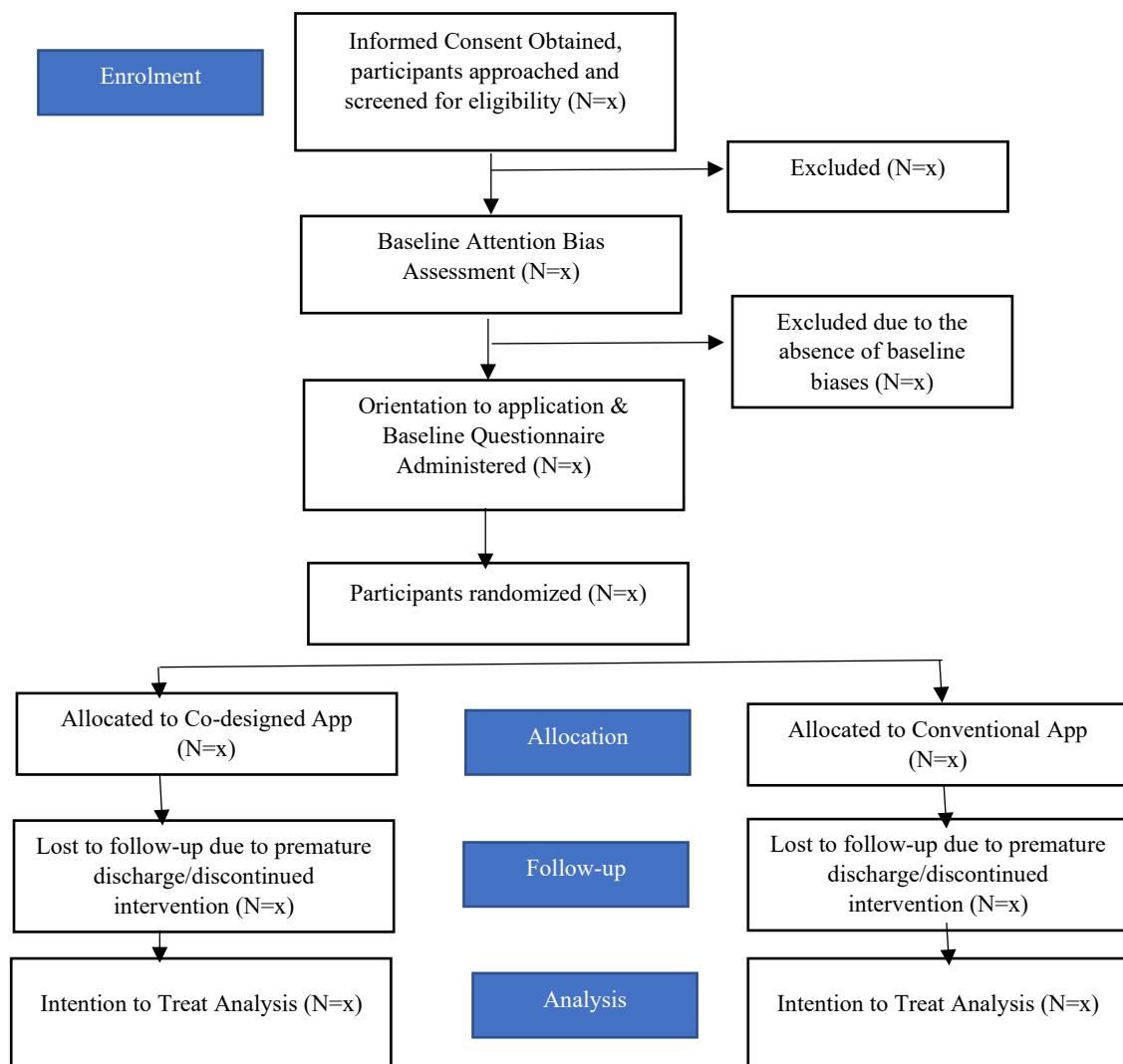
8.3.2 Inclusion and Exclusion Criteria

Participants were recruited if a) they were aged 21–65 years, b) their primary psychiatric diagnosis was opioid use disorder, c) they used opioids as their primary substance if diagnosed with polysubstance use disorder, d) they were able to read and write in English, and e) they had completed their detoxification programme. Participants were screened for participation and had to present with baseline attentional biases (i.e., a positive attentional bias).

8.3.4 Sampling and Recruitment

Recruitment was by convenience sampling and started in November 2019. The study ended in late January 2020 due to the onset of the COVID-19 pandemic. Participants had to perform an attention bias assessment screening task. Only those with baseline biases were recruited and were assigned through simple randomisation. Figure 8.1 provides an overview of the participant flowchart following screening and recruitment.

Figure 8.1 Participant Flowchart



8.3.5 Sample Size

The findings from the prior feasibility and acceptability study informed the design of this pilot study. A power computation was not performed but the sample size was based

on Bell et al.'s guidelines on using a pilot study for designing confirmatory studies, which recommends an estimated 25 participants per intervention arm for studies involving a small effect size (i.e. a Cohen D between 0.1 and 0.3) (205). We therefore planned to recruit 30 participants, 15 to be allocated to the co-designed app and 15 to the conventional app. Given that only 50% of the participants presented with baseline attentional biases, we recruited 60 participants for baseline attentional biases screening.

8.3.6 Randomisation

Simple computer randomisation was used, and each participants' treatment was determined independently, without any constraints. In this study, the method proposed by Simon S was followed (237). Using Microsoft Excel, a spreadsheet was created, with one column indicating the participant number of the 60 participants. Another column was created in which the intended treatment was arranged systematically. Using a column of random numbers, by using the RAND () functionality, the column comprising the random numbers was sorted, which resulted in the treatment conditions being allocated to participants in a random and unpredictable order (237).

8.3.7 Experimental Procedure and Data Collation

a. Screening for Eligibility

For screening purposes, informed consent for eligibility screening was obtained in the presence of an impartial witness on the last day of the patients' detoxification stay (Day 7). For the screening, participants were required to perform an attention bias assessment task on a tablet, in which a fixation cross was displayed for 500 milliseconds, followed by a set of images (one of which was related to opioids; the other was a neutral image matched for colour and complexity). Of these images, 50% were presented for 200 milliseconds, and 50% were presented for 2 seconds. The images were then replaced by a probe (in the form of an asterisk) for 200 milliseconds. Participants had to respond (by tapping buttons on the screen), indicating whether the asterisk appeared on the left or right side. If they did not respond, they were presented with the subsequent trial. In the screening phase, 50% of the trials (100 trials) involved presenting the probe with the substance image, and the remaining 50% involved presenting the probe with the neutral image. Attentional bias was computed by subtracting the reaction time required to respond to probes replacing the substance image from the reaction time for the

neutral image. Considering the participants' perspectives regarding the nature of the stimuli in the co-design study, the set of opioid images presented in this pilot study were images of opioids regularly abused in Singapore. CNB provided images of opioids seized during drug raids, some of which included participants' top-rated opioid images, which were identified in the co-design study. The stimulus set comprised 10 opioid images, with matching neutral images and this set was repeated 20 times, for 200 trials in total.

b. Experimental Procedure

Participants with positive baseline biases were eligible for recruitment into the randomised pilot trial. Ineligible participants (those without baseline biases) were excluded, given due compensation, and allowed to continue with their rehabilitation programme. The study team trained the participants in using the mobile app. All participants were provided a unique username and password to access the study team's app on tablets and completed a baseline demographic and clinical questionnaire, which collected the following information: nationality, gender, marital status, race, religion, educational level, housing conditions, current substance use, substance consumption method, quantity of substance consumed each time, usage frequency, previous treatment history, chronic diseases (psychiatric and physical disorders) and current psychiatric medications. Participants rated their cravings on a VAS before and after performing the intervention task.

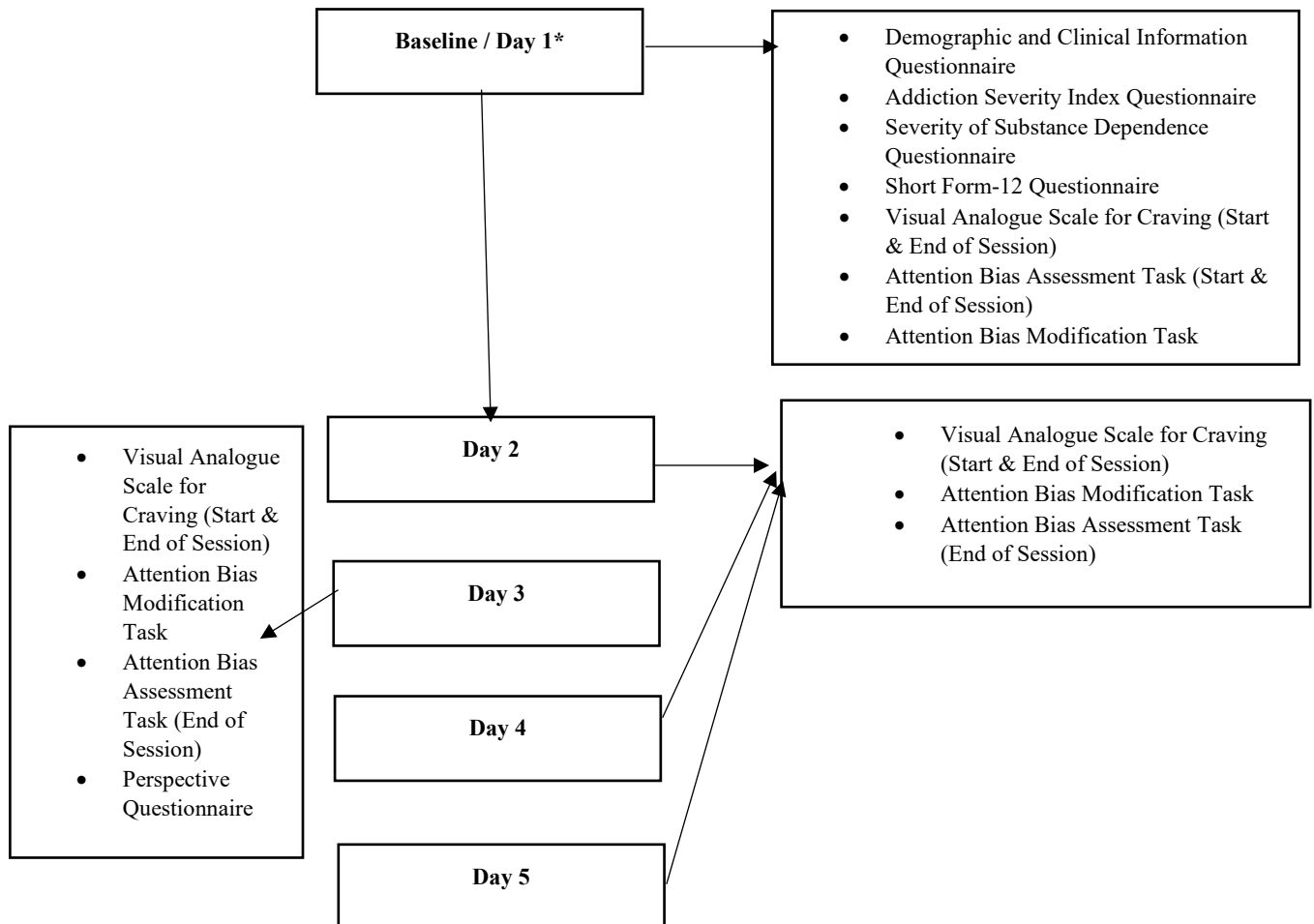
The experimental procedure did not differ between participants who were randomised to the co-designed app and those randomised to the conventional app. Participants spent 10 minutes to complete 200 repetitions of the attention bias modification task. After completing the first attention bias modification task, participants rested for 10 minutes, before spending another 10 minutes to complete 200 repeats of the attention bias assessment task. Participants retook the attention bias modification task daily, for as long as they were inpatients, except on weekends and public holidays. Participants retook the craving questionnaire prior to and after the attention bias modification task on each day they were involved in the study. Participants completed a questionnaire to provide feedback regarding the intervention (after completing three interventions). If participants requested premature discharge from the ward, they were not required to return to the ward to complete the intervention.

The perspective questionnaire comprised the following questions:

1. Prior to using the application, how confident were you in managing your addiction problem? (5-point Likert Scale)
2. How easy was it to use the application? (5-point Likert Scale, ranging from Not at all to Extremely, and free text comments)
3. How engaging was the application? (5-point Likert Scale, ranging from Not at all to Extremely, and free text comments)
4. Did you feel motivated to continue to use the app? (5-point Likert Scale, ranging from Not at all to Extremely, and free text comments)
5. Did the images in the app remind them of their substance use? (5-point Likert Scale)
6. After using the app, how confident were you in managing your addiction problem? (5-point Likert Scale)

Figure 8.2 provides an overview of the data collection time points and tasks to be undertaken by the participants.

Figure 8.2: Overview of the data collection time points and tasks to be undertaken



c. Details of the Intervention Tools

In the conventional and co-designed apps, participants were instructed to undertake the attention bias assessment and modification task daily. In the conventional app, a fixation cross appeared at the centre of the screen for 500 milliseconds for the attention bias assessment task. A set of images were then presented (opioid-related and neutral images), half of which (i.e. 100 sets of images) were presented for 200 milliseconds, with the other half (i.e. 100 sets of images) presented for 2 seconds. The set of images comprised a substance image and a neutral image, matched in colour, size and complexity. The substance images were localised images obtained from CNB, the local drug enforcement authority. Some of the images were also the top-rated images that participants chose in the co-design study. A probe (asterisk) would then appear, replacing either the substance image or the neutral image, for 200 milliseconds before disappearing. Participants were asked to indicate the probe's position by selecting the buttons on the screen (i.e. left button if the probe was on the left side, right button if the probe was on the right side). In the attention bias assessment task, the probe would replace the substance image 50% of the time and the neutral image for the other 50%. Participants were instructed to complete 200 repetitions in the attention bias assessment task. There were 10 sets of images, which were repeated 20 times over the 200 repetitions. The time interval between each repeat was 250 milliseconds. The attention bias modification task resembles the attention bias assessment task, except for the probe always replacing the neutral image (100% of the time), which helped retrain attentional processes away from the opioid images towards the neutral images. The attention bias modification task comprised 200 repetitions of the same paradigm.

The co-designed intervention included features in addition to the attention bias assessment and modification tasks. Before commencing any assessment or intervention, the app provided an instruction video. Participants were allowed 5 practice response trials (assessment task). The attention bias assessment task in the co-designed app similarly presented a fixation cross at the centre of the screen for 500 milliseconds and then presented a set of images. Half of the image sets (i.e. 100) were presented for 200 milliseconds, and half were presented for 2 seconds. An image set comprised a substance (opioid) image and a neutral image, matched in colour, size and complexity. A probe (asterisk) then appeared (replacing either the substance image or the neutral image) for 200 milliseconds before disappearing. Participants were instructed to

indicate the probe's position by selecting the buttons on the screen (i.e. left button if the probe was on the left side; right button if on the right side).

The co-designed app similarly presented a fixation cross at the start of the attention bias modification intervention. The app then presented a set of stimulus images (opioid-related and neutral images), varying the presentation of the stimulus set throughout the interventions. This design approach was suggested by healthcare professionals and patients in the co-design workshop. Thus, on the first day of the intervention, 90% of the stimulus sets were presented for 2 seconds, and 10% were presented for 200 milliseconds. Table 8.1 provides an overview of the stimulus image timings on each day. A probe (asterisk) then appeared, replacing the substance image or the neutral image for 200 milliseconds before disappearing. As before, participants were instructed to indicate the probe's position by selecting the buttons on the screen. If they responded correctly, a smiley emoji would appear; if not, a frowning emoji would appear. The cumulative scores across the trials were presented in the top right-hand corner of the app. Final scores were presented upon completion of the task. The interval between each repetition was 250 milliseconds.

Table 8.1 Overview of timings of the stimulus images by the days of intervention

Day of Intervention	Total Number of Trials	Percentage of Image Sets presenting for 200 milliseconds	Percentage of Image Sets presenting for 2000 milliseconds
Day 1	200	10%	90%
Day 2	200	20%	80%
Day 3	200	30%	70%
Day 4	200	40%	60%
Day 5	200	50%	50%

8.3.7 Outcomes

This pilot study sought to determine whether the intended processes of randomisation, intervention administration and data collection were practical.

8.3.8 Statistical Analyses

I used an intention-to-treat analytical approach, using data from all participants, including those who withdrew or did not complete all planned interventions. The recruitment rate was calculated as the proportion of recruited individuals out of all those invited to participate. The rate of adherence to the planned intervention was calculated by dividing the number of individuals who completed all planned interventions by the number who agreed to participate. SPSS version 24.0 (SPSS Inc, IL, USA) (210) was employed for the data analysis. Participants' baseline demographic and clinical information are summarised using descriptive statistics, means and standard deviations.

Microsoft Excel was used to calculate each participant's attention bias scores for each assessment task, according to the following formula:

$$(\sum T_1 / n_1) - (\sum T_0 / n_0),$$

where T_1 refers to the time during which the probe replaced the neutral image,
 n_1 refers to the number of trials in which the probe replaced the neutral image,
 T_0 refers to the time during which the probe replaced the substance image, and
 n_0 refers to number of trials in which the probes replaced the substance image.

I did not perform a statistical analysis to examine the changes in attentional biases because it was not one of this pilot study's main aims.

The qualitative data that were obtained through the perception questionnaire was coded by two independent reviewers using NVivo 12 (211), and a thematic analytic approach was used in the analysis.

8.4 Results

By the time the study had to be terminated due to the COVID-19 pandemic, 12 patients had been invited to participate, of whom 4 declined and 8 consented, resulting in a recruitment rate of 66.7%. Of the 8 participants, only 3 screened positive (for baseline biases) and were randomised. All three were assigned to the co-designed intervention. These three participants were men aged 50–63 years, and of Singaporean nationality.

Two were Indians, and one was Muslim. All participants had at least a secondary education. All three participants were unemployed, but none completed the planned intervention, resulting in a 100% attrition rate. The greatest number of sessions completed was three out of the five planned sessions. No attritions were due to intervention-related issues. Table 8.2 provides an overview of the changes in the participants' attentional bias scores across the interventions.

Table 8.2 Changes in Attentional Bias Scores

Participants	Baseline Attentional Biases	Allocation	Session 1	Session 2	Session 3	Session 4	Session 5	Change in Attention Bias
Participant 001	0.536082	Co-designed Intervention	-6.97431	-59.8966	-49.4018	NA	NA	49.9
Participant 002	359.2321	Co-designed Intervention	-142.969	NA*	NA	NA	NA	502.2
Participant 003	-6.-00809	Not assigned	NA	NA	NA	NA	NA	NA
Participant 004	-4.92036	Not assigned	NA	NA	NA	NA	NA	NA
Participant 005	-1.80491	Not assigned	NA	NA	NA	NA	NA	NA
Participant 006	-76.3426	Not assigned	NA	NA	NA	NA	NA	NA
Participant 007	10.7233	Co-designed intervention	7.03111	-139.731	NA	NA	NA	150.45
Participant 008	-2.0513	Not assigned	NA	NA	NA	NA	NA	NA

Footnotes: NA* Attentional biases could not be computed in view of the high percentage of errors in the task.

8.5 Discussion

This pilot study was developed based on the previous feasibility study. The aim of the pilot study was to address the issues identified earlier and ensure the success of the definitive randomized trial. Unfortunately, due to the COVID-19 pandemic, the pilot study was terminated prematurely after four months as the NAMS inpatient unit was repurposed as a medical facility. Although COVID-19-related restrictions were later eased, we could not conduct further recruitment due to the cessation of the rehabilitation phase of the inpatient program and the expiration of the funding. Given the small sample size of the recruited participants, we conducted a post-implementation risk assessment to better understand the likelihood of the risks that impacted the study. This risk assessment is critical as it enables us to determine whether further studies are required to test our different methods of conducting the study to mitigate any identified risks.

Table 8.3 Overview of the risk scores for each of the potential risks and potential steps to mitigate risks.

Category	Risk	Probability	Consequences	Risk Score (Probability X Consequence)	Steps to mitigate against these risks (for the definitive study)
Research Team	Insufficient staff	1	1	1	Consider recruiting an experienced research fellow to guide/supervise the research assistants
	Lack of research skills	1	1	1	Consider recruiting an experienced research fellow to guide/supervise the research assistants
Participants	Poor participant recruitment	5	5	25	Allow more time for recruitment Have translated versions of the informed consent form to recruit non-English-speaking participants Conduct the study when normal work processes/admission to ward is restored, and not during exceptional circumstances
	High participant attrition	5	5	25	Consider a reduction in the number of sessions that participants need to undertake. Consider whether it is possible to have an intervention before the patient get started on their treatment, and whether it is possible to get patients started earlier, even when they are undergoing detoxification (keeping in mind that only participants who have recovered well and presenting with low scores on the withdrawal scales ought to be recruited)
Resources	Lack/loss of suitable facilities	3	3	9	The planned study could only be conducted in normal circumstances
	Insufficient Funding	5	5	25	A longer funding period (at least 3 years) should be applied for
Research Methods and Processes	Exceptional or unexpected delays	5	5	25	The study should be suspended during exceptional circumstances and resumed once the situation is over
	Research methods and process not adequately documented	1	1	1	No additional risk mitigation strategies
	Loss of data	1	1	1	No additional risk mitigation strategies
	Findings have little impact	3	3	25	Findings would have a larger impact with improved recruitment rates

Footnotes: Probability: Ranked on a Likert Scale of 5-Likely, 3-Possible, 1-Unlikely; Consequences: 5-Major, 3-Moderate, 1-Minor

The risk assessment clearly indicates that participant recruitment and retention, funding, exceptional/unexpected delays, and the implications of the findings are significant risks. The small sample size recruited over four months may be attributed to several factors. Firstly, most patients with opioid use disorder admitted to the ward stayed only until the completion of their inpatient detoxification treatment. According to data from NAMS, only 17.5% of patients progressed from detoxification to the rehabilitation phase. Secondly, recruitment was complicated due to the strict inclusion/exclusion criteria. Participants with a history of seizures or migraines triggered by flashing lights were excluded because the rapid presentation of stimulus images might trigger a relapse (52), while those with moderate to severe psychiatric comorbidities were also excluded due to the potential impact of other psychiatric disorders on their performance on reaction-time-based tasks. Thirdly, recruiting participants in their sixth or higher decade was challenging due to their limited education (none or primary educational levels) and lack of English proficiency. Poor recruitment rates may also have been influenced by the onset of the COVID-19 pandemic, resulting in fewer individuals seeking elective admissions, or various COVID-19 restrictions limiting access to healthcare facilities. The eventual cessation of inpatient services has also made recruitment difficult, and recruitment on other psychiatric wards was not feasible as patients had to complete detoxification and enrol in a rehabilitation program. This pilot study protocol could only be executed in normal circumstances, as evidenced by the completion of the previous feasibility study, and not under such exceptional circumstances. Lastly, another potential factor that may have limited recruitment rates and subsequent randomization of patients may be related to how baseline attentional biases are computed and detected. In the subsequent chapter (Chapter 9), an overview of a new method of computing attentional biases and the supporting evidence for this new method will be presented.

Adjustments to the definitive study's methods are necessary, considering the likelihood and consequences of participant recruitment and attrition and unexpected delays. Further investigation is needed to resolve issues related to patient recruitment and attrition from the study. For the definitive study, more time is required for recruitment, and sample size calculation needs to consider the percentage of individuals with positive baseline bias and attrition rates from planned interventions. To cater to eligible

participants previously excluded due to difficulties comprehending English, translated versions of the informed consent form and questionnaires might be necessary. The inclusion criteria could be adjusted to consider patients with other psychiatric comorbidities who are clinically stable. Dual diagnosis is common among individuals with addictive disorders (Buckley et al.) (238), making it difficult to identify individuals without other psychiatric comorbidities. Prior research has administered approach bias modification interventions to individuals in the detoxification phase (Manning et al.) (52). Changing the intervention timing to the detoxification phase might improve recruitment rates and reduce attrition.

Considering the unique approach in NAMS regarding the treatment of individuals undergoing detoxification, it is possible that patients at NAMS experience more withdrawal symptoms, making them more lethargic during the detoxification phase. Low dosages of benzodiazepines are prescribed to ease their symptoms, which may affect their performance on the reaction-based task. Patients in acute detoxification should not participate in the study, as recommended by patient participants, who opined that the presentation of substance cues might trigger participants in acute recovery. However, one potential way to boost recruitment while considering the state of patients during detoxification might be to administer a single session of bias modification before or just after admission. In those circumstances, patients are free from any psychotropic medications that might affect their overall magnitude of attentional biases. They would also have support from the multidisciplinary team should they present with intense cravings. Another consideration might be to have participants who have recovered well (during the detoxification phase and presenting with no or low levels of withdrawals) undertake the bias retraining task earlier, rather than waiting for them to progress to the rehabilitation phase. Doing so may extend the study to other sites in the hospital where patients might seek treatment, such as emergency services and other inpatient units. With the onset of COVID-19 and the exigencies of services, it will be increasingly difficult to have patients stay on and complete the rehabilitation program. Therefore, it is wise to reconsider the approach of recruiting patients who have recovered well during the detoxification phase.

Regarding funding, this pilot study was not completed due to the expiration of funding. The ALIVE Serious Game Grant originally supported this pilot study. Two separate extension rounds for the grant were applied for, one to allow for more time due to delays

in the conduct of feasibility study due to ethical issues, and the other due to the COVID-19 pandemic. Unfortunately, because of the prolonged nature of the pandemic, the study was terminated as the grant body could not fund beyond six months. In future research, it is necessary to consider a more flexible period of funding.

Regarding the findings, it may appear that this study had a limited impact. However, the study's findings should be viewed in conjunction with its planned objectives. As previously stated, the objectives were to refine the processes of the definitive pilot study. Due to limited recruitment, this study's objectives realistically highlighted several issues that have impacted the study's processes during normal and extraordinary circumstances. The study's conduct and findings are consistent with the MRC's guidelines on complex interventions (239). Without this study, a more definitive randomized trial would have been conducted, which would likely fail and waste scientific and financial resources. The risk assessment also indicates that further studies are necessary to test our alternatives to the existing methodology to ensure the eventual success of the planned definitive randomized controlled trial.

I decided to compare the new co-designed intervention with that of the conventional attention bias modification intervention instead of having a placebo or sham comparative component for several reasons. The decision to include the mobile attention bias intervention as a comparator was based on the findings of the feasibility study, which demonstrated the mobile app's ability to reduce biases among those with baseline attentional bias. Another consideration against placebo training was to avoid potential practice effects, given that participants randomised to placebo training typically complete repeated measures of the attention bias assessment task, which would affect their reaction time when administered the attention bias assessment task following the completion of the intervention. Not including sham training as a comparator was motivated by recent evidence that sham training does not imply no training. Studies by Cristea et al., Blackwell et al. and Kokoschke et al. reported a lack of significant differences between experimental and control groups, with both improving following intervention, leading to the proposal that 'sham' training is not inherently inert or neutral (240-242). Boffo et al. postulated that the presence of substance cues might (regardless of the contingency of the presentation) result in

participants becoming less sensitive over time (243). With the emerging evidence, it makes sense to compare the new co-designed intervention against the conventional intervention to determine superiority.

The pilot study used simple randomisation to assign participants to the conventional or co-designed intervention. There were limitations to this randomisation method, given that the initial participants (all 3 of those with baseline biases) were all randomised to undergo the co-designed intervention. Nevertheless, block randomisation is preferable for avoiding unbalanced groups should the study stop prematurely and will be used in the definitive trial. Block randomisation involves randomly assigning participants equally within small blocks so that an equal number of participants are allocated to each treatment arm (243). Thus, if a block size of 4 is used, 2 participants will be allocated to A and 2 to B (A, conventional intervention; B, co-designed intervention). An example of the random permuted blocks for allocation are that of ABBA and BABA. This allows for participant allocation through the random selection of the ordering and assignment of the next block of participants to the intervention arms following the specified sequence (244).

8.6 Conclusions

Although I could not complete this pilot study, it has allowed the identification of potential risks that might threaten the definitive randomised trial. It is now necessary to conduct additional studies to refine the intended method.

Chapter 9 Attention Bias Computation and Variability

This chapter presents a new computational method for calculating attentional biases, with an overview of the Trial-level Bias Score (TLBS) method in Section 9.2. Section 9.3 compares our application of the TLBS method with the mean bias method. In Section 9.4, I explain the rationale for using this new method, and Section 9.5 provides an overview of the published literature that has used the TLBS method to date. Section 9.6 presents data from an additional study comparing the TLBS and mean bias score method. Finally, this chapter concludes by discussing potential applications of this method in future studies.

9.1 Introduction

The pilot study described in Chapter 8 was planned and conducted until the COVID-19 pandemic caused the inpatient unit for addiction treatment to close, and the study to be suspended. This pilot study uncovered issues that could affect future definitive randomized trial. However, even after the relaxation of the COVID-19 measures, this study could not be resumed. The inpatient detoxification and rehabilitation program remained closed and was repurposed as a medical facility for COVID-19 patients. From January to February 2022, the inpatient program briefly reopened, but the emergence of Omicron variant led to its cessation once again. The gradual resumption of the service started in April 2022, beginning with medication-assisted detoxification, and later, rehabilitation. However, this resumption has been partial due to repeated COVID-19 waves and bed availability issues, which will be discussed in Chapter 10.

Although the pilot study was not completed, its findings have had a significant impact on the development of this dissertation. As indicated by the title, the focus of this work is to develop a practical approach for creating a mobile attention bias modification intervention that can complement conventional psychotherapies for our patients. Following the completion of the study (Chapter 8), a risk assessment identified three risk factors: (a) participant recruitment and retention, (b) unexpected or exceptional delays, and (c) the impact of the findings. One issue that affected participant recruitment was whether the individuals had a baseline bias. In the feasibility and acceptability study, 53.5% of the participants (16 of 30) did not present baseline biases. Similarly, of the eight participants recruited for the pilot study, five (62.5%) did not present baseline

attentional biases. In Chapter 8, several reasons were suggested for the absence of baseline biases, such as (a) psychotropic medications administered during detoxification treatment potentially reducing the magnitude of baseline bias; (b) the effectiveness of medication-assisted detoxification in reducing the baseline bias; (c) stimulus images not capturing attentional biases; and (d) issues related to the visual probe/dot-probe task paradigm, such as stimulus presentation duration. Although these reasons may account for the lack of baseline biases, further research (Kruijt et al., 244) has highlighted that mean bias scores could lead to difficulties in detection. Recent studies have demonstrated the variability of attentional biases, indicating that mean bias scores assume that attentional bias is a static trait (244).

The objectives of this chapter are threefold. Firstly, recent research advancements in understanding attentional biases and their computation are presented. Secondly, the application of a new computational method to data from previous feasibility and pilot studies is explored to determine its efficacy in detecting underlying attentional biases. Finally, a comparison will be made between the TLBS and mean bias methods in a group of patients recruited at NAMS with opioid or alcohol disorders to investigate potential differences in baseline results. The chapter concludes with a discussion of the potential applications of the TLBS method in future studies.

9.2 Trial-Level Bias Scores

9.2.1 Overview of Trial-Level Bias Score (TLBS)

The negative baseline biases observed in my feasibility and pilot study may be attributed to the computation of attentional biases. According to Zvielli et al. (245), attentional bias research faces several issues, including poor split-half and test-retest reliability of the most used assessment tool, the visual probe task. This affects the detection of interventional effects of attentional bias modification. In addition, the conventional method of computing mean bias scores assumes that attention biases are static in nature, despite recent studies demonstrating variation over time and across trials (Zvielli et al., 245). In their research on individuals with anxiety disorder, Zvielli et al. found that anxious individuals exhibited different patterns of attentional biases towards threatening stimuli, with some expressing biases towards, away, both, and none

(245). The authors challenged the traditional view that attentional biases are static, emphasizing the variability in attentional biases within the same individual. The conventional method of computing attention bias, by subtracting the mean reaction time of congruent trials from incongruent trials, is inaccurate and unrepresentative of how attention bias varies throughout the different trials in the intervention if there is variability in attentional biases. Zvielli et al. proposed a new method that considers the inherent variability of attentional biases, where trial-level bias scores (TL-BS) are computed by subtracting the reaction time of temporally contiguous pairs of congruent and incongruent trials (245). This method generates a time series of the TL-BS for each participant by matching each individual trial with a congruent trial that is temporally as close as possible and no further than five trials away, either before or after (245). Zvielli et al. explained that attentional biases may be expressed as fluctuating phasic bursts towards or away from target stimuli over time, and this new method better captures this variability (245).

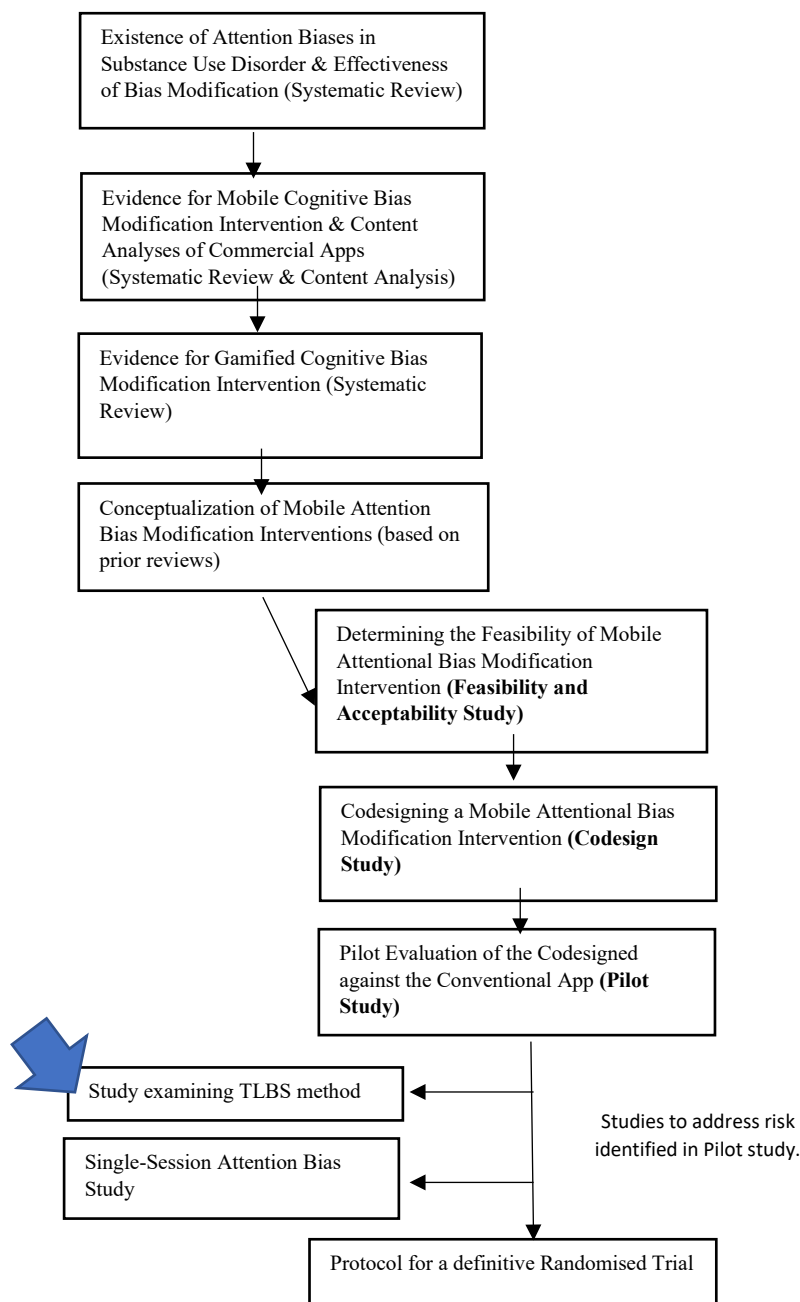
9.2.2 Research Evidence for TLBS

The TLBS method was applied in two experiments, one involving spider phobia (arachnophobia) participants and the other involving smoking participants (245). The results showed phasic variation in the differential allocation of attention among smokers, with attention bias towards and away from smoking images (245). The new method also demonstrated improved reliability compared with the traditional method. Evans et al. applied the TLBS method and reported uniformly higher levels of internal consistency and improvements in test-retest reliability, and the ability to differentiate the temporal nature of attentional bias (246). Gade et al. examined participants with social anxiety disorders and controls using a dot-probe task and reported that the TLBS method showed a higher mean attentional bias towards the threat than the conventional method (247). They also found that TLBS scoring was more sensitive in detecting underlying attentional biases and more accurate in reflecting the underlying psychopathology of social anxiety disorder, even when the mean bias method yielded negative findings.

9.3 Application of TLBS in the computation of Baseline Biases from Prior Studies

With evidence to support the increased reliability of TLBS over the conventional mean bias score and its potential to detect baseline biases, I reanalysed data from the previously completed feasibility and acceptability study (Chapter 6) and the pilot study (Chapter 8). Figure 9.1 presents an overview of the studies included in this PhD dissertation, and how the findings of this chapter integrate with the entire dissertation.

Figure 9.1 Overview of studies included in this PhD dissertation and how this chapter is relevant.



Footnote: The blue arrow signifies the integration process of this chapter

9.3.1 Re-computation of Data from the Feasibility and Acceptability Study

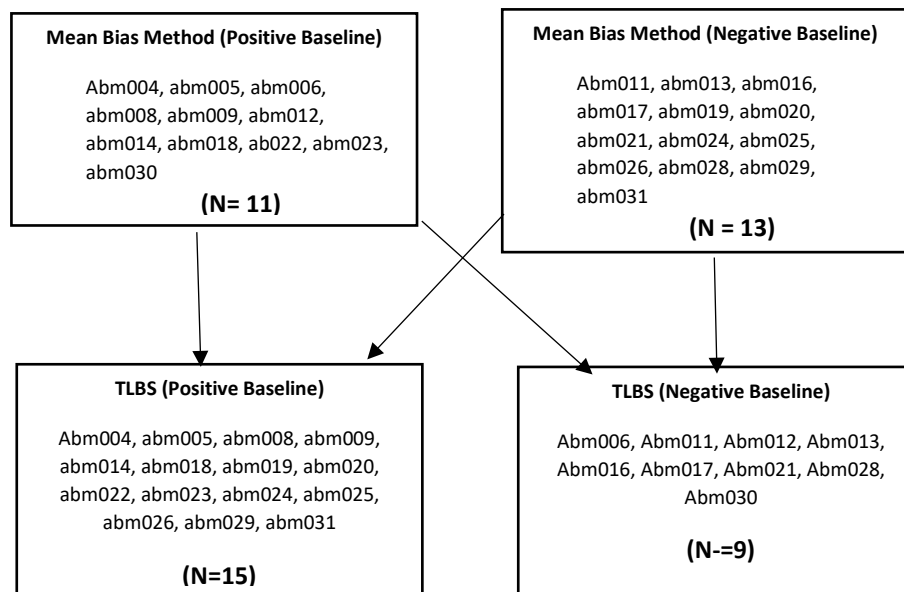
I applied the TLBS method to the feasibility study dataset that included individuals reporting opioid or alcohol use, as these are the target populations for our future studies. To calculate the TLBS score, each congruent trial was paired with the nearest incongruent trial within a five-trial distance (245). The difference between each identified pair was computed to obtain the TLBS score (245). The TLBS variability was computed by summing the distances between all sequential TLBS scores and dividing by the total number of TLBS scores.

The conventional method for computing attentional bias involved calculating the mean reaction time for congruent and incongruent trials. Participants with attention bias would respond faster to probes in the location of the substance stimulus than neutral stimuli, indicating a bias towards the substance stimulus. The traditional formula for bias computation was $(\sum T_1/n_1) - (\sum T_0/n_0)$, where T_1 referred to the time for the probe replacing the neutral image, n_1 referred to the number of neutral trials, T_0 referred to the time for the probe replacing the substance image, and n_0 referred to the number of substance trials.

TLBS was applied to 24 participants with alcohol or opioid issues, and positive baseline biases were detected in 15 participants. However, three participants showed a reversal in the direction of biases, with positive baseline biases detected by the mean bias score method and negative biases detected by TLBS. Table 9.1 summarizes these findings, and Figure 9.2 provides a visual representation of the changes in the baseline biases between the two methods.

Table 9.1. Comparison of two methods of computing baseline attentional biases using data from the feasibility and acceptability Study

Participant / Substance Use	Baseline AB (TLBS Method) (msec)	Original Baseline AB (msec)	Interpretation
004 (Opioids)	29.2	32.1	Positive Baseline remained
005 (Alcohol)	55.3	91.2	Positive Baseline remained
006 (Opioids)	-44.2	98.8	Positive Baseline (old method), Negative Baseline (TLBS)
008 (Opioids)	224.2	58.7	Positive Baseline remained
009 (Opioids)	13.7	25.7	Positive Baseline remained
011 (Opioids)	-142.8	-30.9	Negative Baseline remained
012 (Opioids)	-6.2	0.7	Positive Baseline (old method), Negative Baseline (TLBS)
013 (Alcohol)	-84.0	-20.9	Negative Baseline remained
014 (Alcohol)	243.1	397.7	Positive Baseline remained
016 (Opioids)	-17.9	-27.3	Negative Baseline remained
017 (Opioids)	-23.8	-42.5	Negative Baseline remained
018 (Alcohol)	25.7	27.9	Positive Baseline remained
019 (Opioids)	2.9	-3.8	Negative Baseline (Old method), Positive Baseline (TLBS)
020 (Opioids)	15.6	-10.1	Negative Baseline (Old method), Positive Baseline (TLBS)
021 (Alcohol)	-222.7	-224.4	Negative Baseline remained
022 (Opioids)	21.8	52.9	Positive Baseline remained
023 (Opioids)	8.5	36.4	Positive Baseline remained
024 (Opioids)	2.4	-16.9	Negative Baseline (Old method), Positive Baseline (TLBS)
025 (Opioids)	47.6	-12.8	Negative Baseline (Old method), Positive Baseline (TLBS)
026 (Opioids)	74.6	-77.1	Negative Baseline (Old method), Positive Baseline (TLBS)
028 (Alcohol)	-38.6	-33.3	Negative Baseline remained
029 (Alcohol)	15.9	-41.4	Negative Baseline (Old method), Positive Baseline (TLBS)
030 (Opioids)	-31.4	1.33	Positive Baseline (old method), Negative Baseline (TLBS)
031 (Opioids)	10.7	-38.4	Negative Baseline (Old method), Positive Baseline (TLBS)

Figure 9.2 Changes in baseline scores for the participants recruited into the Feasibility study.

9.3.2 Re-computation of Data from the Pilot Study

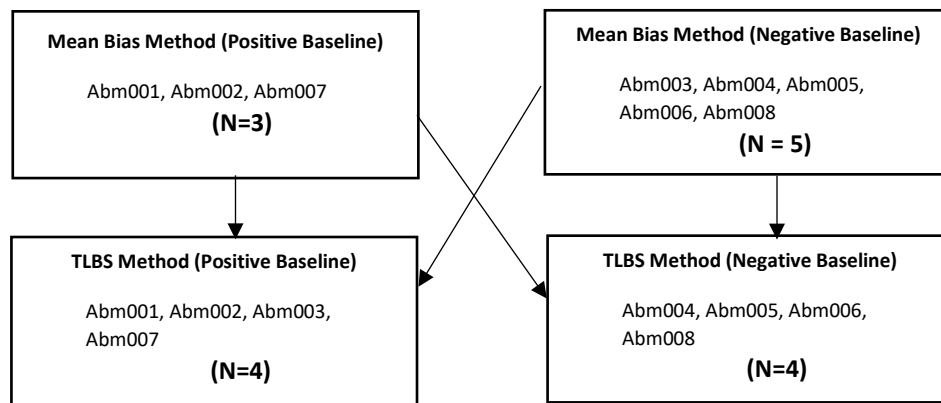
The second analysis used data from the pilot study that was disrupted by the COVID-19 pandemic. Baseline attentional biases for all participants in the pilot study were recalculated and compared to the mean bias score. Table 9.2 presents the scores, individual allocations, and how the new scores would affect the original allocation. The conventional mean bias score method could only assign three out of eight (37.5%) participants, whereas the new method allowed for four out of eight (50%) participants to be assigned to different treatment allocations. Ultimately, only one of the eight participants could be reassigned based on the findings of the new computational method. Figure 9.3 provides a visual representation of the changes in baseline biases between the two methods.

Table 9.2 Comparison of two methods of computing baseline attentional biases using data from the pilot study

Participant	Baseline AB (Recomputed) (msecs)	Original Baseline AB (msecs)	Allocation	Implications
001	32.03	0.536	Codesigned	Already assigned
002	56.06	359.23	Codesigned	Already assigned
003	47.14	-6.81	Not assigned	Can be assigned
004	-13.59	-4.92	Not assigned	Cannot be assigned
005	-27.85	-1.8	Not assigned	Cannot be assigned
006	-79.14	-76.3	Not assigned	Cannot be assigned
007	31.16	10.72	Codesigned	Already assigned
008	-2.25	-2.0513	Not assigned	Cannot be assigned

Footnote: AB: Attention Bias. Co-designed: Refers to the allocation to receiving the co- designed version of a mobile attention bias modification intervention.

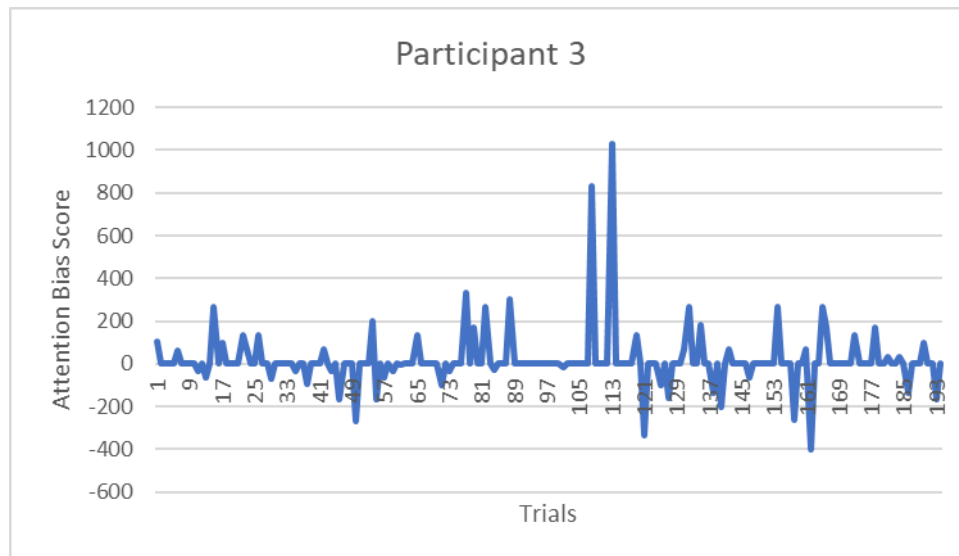
Figure 9.3 Changes in baseline scores for the participants recruited into the Pilot study.



9.3.3 Variability in Attention Biases

The TL-BS method demonstrates that attentional biases are unstable traits and can vary over time. Figure 9.4 illustrates the variability of TL-BS scores for the entire task for participant 003 (from the pilot study). The participant's baseline bias, previously calculated using the mean bias score, was negative (-6.81 milliseconds), but when the TL-BS was applied, the new baseline bias was found to be positive (47.14 milliseconds). This figure supports the notion that attentional bias is dynamic and not static.

Figure 9.4. Variation in Attention Bias across trials included in the baseline attention bias assessment.



9.4. Further Studies examining Trial-Level Bias Scores

Since the initial studies published by Zvielli et al. (2015) (245), there have been publication of other studies examining TLBS. A summary of the main findings of these studies are tabulated in Table 9.3.

Table 9.3. Summary of the main findings of studies investigating TLBS

Authors & Year of Publication	Sampled Condition	Characteristics of Sample and Nature of Visual Probe Task	Main Findings
Carlson et al. (2019) (248)	Not specified	106 undergraduates aged 18 to 39 years old. Fearful or Happy face dot-probe task	This study illustrates the temporal dynamics of attentional biases, which were observed to be the most pronounced at the longest SOA, more prominent in females than males, and unaffected by stimulus valence.
Mazidi et al. (2019) (249)	Post-traumatic stress symptoms	54 veterans (mean age 51.44 years) and 30 controls (mean age 49.17) Modified version of dot-probe task with painful, happy, and neutral facial expressions	Veterans showed attentional biases away from painful facial expressions. They also exhibited higher variability in attentional biases towards both happy and painful facial expressions, which was found to be associated with post-traumatic stress symptoms.
Clarke et al. (2020) (250)	Anxiety	195 undergraduate students with a mean age that of 22.64 Attentional probe task with stimulus subset comprising of 24 negative and 24 neutral words	Attention bias variability was associated with anxiety and attentional control.
Molly et al. (2022) (251)	Social anxiety disorder	56 adults Facial dot probe task	TLBS, including mean bias towards threat and attention bias variability, demonstrated high reliability.
Yang et al. (2022) (252)	Smoking	48 participants with mean age of 33.96 Modified dot probe task presenting smoking images	TLBS showed higher internal consistency and test-retest reliability compared to the mean bias score, indicating its superiority as a measure of attention biases.

Footnotes: SOA: Stimulus Onset Asynchrony

These findings provide evidence of the temporal variation in attentional biases and their association with anxiety and post-traumatic symptoms. Recent studies have shown that the TLBS is a more reliable measure of attentional biases than the mean-bias score (251,252). While TLBS has primarily been investigated in anxiety and addictive

disorders (limited to smoking disorders), there has been no investigation of this method in individuals with opioid and alcohol use disorders (250-252). The application of this new method could potentially improve the identification and characterization of biases in these individuals.

9.5 Comparison of TLBS and Mean bias Computational Methods in Individuals with Addictive Disorders presenting at NAMS

This chapter primarily focuses on the evidence and updates regarding TLBS. Earlier, TLBS scoring was found to potentially improve the identification of baseline biases through a secondary analysis of data from a previous feasibility study. In a similar fashion, I compared TLBS with the mean bias method in a new study conducted at NAMS in 2022, to determine whether it can detect more individuals with baseline biases.

9.5.1 Study design and Setting

The study utilised a cross-sectional design, with participants screened for baseline attentional biases using two computational methods: mean bias and trial-level bias scores. Positive screens on the trial-level bias score underwent a single session of bias modification, and post-modification re-assessment of attentional biases. Recruitment for the study was conducted at specialist outpatient clinics of the National Addictions Management Service, Institute of Mental Health in Singapore. Participants scheduled for inpatient admission were able to participate in the study during their ward stay if there was insufficient time before their admission at the clinics.

9.5.2 Inclusion and Exclusion Criteria

All participants who expressed interest in the study were screened to determine baseline attention biases. Participants were asked to undertake an attention bias assessment task (based on the visual probe task, as described under “Experimental Procedure”). Attention bias was deemed present if the TLBS score was positive. Those with positive baseline biases were recruited into the study if they satisfied the following inclusion criteria: (a) they had a primary diagnosis of Opioid or Alcohol Use disorder and were primarily using opioids or alcohol on presentation; (b) for individuals diagnosed with polysubstance dependence, their primary drug of abuse was either an opioid or alcohol; (c) if they were diagnosed with a co-morbid psychiatric disorder, they were assessed to

be clinically stable; (d) they could comprehend and read English and; (e) they were aged between 21 and 70 years old. Participants were ineligible for the study if (a) their primary substance of abuse was not opioids or alcohol; (b) they were assessed to have a severe psychiatric condition (such as psychosis, intellectual disability, or dementia) and were clinically unstable; (c) they had an underlying history of seizures or migraines triggered by flashing lights.

9.5.3 Experimental Procedure

Informed consent was obtained from all participants. All the participants completed an attention bias assessment task. Two variants of the task existed, depending on whether they were diagnosed with opioid or alcohol use disorder. For opioid use disorder, in the assessment task, a fixation cross appeared at the centre of the screen for 500 milliseconds. A set of images was then presented, half of which (100 sets of images) were presented for 200 milliseconds, and the other half presented for 2 seconds. This stimulus timing was selected based on the evidence review by Zhang et al. (253), which suggests that the presentation of two stimulus timings in individuals with opioid use, enables the measurement of initial orientation and delayed disengagement. The set of images comprised a substance image and a neutral image, both matched in terms of colour, size, and complexity. The substance images were obtained from Singapore's Central Narcotics Bureau. Some of the images were also the top-rated images participants chosen in the previous co-design study conducted by Zhang et al. (2018) (234). Following the images, a probe (in the form of an asterisk) would appear, in the position of either the substance or the neutral image, for 200 milliseconds. Participants were required to indicate the position of the probe by selecting either the left or the right button on the screen. In this assessment task, the probe would replace the substance image 50% of the time and the neutral image the other 50%. Therefore, participants needed to complete 200 repetitions. There would be 10 sets of images, which will be repeated 20 times across the 200 trials.

For alcohol use disorder, the task parameters are as per the baseline assessment task for alcohol use disorder, except that the pair of substance and neutral images were presented at only one interval: 500 milliseconds (253). The decision to present images at only one stimulus interval was guided by Field et al. (2010)'s research, as 500 milliseconds was the most common stimulus presentation interval for individuals with

alcohol use (80). In addition, the substance images were localised images of commonly available alcoholic beverages in Singapore. Likewise, some of these images were also the top-rated images that participants chose in the previous co-design study.

The baseline attentional biases were computed using the (a) mean bias score method and (b) the TLBS methods. Only participants who screened positive, by means of the TLBS method, were recruited for the rest of the study (which will not be described in this context, as this paper focuses on the comparison between the computational methods).

9.5.4 Assessment methods for Comparison

The computational methods are described in section 9.3.1.

9.5.5 Sample Size

As this was a cross-sectional feasibility study, the projected number of participants recruited was 30, which was similar to that of the previously completed feasibility and acceptability study.

9.5.6 Ethics

The protocol for this study was approved by the National Healthcare Group Domain Specific Research Board (DSRB Reference Number: 2022/00100).

9.5.7 Results

Of the 49 invited participants, 26 participated while the remaining 23 declined. Of these, 18 (69%) actively used opioids (heroin, codeine, or other opioids), and 8 (31%) actively used alcohol. Both the TLBS and mean bias methods detected positive baseline biases in 46% of the participants, although the TLBS method identified 3 patients with positive biases who were missed by the mean bias method. Figure 9.5 presents a graphical representation of the baseline biases computed by both methods, while Table 9.4 provides an overview of the baseline bias scores. This study focused on the impact of computational methods on baseline scores, and therefore, the changes in biases following interventions will not be discussed in this article.

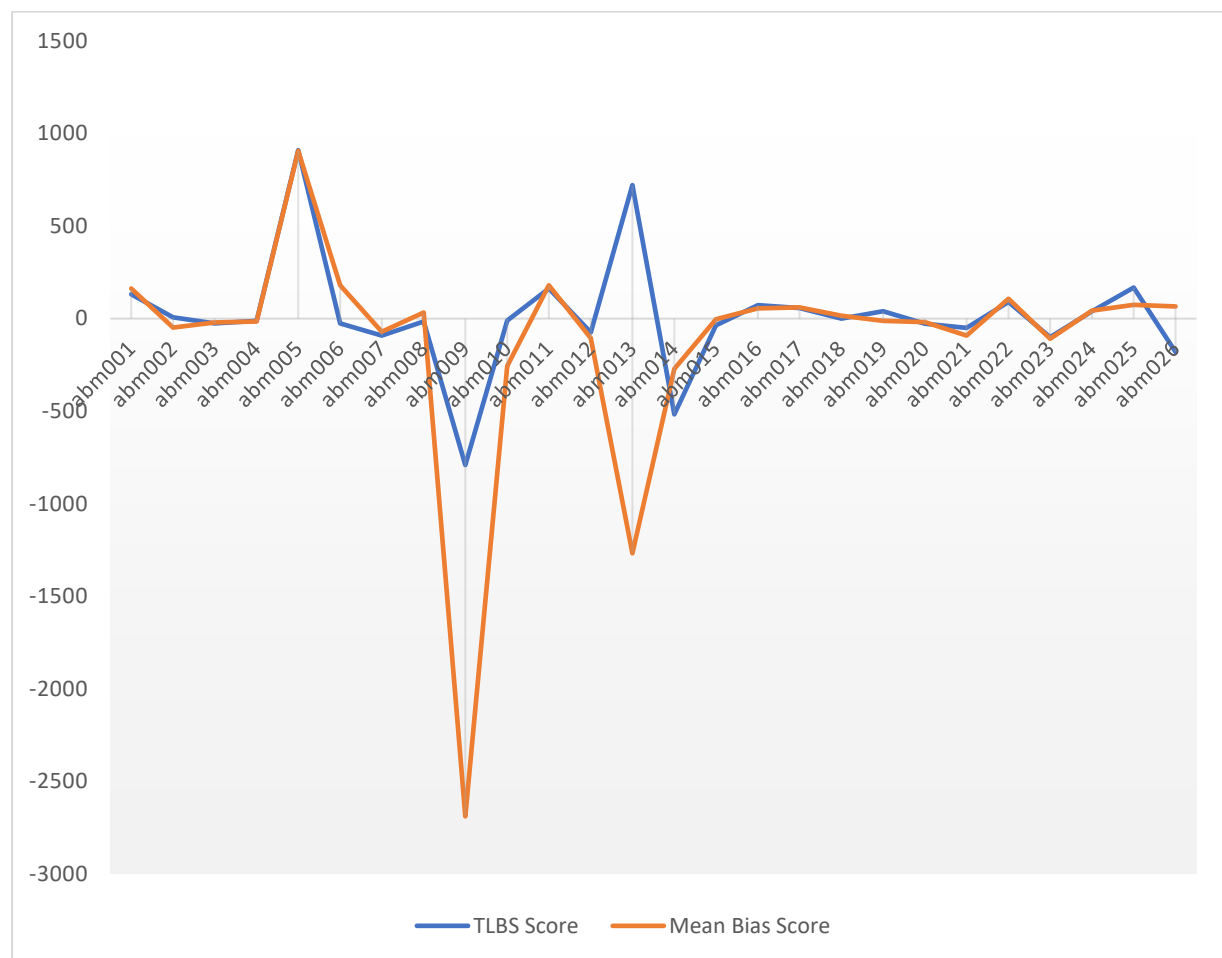
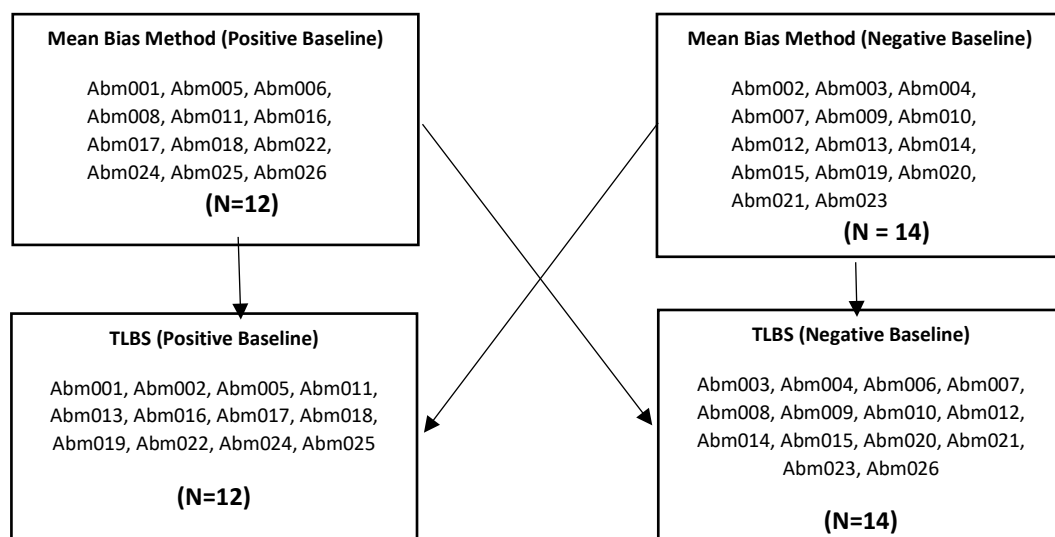
Figure 9.5 Baseline biases as computed by the TLBS and Mean Bias Methods

Table 9.4. Baseline attention bias scores by the TL-BS and Mean Bias Methods

Participant	Drug	Baseline AB score and related TL-BS variables (msecs)	Baseline AB (mean bias method) (msecs)
abm001	Opioids	TL-BS/AB: 131.49 TL-BS(t): 355.95 TL-BS(a): -444.47	163
abm002	Opioids	TL-BS/AB: 6.16 TL-BS(t): 74.47 TL-BS(a): -166.17	-49.08
abm003	Opioids	TL-BS/AB: -25.32 TL-BS(t): 58.96 TL-BS(a): -298.64	-20.34
abm004	Opioids	TL-BS/AB: -12.36 TL-BS(t): 118.95 TL-BS(a): -200.42	-15.42
abm005	Opioids	TL-BS/AB: 909.85 TL-BS(t): 1593.59 TL-BS(a): -493.63	906.04
abm006	Opioids	TL-BS/AB: -25.59 TL-BS(t): 558.35 TL-BS(a): -1070.53	180.36
abm007	Alcohol	TL-BS/AB: -91.19 TL-BS(t): 56.5 TL-BS(a): -438.71	-70.48
abm008	Opioids	TL-BS/AB: -16.14 TL-BS(t): 136.7895 TL-BS(a): -339	33.51
abm009	Alcohol	TL-BS/AB: -791 TL-BS(t): 0 TL-BS(a): -791	-2868.55
abm010	Opioids	TL-BS/AB: -10.27 TL-BS(t): 492.40 TL-BS(a): -779.70	-255.34
abm011	Opioids	TL-BS/AB: 161.97 TL-BS(t): 459.36 TL-BS(a): -815.21	179.56
abm012	Opioids	TL-BS/AB: -74.73 TL-BS(t): 105.29 TL-BS(a): -514.78	-105.01
abm013	Opioids	TL-BS/AB: 720.38 TL-BS(t): 2608.42 TL-BS(a): -2111.69	-1267.64
abm014	Opioids	TL-BS/AB: -516.92 TL-BS(t): 452 TL-BS(a): -1174.39	-271.85
abm015	Alcohol	TL-BS/AB: -35.42 TL-BS(t): 106.72 TL-BS(a): -200.48	-3.99
abm016	Opioids	TL-BS/AB: 73.33 TL-BS(t): 147.30 TL-BS(a): -500.43	55.10
abm017	Opioids	TL-BS/AB: 56.5 TL-BS(t): 297.54 TL-BS(a): -295.54	60.63
Participant	Drug	Baseline AB score and related TL-BS variables (msecs)	Baseline AB (mean bias method) (msecs)

abm018	Alcohol	TL-BS/AB: 0 TL-BS(t): 140.6222 TL-BS(a): -372.235	15.0
abm019	Alcohol	TL-BS/AB: 40.61 TL-BS(t): 149.16 TL-BS(a): -347.07	-12.38
abm020	Alcohol	TL-BS/AB: -27.7 TL-BS(t): 145.29 TL-BS(a): -260.77	-18.21
abm021	Opioids	TL-BS/AB: -50.65 TL-BS(t): 589.2 TL-BS(a): -589.57	-91.53
abm022	Opioids	TL-BS/AB: 90.04 TL-BS(t): 266.36 TL-BS(a): -246.55	108.10
abm023	Alcohol	TL-BS/AB: -100.83 TL-BS(t): 160.08 TL-BS(a): -424.72	-108.43
abm024	Alcohol	TL-BS/AB: 40.22 TL-BS(t): 56.5 TL-BS(a): -135.6	42.94
abm025	Opioids	TL-BS/AB: 167.41 TL-BS(t): 1172.38 TL-BS(a): -1294.36	74.34
abm026	Opioids	TL-BS/AB: -180.19 TL-BS(t): 2011.4 TL-BS(a): -991.89	65.52

Figure 9.6 Baseline biases by the two different methods

9.6 Discussion

This study is the first to apply the TLBS method to compute baseline attentional biases in a sample of individuals using opioids or alcohol. Prior research exploring this method in substance-using samples is limited, with the most recent study examining individuals who smoke (Yang et al., 2022) (255). Our results demonstrate the feasibility of using TLBS to compute baseline biases and the method's ability to reclassify three participants with negative biases (as per the mean bias method) as having positive biases.

The results revealed four participants with positive baseline biases computed using the mean bias method; however they had negative biases or no baseline biases (i.e. scored zero) at baseline when the TLBS method was applied. Nevertheless, previous studies have demonstrated the higher reliability of the TLBS method than the mean bias method in various populations such as those with phobias, depression, obesity, alcohol use, and social anxiety disorder. For example, Molly et al. (2022) examined 56 adults with social anxiety disorder and reported that the TLBS method had the highest reliability, while Yang et al. (2022) found that the TLBS score had superior internal class correlation and test-retest reliability than the mean bias score in 48 participants with smoking disorder (255,256). The internal consistency of the TLBS indices ranged from 0.79 to 0.95 (255). However, the authors cautioned that the TLBS peak scores had relatively lower test-retest reliability than other TLBS indices, and further exploration is needed regarding their utility and implications. Therefore, the computed positive findings in my study using the mean bias method may be false positives, considering the demonstrated reliability of the TLBS method. Three patients who reported negative baseline biases using the mean-bias method presented positive baseline biases by the TLBS method; they could also be allocated as per my aforementioned reasoning. Previous studies have shown the reliability of the TLBS method in both clinical and non-clinical populations; thus, repeated assessments of its reliability parameters may not be necessary. In this study, I focused on computing the TLBS indices of variability, mean towards, and mean away scores; I did not compute the peak scores due to the lack of clarity about their implications.

Although the TLBS method has been shown to have better reliability than the mean-bias method, it has limitations, particularly in terms of external validity, general

variability, task timing, and sex differences. Yang et al. (2022) attempted to investigate the external validity of the TLBS measure but found that it was not significantly associated with either bio-behavioural or self-reported indices of smoking reinforcement (255). In this study, I tested the TLBS method's applicability in a clinical cohort of individuals with opioid and alcohol issues. However, in future studies involving this cohort, correlating the TLBS indices with objective measures would be important to test its external validity. An example of this would be the use of a visual analogue scale to examine participants' cravings.

Other researchers have noted that the computed indices of attention bias remain sensitive to the overall variation in reaction times (Krujit et al., 2016) (257). However, this study was conducted using stimulated data and was not based on a clinical or non-clinical sample. A recent publication by Carlson et al. (2022) demonstrated a high correlation between attention bias variability and general reaction time variability (258). Furthermore, the overall reliability of attention bias variability decreased when controlling for the general reaction time. However, the authors acknowledged that attention bias variability is higher in clinical cohorts. Both Krujit et al. (10) and Carlson et al. reported that other factors, such as neuroticism and cognitive control, could contribute to variability and recommended further investigation to control for this variability (257,258). Yang et al. (2022) suggested the incorporation of sufficient trials involving the presentation of only neutral stimuli to calculate general reaction time variability (255). Given these findings, future research should consider how the variability in reaction time can be corrected for when computing the TLBS. Regarding task timing and sex differences, Carlson et al. (2019) reported that the temporal dynamics of attentional biases were affected by the stimulus onset asynchrony intervals, with the temporal variation being greatest at the longest intervals, and greater in females than in males (248). Further research is necessary to investigate whether the variability and temporal dynamics are due to gender differences or whether other demographic and individual characteristics might influence them.

The novelty of this work lies in the application of the TLBS method to a substance-using population, specifically those with opioid and alcohol use. To the best of our knowledge, no previous studies have evaluated these populations using this method, and I was able to apply it to a clinical cohort of participants. Our scores have

demonstrated the variability of attentional biases, which cannot be differentiated by the mean bias score. However, our study had some limitations. I did not adjust for general variability or examine demographic and clinical variables that might have affected overall reaction time variability. Future research is needed to address these factors and refine the computational method.

9.6 Conclusions

Although recent findings from the literature (as summarized in Table 9.3), have demonstrated the better reliability of the TLBS score, in my study population, this did not result in the overall identification of more individuals with positive baseline biases. Nonetheless, I was able to confirm the feasibility of applying this more reliable method for the computation of baseline attentional biases and demonstrated that the TLBS method is not inferior, as compared to, the mean bias method. Given the emerging evidence for the superiority of the TLBS, I propose that this method should be used to examine biases in future research, characterizing and assessing changes in attentional biases of individuals with substance use disorders.

Chapter 10 Single Session Attention Bias Modification

This chapter describes the impact of the COVID-19 pandemic on the NAMS service and its effect on my PhD research. The rationale for conducting this additional study is provided in Section 10.3. Section 10.4 outlines the protocol for a single-session attention bias modification approach. The remainder of the chapter presents the study's findings. Finally, the chapter concludes by discussing the implications of these findings and their impact on the plan for the definitive randomised controlled trial.

10.1 Introduction

One of the risks identified that threatened the completion of the pilot study was the high rate of attrition. In the previously described pilot study, participants had to complete five bias retraining sessions during their week-long rehabilitation stay. The preliminary data showed that out of the three recruited participants, two dropped out after completing only one or two sessions of bias retraining. However, since the sample size was small, the findings from the previous feasibility study were also examined. Among the participants using opioids, the mean number of completed sessions was 3.5, and 25% completed fewer than 2 attention bias modification sessions.

The high attrition rates are largely attributed to the voluntary nature of the NAMS program. Participants are free to request premature discharge from the inpatient unit, and some have opted to do so after completing their inpatient detoxification and perceiving no further benefits from the rehabilitation program. Given that this doctoral thesis focuses on developing a pragmatic approach to a mobile attention bias modification intervention for individuals with addictive disorders, it makes sense to consider whether a reduced number of bias modification interventions could bring about the same changes in attentional biases. Previous research explored a single-session approach towards bias modification in alcohol and smoking disorders. Section 10.3 summarises the evidence from the literature.

As highlighted in Chapter 8, the onset of the COVID-19 pandemic resulted in the disruption of the pilot study and suspension of the NAMS service. Section 10.2

elaborates on the full impact of COVID-19 on the NAMS service and implications of COVID-19 on this body of work. Given the challenges introduced by the pandemic and the high attrition rates observed in studies conducted before the pandemic, it is necessary to reconsider the number of interventions administered.

10.2 Impact of COVID-19 on the NAMS Service and Implications on PhD Work

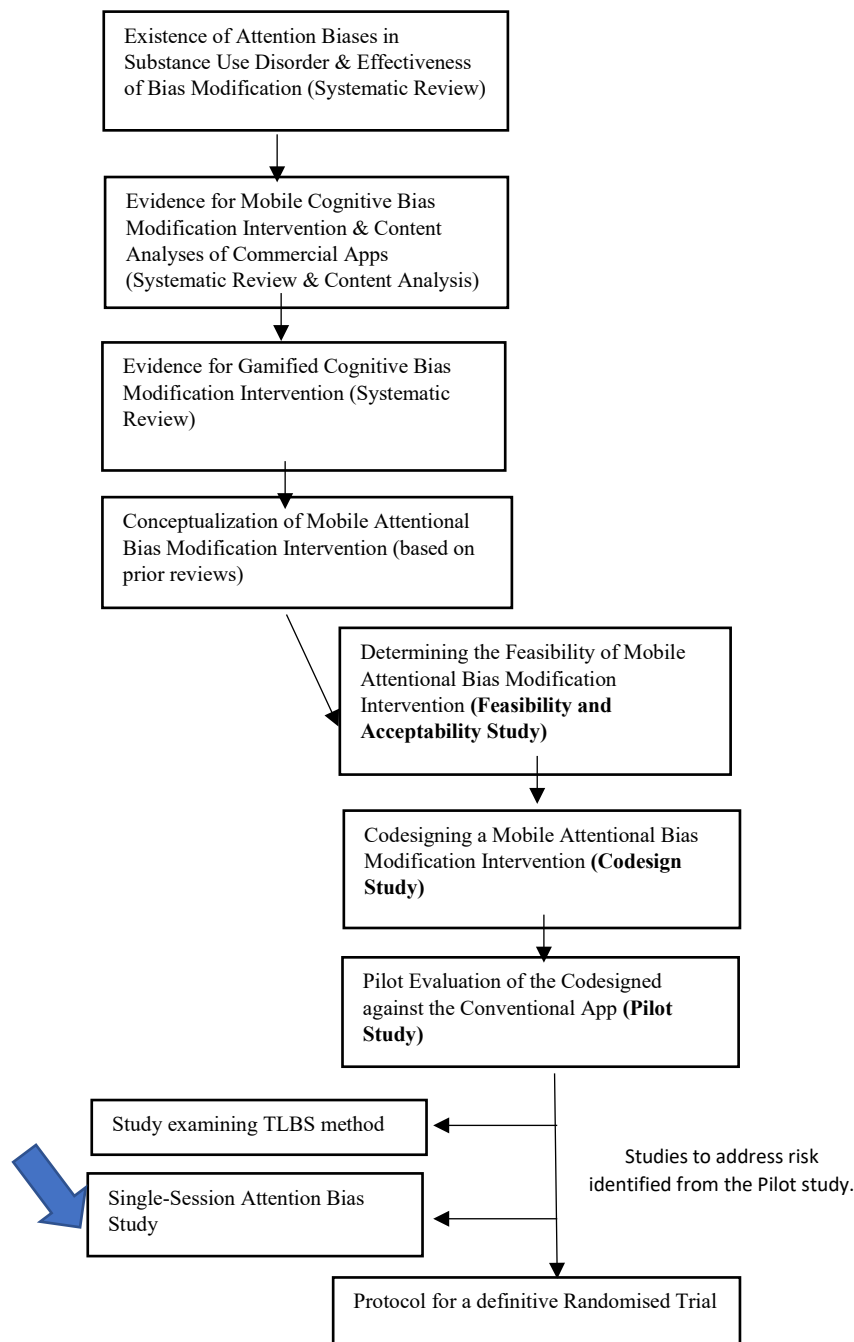
The outbreak of COVID-19 in late 2019 and early 2020 had a significant impact on the provision of services at NAMS. NAMS typically offers a week-long medication-assisted detoxification program and week-long rehabilitation program. However, due to circuit breaker measures implemented in Singapore, the inpatient program was initially modified to cater only to patients in need of medication-assisted detoxification, and all family sessions and halfway house interviews were suspended. As the pandemic progressed, the NAMS inpatient facility was converted into a medical unit for psychiatric patients. Patients requiring admission for medication-assisted detoxification were admitted to a general ward and discharged as soon as their withdrawal symptoms were controlled. These changes in service delivery had a serious impact on the pilot study, as the closure of the NAMS rehabilitation program meant that no patients were available for recruitment into the study.

The reopening of the NAMS ward was further complicated between October and November 2021 by widespread COVID-19 infections among patients and staff at the Institute of Mental Health, making it impossible to complete the previously planned pilot study (259, 260). Research funding from the LKC-NHG ALIVE Serious Game Grant expired, and it was impossible to replicate the pilot study elsewhere because the inclusion criteria required patients to have completed a rehabilitation program. In addition, COVID-19 restrictions limited the movement of the study team across different research sites, even within the hospital itself, further hindering clinical studies.

Although the NAMS ward gradually resumed operations in early 2022, resumption experienced some challenges. Compared to pre-pandemic times, the availability of beds was reduced because some beds were converted to isolation beds and others were being used to house patients with other psychiatric conditions. Currently, most patients only complete the inpatient detoxification phase, and only a minority progress to the rehabilitation stage of the program.

10.3 Mitigating Risks identified in the Pilot Study

Although COVID-19 disrupted recruitment, it also facilitated a risk assessment (as highlighted in Chapter 8), which helped identify potential risks and ways to mitigate them. Apart from the risks related to participant recruitment and retention, some were also associated with funding and unexpected delays. According to the literature, the pandemic disrupted many clinical trials worldwide, which impacted recruitment, intervention delivery, and data collection for several randomised trials (Chatters et al., 261). Some studies had to be halted because of reduced manpower, social distancing rules, and limited direct contact with participants (261). To deal with these issues, adaptations such as split remote-first eligibility assessment, implementation of remote consent and recruitment from other non-clinical sites were considered (261). Some of these adaptations required further testing to determine their feasibility and effectiveness (261). Workgroups, such as Trial Forge (262), recommended the conduct of additional studies to overcome such issues, that might affect the delivery of the intended interventions in a clinical trial. Given these, in this work, I sought to conduct additional studies to address recruitment issues (as described in Chapter 9, investigating a new TLBS method to better identify baseline biases). Furthermore, in this chapter, I have described the implementation of a single-session attention bias modification to mitigate the risks of attrition. Figure 10.1 presents an overview of the studies included in this PhD body of work, and how this chapter integrates therein.

Figure 10.1 Studies included in this PhD body of work and how this chapter integrates.

10.4 Overview of Single-Session Approach in the Literature and Implications for Current Work

To address the issue of attrition, I aimed to investigate the extent of change in attentional biases following a single session of bias retraining. Limiting participants to a single session has practical advantages, as it may be challenging for patients to repeat interventions multiple times. Prior research has examined the efficacy of a single-session approach for individuals with addictive disorders. For instance, Luehring-Jones

et al. investigated a single-session attentional bias modification among 60 young adults with drinking problems who were not seeking treatment (263). The authors found that a single session of attentional bias modification significantly altered alcohol-related attentional biases, reducing the reaction time to respond to an alcohol incongruence condition (263). Similarly, the effectiveness of single-session bias modification has been documented for other conditions, such as anxiety disorders. Salemkink et al. (264) attempted to determine whether a single session of cognitive bias modification for interpretations would reduce alcohol-related interpretations of negative affect situations and the corresponding alcohol consumption when the individual is in a negative mood state. The authors reported that their single-session CBM-I, tested among 134 participants, successfully reduced interpretative biases but did not lower overall alcohol consumption (264).

Furthermore, other studies have evaluated a single session approach. Martinelli et al. conducted a recent systematic review and meta-analysis of bias modification paradigms, comprehensively mapping out studies involving attention or interpretative bias modification (265). In this review, the authors identified 91 studies for attention bias modification (265). This section aimed to summarise studies identified by Martinelli et al. that involved the use of a single session approach for substance use disorder (265). The objective of this summary was to provide an overview of the existing evidence base for a single session approach among individuals with substance use disorder. Table 10.1 summarised these studies.

Table 10.1. Summary of Single Session Attention Bias Modification Studies for Substance Use Disorder

Authors	Nature of Substance Use & Characteristics of Sample	Nature of the Training Paradigm	Main Findings
Field et al. (2005) (266)	Heavy social drinkers, N=40	Attentional training procedure. Half the participants were trained to attend to alcohol-related cues; and the other half were to direct their attention away from these cues	Changes in attentional biases occurred in the anticipated direction. The urge to drink increased in the attend group following attentional training
Schoenmakers et al. (2007) (267)	Heavy drinkers, 106 male college and university students	Visual probe task and flicker paradigm	Following attentional retraining, participants had learnt to avoid alcohol stimuli and developed an AB for soft drinks
Attwood et al. (2008) (268)	Smoking disorder, 54 male and female smokers	Single session attentional training which participants either trained to attend to a smoking-related pictorial stimulus or to a neutral pictorial stimulus	Attentional training increased attentional biases in the attend group; and decreased attentional biases in the avoid group. Cravings in the attend group increased.

As Table 10.1 shows, the use of a single session of attention bias modification may decrease the magnitude of attentional biases, with the possibility of further reductions following repeated sessions. The studies included in the summary focused solely on tobacco and alcohol use disorders. Currently, there is no research on the potential or effectiveness of a single-session attention bias modification for individuals with other substance use disorders, such as opioid use disorder.

10.5 Conceptualization of the Single-Session Attention Bias Modification Study

This study sought to address the risks issues of the pilot study. The main aim of this new study was to evaluate the feasibility of a single-session attention bias modification intervention for treatment-seeking individuals with opioid and alcohol use disorders.

10.5.1 Study Design

The research was designed as a feasibility study. Pearson et al. (2020) (269) highlighted that pilot and feasibility studies are increasingly considered to identify potential challenges, refine interventions, address issues with trial methods, and determine the preliminary effects of an intervention (269).

Participants were recruited from specialist outpatient clinics at the National Addictions Management Service, Institute of Mental Health, Singapore. Participants scheduled for inpatient admission undertook the study on the ward if there was no time prior to their admission in the clinics. All participants were screened for the presence of baseline

attentional biases. Those who screened positive underwent a single session of bias modification, followed by a reassessment of their attentional biases.

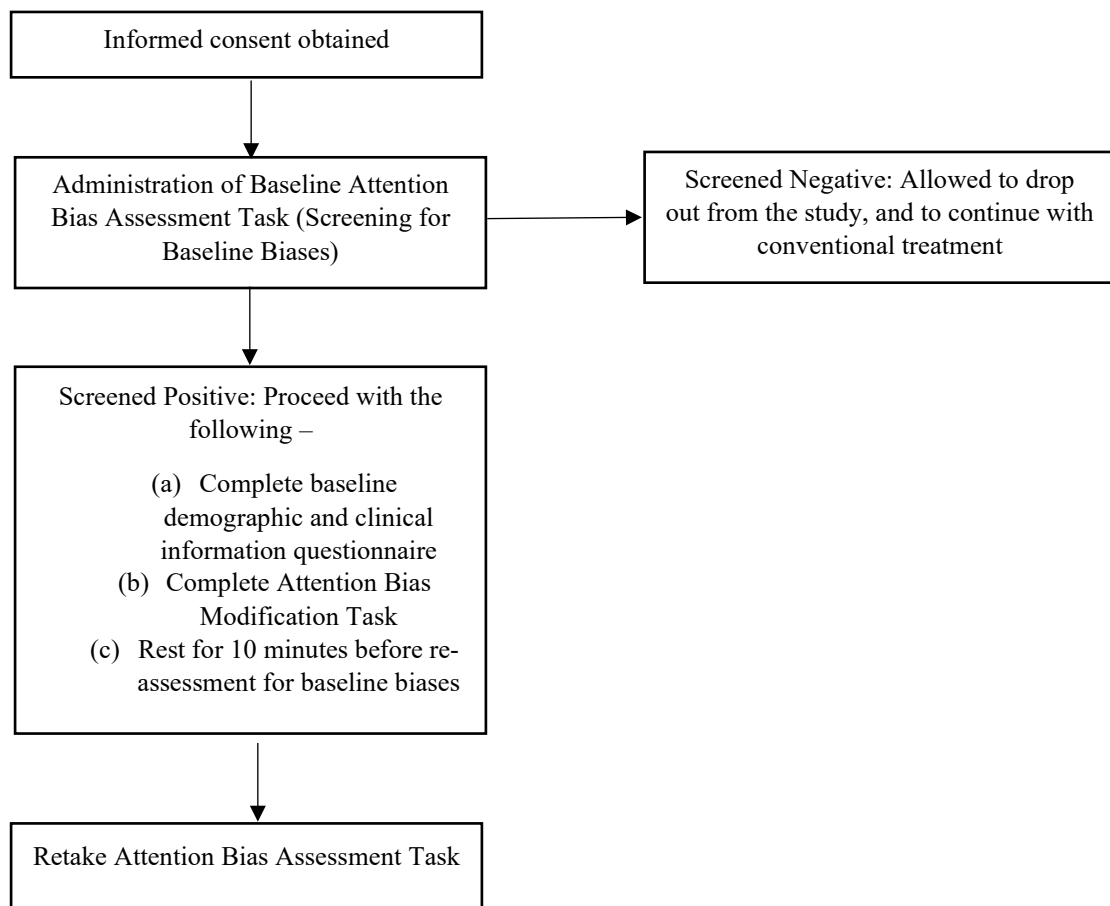
10.5.2 Inclusion and Exclusion Criteria

All participants who expressed interest in the study were screened for baseline attentional biases. As part of the screening process, all participants were administered an attention bias assessment task (refer to experimental procedure in Section 10.5.3). Baseline attention bias was deemed present if the overall trial-level bias scores were positive.

Participants who screened positive were further recruited into the study if they met the following criteria: (a) they were diagnosed with opioid or alcohol use disorder, and were primarily using opioids or alcohol on presentation; (b) for individuals diagnosed with polysubstance use disorder, the primary drug of abuse needed to be that of either an opioid or alcohol; (c) if they were also diagnosed with a co-morbid psychiatric disorder, they needed to be clinically stable; (d) they were capable of comprehending and reading English, and (e) they were aged between 21 to 70 years old. Participants were considered ineligible if they fulfilled the following criteria: (a) their primary substance of abuse was not that of an opioid or alcohol; (b) they were assessed to be experiencing a severe psychiatric condition and were clinically unstable; (c) they had an underlying history of seizures or migraines that were triggered by flashing lights.

10.5.3 Experimental Procedure

Informed consent was obtained from all participants. Participants who screened negative for baseline attentional biases were ineligible to continue in the rest of the study. They were allowed to drop out and continued with their routine medical management. Participants who screened positive were recruited into the study. Figure 10.2 provides an overview of the experimental procedure.

Figure 10.2: Overview of the Experimental Procedure

10.5.4 Details of the Attention Bias Assessment and Modification Tasks

These tasks, as described, were conceptualized based on Zhang et al. (2018)'s co-design study (235).

Baseline Attention Bias Assessment Task for Opioid Use Disorder

In this assessment task, a fixation cross appeared at the centre of the screen for 500 milliseconds. A set of images were then presented, half of which (100 sets of images) were presented for 200 milliseconds, and the other half, presented for 2 seconds. This stimulus timing was selected, based on the evidence review by Zhang et al. (253), which suggests that the presentation of two stimulus timings in individuals with opioid use, enabled the measurement of initial orientating and delayed disengagement. The set of images comprised a substance image and a neutral image, which were matched in terms of colour, size, and complexity. The substance images were images obtained from Singapore's Central Narcotics Bureau. Some were also the top-rated images participants chose in the previous co-design study conducted by Zhang et al. (2018).

(234). Following the presentation of the images, a probe (in the form of an asterisk) appeared, in the position of either the substance or the neutral image, for 200 milliseconds before disappearing. Participants were required to indicate the position of the probe by selecting either the left or right button on the screen. In this assessment task, the probe replaced the substance image 50% of the time and the neutral image 50% of the time. Therefore, participants needed to complete 200 repetitions. There were 10 sets of images, which will be repeated 20 times across the 200 trials.

Baseline Attention Bias Assessment Task for Alcohol Use Disorder

The task parameters were as per the baseline assessment task for alcohol use disorder, except that the pair of substance and neutral images were presented at only one interval, that of 500 milliseconds. The decision to present images at only one stimulus interval was guided by Field et al. (2010)'s research, as 500 milliseconds was the most common stimulus presentation interval for individuals with alcohol use disorder (254). The substance images in the image set were localised images of commonly available alcoholic beverages in Singapore for the image set. Likewise, some of these images were also the top-rated images participants chose in the previous co-design study.

Attention Bias Modification task

The parameter for this task was similar to that of the assessment task, with the exception that the probe would consistently replace the neutral image, instead of the substance image, to facilitate a change in the biases.

Post-Intervention Attention Bias Assessment task

This was similar to the baseline assessment task for opioids and alcohol use disorders.

10.5.5 Sample Size

A sample size of 30 participants was proposed, based on the recommendations of Bell et al.'s audit of the sample sizes for pilot and feasibility studies (270). Power computation was not performed, as it was not the intent of this study to determine any effectiveness.

10.5.6 Data Analysis

An intention to treat analytical approach was utilised, using data from all participants, including those who withdrew or did not complete all planned interventions. SPSS version 24.0 was employed for the data analysis.

Baseline Characteristic of Participants

Participants' demographic and clinical information were summarised using descriptive statistics, means and standard deviations.

Computation of Attention Bias

The trial-level bias score computational method was applied in this study. The Trial-level bias score (TL-BS) was computed by subtracting the reaction time for temporally contiguous pairs of congruent trials and incongruent trial's reaction time (245). Each of these individuals' trials was matched, such that a congruent trial was temporally as close as possible and no further than five trials away (either before or after) from each of the individual trials (245). This helped to generate a time series of the TL-BS for each participant. The TL-BS mean attention bias/TL-BS variability toward stimulus index was calculated by taking the average value of all trial-level bias scores in which the stimulus-congruent trial was shorter than the stimulus-incongruent trial, indicating an attention bias toward stimulus (245).

Computation of Feasibility Outcome Parameters

To ascertain the feasibility of this study, I computed the following:

- a. Acceptance rates (Number of participants who were invited, and agreed/Total number of participants invited)
- b. Recruitment rate (Participants recruited/Total Participants projected to be recruited)
- c. Attrition Rate (Participants who failed to complete all interventions/Total Participants recruited)

10.5.7 Outcomes

Feasibility was the primary outcome, which was defined by the number of participants recruited and participants adherence to the intervention. Based on our prior feasibility study conducted on the ward (Zhang et al.) (212), we had an acceptance rate of 75%,

recruitment rate of 100% and adherence rate of 63%. For this study, it was considered feasible if the acceptance rate was at least 50%, the recruitment rate at least 70% and the attrition rate was 30%. For this study, I adjusted the targets because the COVID-19 pandemic had reduced the attendance at outpatient clinics. The case-mix of patients presenting tended to be those who had moderate to severe symptoms of withdrawal, and hence, were less able or inclined to participate in research.

10.6 Results

10.6.1 Feasibility of Study

Of the 49 invited participants, 23 declined, resulting in an acceptance rate of 53.1%. We recruited 26 participants, 86.7% of our intended recruitment target of 30 participants. 15 (57.7%) participants did not proceed to the intervention phase as they did not demonstrate baseline biases during testing. The attrition rate was 0%, as all participants with positive baseline biases completed the bias modification intervention. Among the 26 recruited participants, 18 (69.2%) were actively using opioids (heroin, codeine, or other opioids), and 8 (30.8%) were actively using alcohol at presentation. Only 11 participants completed the baseline demographic questionnaire, and their data were analysed.

Baseline Demographic and Clinical Characteristics of Sample

Table 10.2 presents an overview of the participants' demographics. Table 10.3 provides an overview of the core clinical characteristics of participants who screened positive for baseline biases. Table 10.4 provides an overview of the changes in the magnitude of attentional bias observed in the study. Of the 11 individuals who completed the baseline demographic questionnaire and underwent attention bias modification, eight (72.7%) were successfully retrained to reduce their attentional bias following a single session of the intervention. The range of AB magnitude changes varied from 68.4 to 1931.51 milliseconds and as compared to the baseline; this represented a percentage decrease in attentional bias by 62 to 331%. However, the attentional bias of three participants increased after the single session of bias modification.

Table 10.2. Baseline Characteristics of Participants

Demographic Characteristics	Alcohol Dependence (n=2)	Opioid Dependence (n=9)
Age (years), Mean (SD)	47.5 (2.12)	50.9 (10.5)
Nationality, n (%)		
Singaporean	2(100%)	9(100%)
Others	0 (0%)	0(0%)
Gender, n(%)		
Male	2(100%)	9(100%)
Female	0 (0%)	0(0%)
Race, n(%)		
Chinese	0 (0%)	1(33.3%)
Malay	0 (0%)	1 (11.1%)
Indian	1(50%)	5 (55.5%)
Others	1(50%)	0 (0%)
Religion, n(%)		
Christianity	0	4 (44.4%)
Hinduism	0	0 (0%)
Muslim	1(50%)	5 (55.6%)
Others	1(50%)	0 (0%)
Education n(%)		
Primary education	0(0%)	1(22.2%)
Secondary education	1(50%)	6 (66.7%)
Junior college/polytechnic/technical studies	0 (0%)	1 (16.7%)
Undergraduate studies		
Graduate Studies	0 (0%)	0 (0%)
	1(50%)	0 (0%)
Housing, n (%)		
Homeless	0 (0%)	1(11.1%)
1 room	0 (0%)	1(33.3%)
2 room	0 (0%)	1(33.3%)
3 rooms	0(0%)	2 (22.2%)
4 rooms	1 (50%)	0 (0%)
5 rooms	0 (0%)	0 (0%)
Others	1(50%)	0 (0%)
Presence of other chronic diseases, n (%)	1 (50%)	3 (33.3%)
Presence of psychiatric disorders, n (%)	1 (50%)	0 (0%)

Table 10.3. Clinical Characteristics of Participants who Screened Positive for Baseline Biases

Participant	Age	Current Drug	Age of Onset	Age of Problematic Use	Frequency of Use Prior to Admission
abm001	39	Heroin	19	19	Daily use (4grams, 3 times per day, smokes and injects)
abm002	53	Heroin	18	NA*	Daily use (1 stick, 3-4 times per day, smokes)
abm005	58	Heroin	18	18	Daily use (0.5 stick, 3 times, smokes)
abm011	51	Heroin	15	21	Daily use (1 stick, 3 times, smokes)
abm013	55	Heroin	18	18	Daily use (1 packet, 20 times, smokes)
abm106	63	Heroin	16	23	Daily use (0.5 stick, 7-8 times, smokes)
abm017	32	Codeine	17	27	Daily use (4 bottles, 4 times, orally)
abm019	49	Alcohol	14	44	Daily use (12 cans, 3 times, orally)
abm022	45	Heroin	16	20	Daily use (3 sticks, 5 times, orally)
abm024	46	Alcohol	14	34	Daily use (4-6 cans, 2 times per day, orally)
abm025	62	Heroin	17	45	Daily use (1 stick, 2-3 times, orally)

Footnote: *NA: Not applicable – Participant did not provide the specific data

Table 10.4 Baseline Attention Biases and Changes in Biases

Participant	Drug	Baseline AB Score (msec)	Final AB Score (msec)	Change in AB and Direction of Change	Percentage Change from Baseline (Magnitude of Change/Baseline AB)
abm001	Opioids	131.49	-68.27	199.76, Decrease in AB	151.85%
abm002	Opioids	6.16	264.33	258.17, Increase in AB	4901%
abm003	Opioids	-25.32	NA	NA	NA
abm004	Opioids	-12.36	NA	NA	NA
abm005	Opioids	909.85	-44.47	954.32, Decrease in AB	104.89%
abm006	Opioids	-25.59	NA	NA	NA
abm007	Alcohol	-91.19	NA	NA	NA
abm008	Opioids	-16.14	NA	NA	NA
abm009	Alcohol	-791	NA	NA	NA
abm010	Opioids	-10.27	NA	NA	NA
abm011	Opioids	161.97	60.85	101.12, Decrease in AB	62.43%
abm012	Opioids	-74.73	NA	NA	NA
abm013	Opioids	720.38	-1211.13	1931.51, Decrease in AB	168.12%
abm014	Opioids	-516.92	NA	NA	NA
abm015	Alcohol	-35.42	NA	NA	NA
abm016	Opioids	73.33	17.38	55.95, Decrease in AB	76.30%
abm017	Opioids	56.5	-130.65	187.15, Decrease in AB	331.23%
abm018	Alcohol	0	NA	NA	NA
abm019	Alcohol	40.61	-27.79	68.4, Decrease in AB	168.43%
abm020	Alcohol	-27.7	NA	NA	NA
abm021	Opioids	-50.65	NA	NA	NA
abm022	Opioids	90.04	-13.40	103.44, Decrease in AB	114.88%
abm023	Alcohol	-100.83	NA	NA	NA
abm024	Alcohol	40.22	92.14	51.92, Increase in AB	129%
abm025	Opioids	167.41	586.19	418.78, Increase in AB	250.15%
abm026	Opioids	-180.19	NA	NA	NA

Footnote: Positive attentional bias refers to any magnitude of attentional bias score greater than 0 milliseconds. Negative attentional bias (or bias away) refers to any magnitude of attentional bias score less than 0 milliseconds.

10.7 Discussion

The present study is the first to examine the application of a single-session attentional bias modification approach for individuals seeking treatment for alcohol or opioid use disorders. The results showed that more individuals with opioid use disorders met the inclusion criteria than those with alcohol use disorders. The feasibility of the study was validated, with an acceptance rate of 53.1%, a recruitment rate of 86.7%, and an attrition

rate of 0%. Of the 26 participants recruited, 11 (42.3%) had positive baseline biases that could be modified, and 8 (72.7%) successfully retrained their attention bias following a single session of attention bias modification.

While the study was not designed to assess the impact of the intervention, the fact that 72.7% of participants successfully retrained their attention bias after just one session is notable. This contrasts with our previous feasibility study, in which only 47.8% of participants required multiple sessions of training to retrain their biases. In that study, the overall magnitude of the attentional biases of 11 of 23 patients using opioids or alcohol decreased following interventions. In addition, as compared to the baseline scores, the percentage decrease in attentional biases ranged from 62 to 331%, which represents a substantial change in the magnitude of biases. These findings validate the use of a single-session approach and demonstrate that biases can be effectively retrained using attention bias modification.

A small proportion of individuals had experienced an acute increase in the magnitude of their attentional biases following the single session of bias modification. This observation is consistent with the findings of feasibility study, where we also observed an increase in the magnitude of attentional biases after the first session of bias modification. Although this phenomenon could be explained by how the presentation of highly triggering images results in an acute increase in attentional biases, further research is needed to determine whether patient characteristics contribute to this. In all the studies conducted to date, provisions for added support (i.e., ensuring that participants have access to a counsellor if needed) were set aside. However, thus far, none of our participants have utilised these resources. This consideration remains of importance when planning future studies. The findings highlight the need for personalised delivery of attentional bias modification, as some individuals may benefit from a single session, while others may require more sessions to achieve a change.

The COVID-19 pandemic has led to major changes in service delivery, with more patients having increased access to outpatient services. Even if admitted, some patients may only stay for medication-assisted detoxification and return to outpatient clinics for rehabilitation. A single-session approach is more inclusive, as some patients may be

discharged to halfway homes with rules that prevent them from leaving the residential program. In addition, some patients may be sentenced to imprisonment after hospitalisation, making it challenging for them to undertake interventions upon release.

A recent Delphi consensus study recommended implementing cognitive bias training during early remission, which is the first three months after recovery and following detoxification (271). It was also suggested that cognitive bias modification be administered multiple times per week over the course of three months. However, a major limitation of this Delphi study was the limited involvement of frontline clinicians and individuals with lived experiences (271). I benefited from the findings of my previous codesign work and have taken on board many of its recommendations (235). These findings inspired our pragmatic approach to examining a single-session approach. In some respects, the consensus arising from Verdejo-Garcia et al.'s research is congruent with the work done thus far (271). One of the areas of agreement is how cognitive bias modification can help reduce cue-related biases (271). Experts have also endorsed the use of gamification methods for cognitive bias modification, which is one of the strategies that have been actively researched in much of our work. The experts' perspectives regarding the adjunctive use of cognitive bias modification to complement the existing program are also in line with our direction. Additionally, the need for personalized and individualized cognitive bias modification interventions was emphasized, and this was explored to some extent through our codesign workshops. In this study, I have evaluated the codesign version of attention bias modification and demonstrated that a single session of bias modification could bring about a reduction in biases.

One key strength of this study is that the feasibility of a single-session attention bias modification approach using our codesigned intervention was demonstrated. I recruited participants just before they enrolled in a medication-assisted detoxification program and provided preliminary evidence for the effectiveness of a single session approach in a clinical sample. The finding that some individuals benefited from a single-session approach while others did not, highlights the need for personalised interventions beyond a single session. Despite these strengths, our study has several limitations. I did not directly compare the effectiveness of the codesigned intervention with the original intervention in reducing baseline biases. In addition, most of the clinical information

that was obtained from patients was based on self-report, which may be subject to recall biases. While some patients have a reduction in their attentional biases, there remains uncertainty as to how long this change would be sustained for, and whether additional sessions of bias retraining are necessary.

10.8 Conclusions

The findings of this single-session study demonstrate that it is possible for a single-session approach to reduce the attention biases in our group of participants. The results also highlight that some patients might need more than a single session of attention bias modification. The findings will help in the conceptualising of the protocol for the definitive randomised trial.

Chapter 11 Definitive Randomised Trial Protocol Comparing the Effectiveness of Co-designed versus Conventional Interventions

This chapter describes the protocol for a definitive study comparing the effectiveness of a conventional mobile attention bias modification intervention against a co-designed intervention. The chapter begins with a brief overview of how the prior studies have shaped the protocol's design, describes the plan for a definitive trial and then highlights the potential challenges of conducting such a trial.

11.1 Introduction

The previous chapters (9 & 10) outlined the results of applying a new computational method for attentional biases and the feasibility of a single-session approach in retraining attentional biases. The conduct of the studies in Chapters 9 & 10 is instrumental, given that they attempt to address two of the identified risks arising from the suspended pilot study (recruitment of participants and attrition). These studies have provided further insights into developing the methods of the definitive randomised trial. The next step is to determine if the co-designed intervention is more effective than the conventional attention bias modification intervention. As of December 2022, no studies have examined a personalised/co-designed attention bias modification intervention for individuals with opioid use disorders. This planned definitive randomised trial will add to our understanding of attention bias modification interventions.

11.2 Aims and Objectives

The primary objective of the randomized controlled trial will be to compare the effectiveness of a single session and two follow-up sessions of attention bias modification using the co-designed application to the conventional intervention in reducing attentional biases. We will consider a total of 3 sessions of bias modification interventions based on feasibility study data showing that 25% of participants completed less than two interventions and an average of 3.5 sessions completed.

The secondary objectives are:

1. Measuring the percentage reduction in attentional biases immediately after the first session and comparing it to the reduction at the end of the two follow-up sessions (i.e., after three sessions of bias modification).

2. Testing if the co-designed intervention reduces cravings more effectively than the conventional intervention.
3. Assessing the overall acceptability of the co-designed intervention compared to the conventional intervention.

11.3 Trial Design

The study is a randomized controlled trial that aims to compare the reduction in attentional biases between participants assigned to the co-designed intervention and those assigned to the conventional intervention. The current protocol follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines (272). Before randomisation, all participants will be assessed for eligibility based on the presence of positive baseline bias. Baseline attentional biases will be calculated using the trial-level bias scoring method (as described in Chapter 10). Participants will undergo the first attention bias modification session upon admission to the inpatient unit. They will then be allowed to complete the remaining two planned interventions (i.e., the two other bias modification sessions) once they have stabilized on the inpatient unit (as clinically determined by participants having low withdrawal scores on the Clinical Opiate Withdrawal Scale (COWS)). The study uses a 2x2 design (intervention: co-designed vs. conventional; time: baseline, completion of the intervention) to compare changes in attentional biases following a single session and overall changes following the two follow-up sessions.

11.4 Randomisation and Blinding

11.5 Study Setting

To expand the recruitment pool, we will recruit participants from three study sites: (a) patients presenting to the Emergency Services at the Institute of Mental Health (IMH) and scheduled for admission, (b) patients admitted to the general psychiatric ward at IMH, and (c) patients admitted to the inpatient unit at the National Addictions Management Service (NAMS). By extending recruitment to three sites, we aim to increase the pool of potential participants and achieve the desired sample size for power calculation. Traditionally, individuals with opioid use disorders seek treatment through the emergency services at IMH, as the NAMS service operates only during office hours, or they are admitted to other inpatient units for treatment following their presentation to the emergency services.

11.6 Sample Size

This study will be the first to investigate a novel mobile co-designed attention bias modification intervention compared to conventional attention bias modification among individuals with opioid use disorders. To estimate the required sample size, we referred to Boffo et al.'s recent work, which found the effect size for cognitive bias modification among individuals with alcohol and smoking addiction to be Cohen's D of 0.23 (149).

Using this effect size (as reported by Boffo et al.), we conducted an a priori power analysis using G*Power 3.1.9.7 for a 2x2 repeated measures ANOVA design to detect this small effect size ($d = 0.23$) for the interaction between the experimental condition (conventional versus co-designed) and the assessment time (baseline and end of intervention) (149). The calculation used an alpha of 0.05 and a correlation of 0.5 among repeated measures. It showed that a sample of 64 participants, with two equal groups of 32, was required to achieve a power of 0.80.

Based on the findings from the single-session study, we estimate that 46% of the participants will have baseline biases and could be randomised. Therefore, a sample of 140 participants is required. Given that the attrition rate was 37% in the prior completed feasibility study, a total sample of 222 participants (111 per group) needs to be recruited.

To recruit such a sample, we anticipate that the study will need to be conducted for at least three years. It took almost 10-12 months to recruit 26 participants from our outpatient services, and we anticipate that we could recruit 30-40 participants per service (NAMS/Emergency Services and Inpatient Unit) per year, giving us approximately 120 patients per year. In addition, with the expansion of the inclusion criteria to include patients who cannot comprehend English, more patients may be eligible. From our previous experiences, between 20-30% of those who were invited were not subsequently recruited due to language issues.

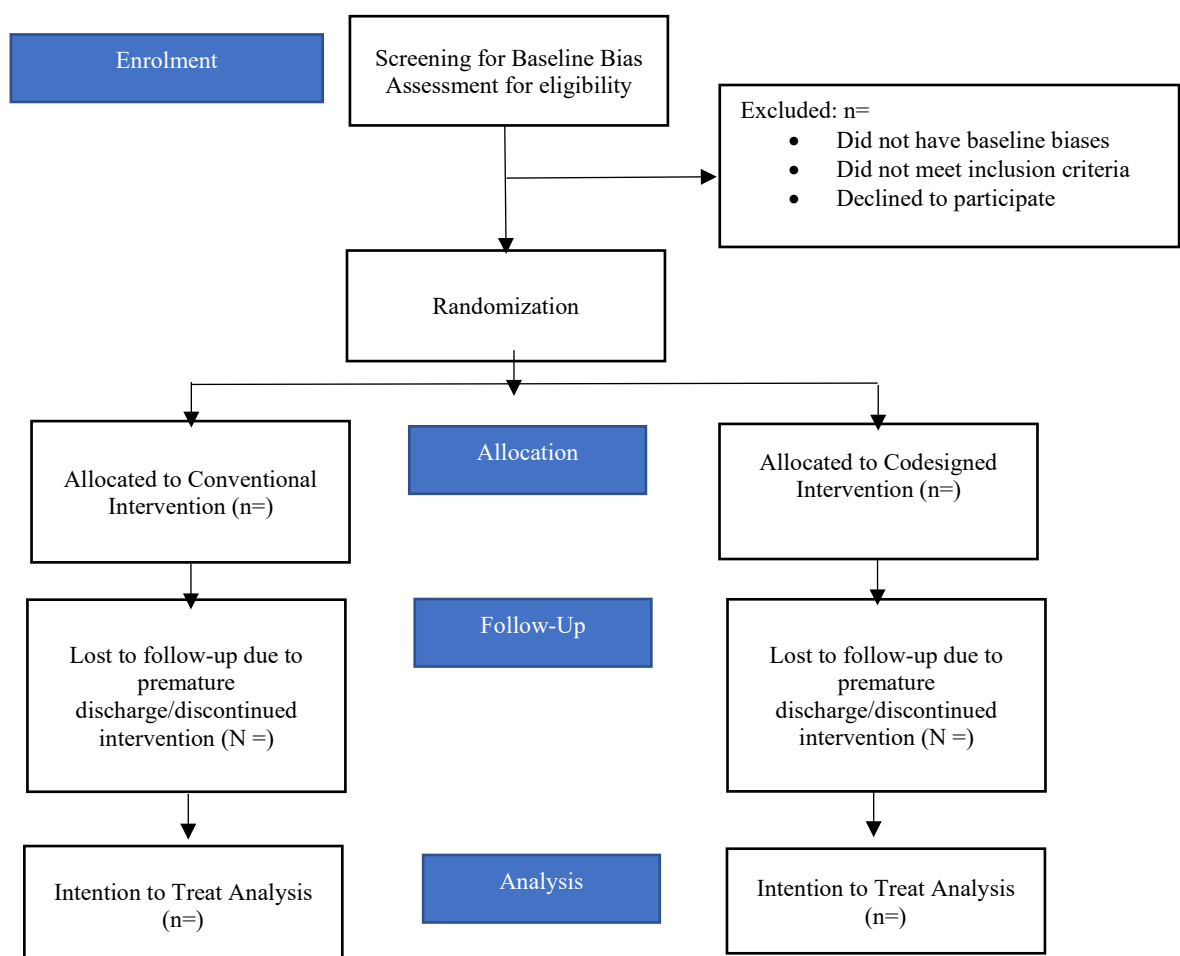
11.7 Inclusion and Exclusion Criteria

Only participants who exhibit a positive baseline attentional bias, defined as having any attentional bias with a magnitude greater than zero at baseline, as determined by the trial-level bias score, will be eligible for recruitment. Additional inclusion criteria include: 1) aged between 21 and 70 years; 2) primary diagnosis of opioid use disorder;

3) if they are a polysubstance user, opioids must be their primary drug of abuse, and 4) ownership of a smartphone device. Exclusion criteria include: 1) absence of baseline biases; 2) underlying cognitive impairment or diagnosis of any form of dementia, 3) history of seizures (including withdrawal seizures) or migraines triggered by flashing lights; 4) clinically unstable, with moderate to severe relapses of their underlying psychiatric disorders, and 5) currently experiencing moderate to severe opioid withdrawal, as assessed by scores on the Clinical Opiate Withdrawal Scale (COWS). Participants do not need to have a basic understanding of written or spoken English, as the study team members will provide translated versions of the informed consent forms, questionnaires, and application instructions.

Figure 11.1 provides the Consolidated Standards of Reporting Trials (CONSORT) diagram of participant recruitment.

Figure 11.1 Overview of Participant Recruitment



11.8 Measures

11.8.1 Baseline Demographic and Clinical Information

For the baseline demographic and clinical demographic questionnaires, the following variables will be collected:

- a. Nationality
- b. Gender
- c. Marital Status
- d. Race
- e. Religion
- f. Educational level
- g. Housing conditions
- h. Current substance used
- i. Substance consumption method
- j. Quantity of substance consumed each time
- k. Frequency of use
- l. Previous treatment history
- m. Presence of chronic diseases (psychiatric and physical disorders)
- n. Current psychiatric medications

The questions regarding substance use (h – k) have been modified and adapted from the ASI-Lite (Addiction Severity Index-Lite) questionnaire.

11.8.2 Attention Bias Assessment

The visual probe task will be used to assess baseline attentional bias and to measure the magnitude of attentional bias following the intervention. The task will display a fixation cross for 500 milliseconds, followed by a set of images consisting of an opioid-related image and a neutral image matched in terms of colour and complexity. Half of these images will be presented for 200 milliseconds and the other half for 2 seconds. A probe in the form of an asterisk will then be presented for 200 milliseconds, and participants must indicate (by pressing buttons on the screen) whether the asterisk is on the left or right side. If they do not respond, the next trial will be presented. Attentional bias will be calculated by subtracting the reaction time to respond to the probes that replaced the substance image from the time required for the neutral image.

The magnitude of attentional bias will be assessed using the Trial-Level Bias Score (TLBS) computational method, in which the variability in the TLBS score reflects the magnitude of the attentional biases. To compute the TLBS score, each congruent trial will be paired with the nearest incongruent trial, with the nearest incongruent trial being within 5 trials of the congruent trial. TLBS is computed as the incongruent minus congruent difference for each of these identified pairs. Based on the computed difference (TLBS), several additional parameters can be derived, including:

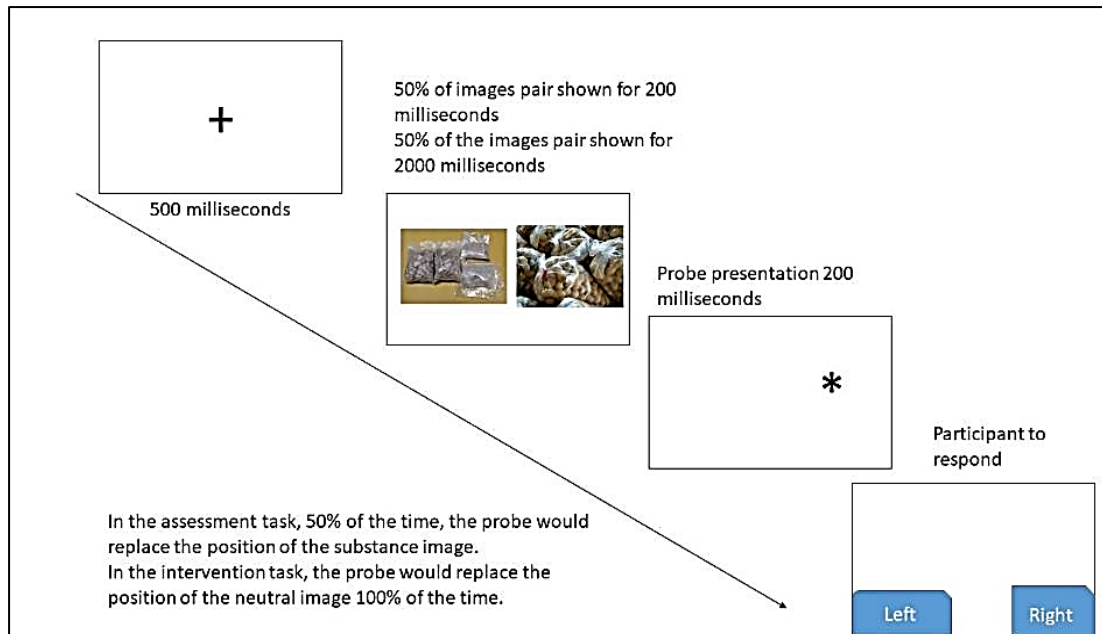
- Mean(towards): Mean of trial level bias score greater than 0 milliseconds
- Mean(away): Mean of trial level bias score less than 0 milliseconds
- TL-BS Variability: Sum of all the distances between all sequential TLBS divided by the total number of TLBS. The TL-BS variability score reflects the magnitude of the attentional biases.

The opioid image set will consist of images of opioids commonly abused in Singapore, provided by CNB from drug raids. The stimulus set will include 10 opioid images with matching neutral images, and it will be repeated 20 times, resulting in a total of 200 trials.

11.8.3 Attention Bias Modification in the Conventional Intervention

The attention bias modification task resembles the attention bias assessment task, except for the probe always replacing the neutral image, thereby retraining attentional processes from opioid stimuli. Figure 11.2 shows the flow of the attention bias modification intervention. Participants are required to complete 200 trials and are presented with the same images as per the assessment task (i.e., 10 opioid and 10 neutral images, repeated 20 times).

Figure 11.2 Flow of the Conventional Intervention



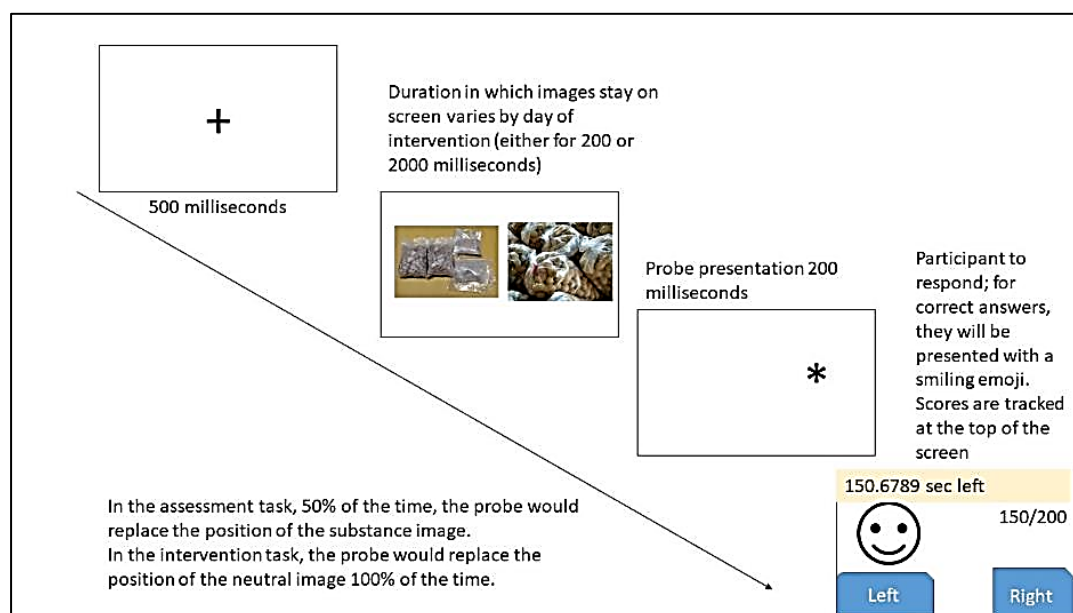
11.8.4 Attention Bias Modification in the Co-designed Intervention

The co-designed intervention differs from conventional attention bias assessment and modification tasks in three ways, as suggested by participants in the co-design workshop. First, before starting the intervention, an instructional video is provided through the app to help participants understand how to use it. The video, created by the doctoral candidate, presents a screen recording of how to complete the attention bias tasks and is approximately 5 minutes long. Participants are given five practice trials for the assessment task to understand how to respond within the app. Similarly, the co-designed intervention presents a fixation cross at the start of the intervention for the attention bias modification.

Second, although the same set of stimulus images (opioid-related and neutral images) are presented, the presentation timing of the stimulus set varies across sessions. Thus, in the first session, 90% of the stimulus set is presented for 2 seconds, and 10% is presented for 200 milliseconds. In the second session, 30% of the stimulus set is presented for 2 seconds, and 70% is presented for 200 milliseconds. By the last session (3rd session), 50% of the stimulus set is presented for 2 seconds, and 50% is presented for 200 milliseconds. A probe (asterisk) then appears, replacing either the substance image or neutral image for 200 milliseconds before disappearing. Participants have to indicate the probe's position by selecting buttons on the screen (i.e., left button if on the left side, right button if on the right side).

Third, a smiley emoji is presented if the response is correct, and a frowning emoji is presented if incorrect. The cumulative scores across the trials are presented in the top right-hand corner of the app. Final scores are presented upon task completion. The interval between each repetition is 250 milliseconds. Figure 11.3 provides an overview of the nature of the co-designed intervention.

Figure 11.3 Flow of the Co-designed Intervention



11.8.5 Assessment of Cravings

Participants are asked to rate their cravings on a Visual Analogue Scale (VAS) from 0 to 100, with 100 the highest level of cravings.

11.8.6 Acceptability of Intervention

The perspective questionnaire consists of the following questions:

1. Prior to using the application, how confident were you in managing your addiction problem? (5-point Likert Scale, ranging from not at all to extremely)
2. How easy was it to use the application? (5-point Likert Scale, ranging from not at all to extremely, and with space for written comments)
3. How engaging was the application? (5-point Likert Scale, ranging from not at all to extremely, and with space for written comments)
4. Did you feel motivated to continue using the app? (5-point Likert Scale, ranging from not at all to extremely, and with space for written comments)

5. Did the images in the app remind you of your substance use? (5-point Likert Scale)
6. After using the app, how confident are you in managing your addiction problem? (5-point Likert Scale)

This perspective questionnaire was used previously in the feasibility study to enable comparison of the results. Other questionnaires, such as the Mobile application rating scale (MARS) and the user mobile application rating scale (uMARS) that may help assess perspectives regarding acceptability were not considered, as they do not allow comparison with our previous results (273,274).

11.9 Experimental Procedure

After completing the informed consent form, participants will undergo the attention bias assessment task to determine whether they have a positive baseline bias (i.e., a magnitude of attentional bias greater than zero), and those who are eligible will be randomized. During the first session of the study, the study team will provide participants with unique usernames and passwords and guide them in using the application on a tablet device (provided by the study team). Participants are required to complete the baseline questionnaires and rate their opioid cravings on the VAS. They must then complete an attention bias modification task. After completing the attention bias modification task, they should rate their cravings and undergo another assessment of their attentional biases. This completes the initial experimental procedure. Participants are allowed to have a 10-minute break between different tasks.

The study team will then coordinate with the treating team to determine when the participant is ready for Sessions 2 and 3. Participants are eligible for subsequent sessions if they are not deemed clinically unstable and have moderate to severe relapse of their psychiatric conditions. They are considered eligible only if they have low scores on their COWS scoring. For each subsequent session, they must rate their cravings on the VAS before and after completing the attention bias modification task. Participants do not have to undertake the attention bias assessment task after completing the bias modification task during the second session. For the third session, participants must complete the attention bias modification task, rest for 10 minutes, and then complete the attention bias assessment task. They must also complete the perspective questionnaire. Should the participant be discharged prematurely from the ward, the study team will not contact the participant. The participant will not be required to return

to complete any outstanding tasks. Table 11.2 provides an overview of the schedule of enrolment, assessment, and interventions.

Table 11.1 Schedule of enrolment, assessment, and interventions

Timepoint	Enrolment	Allocation	Session 1	Session 2	Session 3
Enrolment:					
Screening for eligibility	X				
Informed consent	X				
Screening for baseline biases	X				
Allocation		X			
Orientation to App		X			
Assessments:					
Baseline demographic questionnaire		X			
Clinical Information questionnaire		X			
Visual Analogue Scale for Cravings			X (Pre and Post Intervention)	X (Pre and Post Intervention)	X (Pre and Post Intervention)
Perspective Questionnaire					X
Interventions:					
Bias Modification			X	X	X
Bias Assessment			X		X

11.10 Data Management

To protect participants' privacy and to anonymise data, each participant will receive a unique number upon recruitment. The hardcopy questionnaires will be labelled with the unique number and contain no other patient-related identifiers. The informed consent form and completed hardcopy questionnaires will be stored in secured, locked cabinets located in restricted areas. Electronic data, which mainly consists of participants' reaction times, will automatically synchronize to a cloud database in Singapore (Digital Ocean, Singapore) (275). A copy of the electronic data will be downloaded daily onto

a locally secured computer, and the password will be changed frequently. The study team will code the data, and an independent coinvestigator will routinely check the data coding for reliability and quality. All hardcopy forms and electronic data will be kept for at least six years following the study's completion.

11.11 Outcomes

This study's primary outcome is the magnitude of change in attentional bias for opioid-related cues following the intervention. The time points for assessing change are the baseline and the intervention's completion. The secondary outcomes include 1) the changes in opioid craving scores from baseline to intervention completion and (2) intervention acceptability.

11.12 Data Preparation and Planned Statistical Analyses

An intention-to-treat analytical approach will be used for the final analysis, which will include data from all participants, including those who withdraw or fail to complete all planned interventions. Imputation methods will not be used to address missing data. The magnitude of attentional biases following the administration of the assessment or intervention task will be computed using Microsoft Excel, following this process:

The magnitude of attentional biases will be assessed using the Trial-Level Bias Score (TLBS) computational method, where the variability in the TLBS score is indicative of the magnitude of the attentional biases. To compute the TLBS score, each congruent trial will be paired with the nearest incongruent trial within 5 trials distance. TLBS is computed as the incongruent – congruent difference for each identified pair. Based on the computed difference (TLBS), several other additional parameters can be derived, including:

- Mean (towards): Mean of trial level bias score > 0 milliseconds
- Mean (away): Mean of trial level bias score < 0 milliseconds
- TL-BS Variability: Sum of all the distances between all sequential TLBS divided by the total number of TLBS. The TL-BS variability score is indicative of the magnitude of the attentional biases.

All demographic and clinical characteristics will be summarized using descriptive statistics and frequency tables through SPSS version 24.0 (210). To determine whether the co-designed app is more effective than the conventional app, a mixed-effects analysis of variance will be conducted. The dependent variable will be attentional biases, and the within-subjects factor will be time. The between-subject factors are the experimental conditions (conventional vs. co-designed). A mixed ANOVA will help determine whether the change in attentional bias results from the interaction between the experimental condition and time.

11.13 Funding and Ethical approval

Table 11.3 provides an overview of the estimated funding that is required.

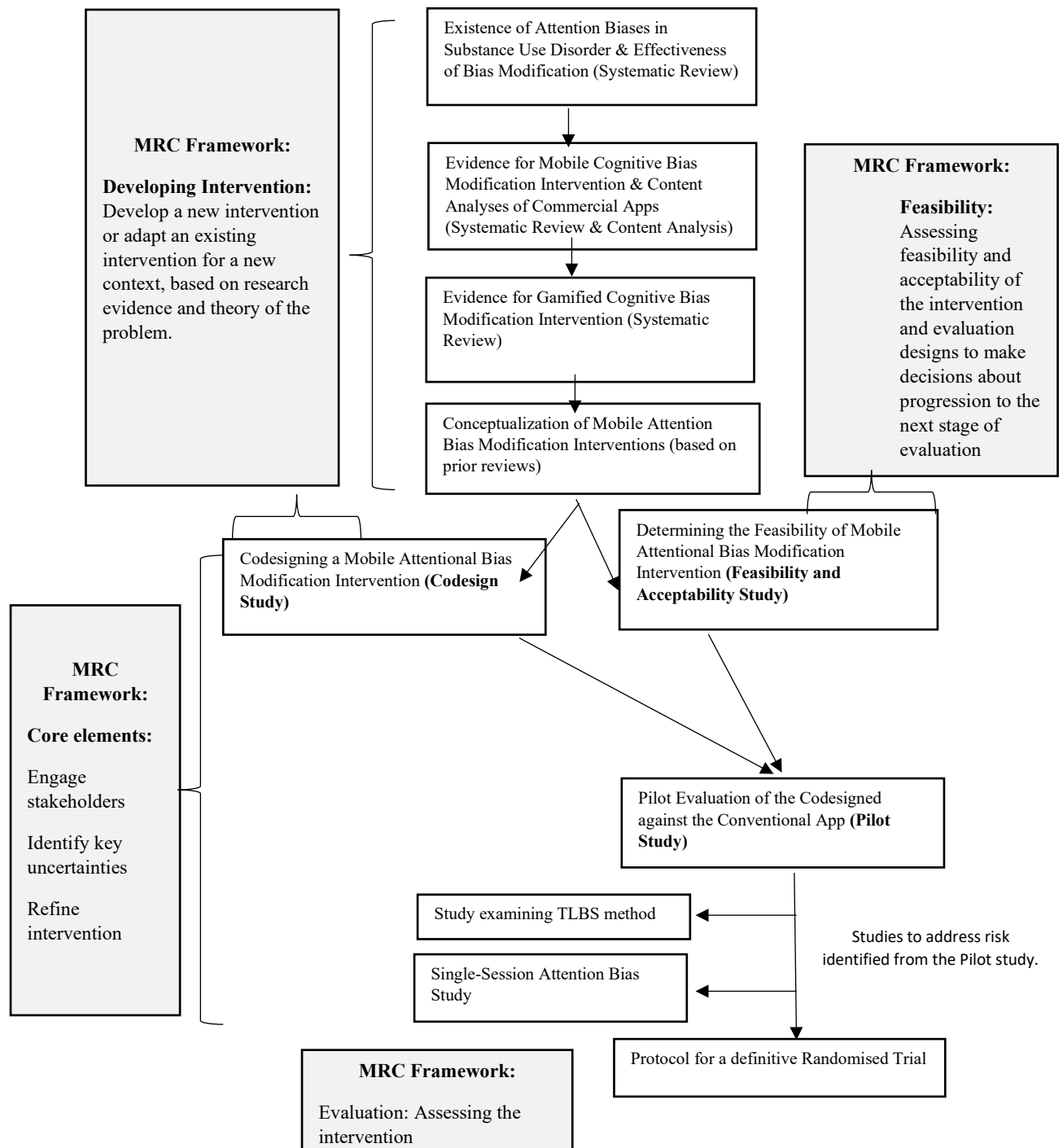
Table 11.3 Projection of Costs Involved

Manpower	Justification	Total Estimated Cost
Research Assistant	To assist in recruitment and intervention administration	\$62,160 (per year) $\times$ 3 years $\times$ 3 person (1 person per site) = \$559,440
Research Fellow	To coordinate recruitment, intervention administration, and to lead coding and data analysis	\$104,000 (per year) $\times$ 3 years = \$312,000
Equipment	Tablet Devices (Android)	\$200 $\times$ 10 tablets = \$2000
Other Operating Expenses	Stationery and Recruitment Posters Inconvenience fees for participants Cloud Server	\$500 \$30 (per participant) $\times$ 222 = \$6600 \$1200 (per year) $\times$ 3 years = \$3600
Total Projected Expenses		\$884,200

External funding from the National Medical Research Council or Ministry of Health, will be sought to cover this study's cost. Once funding has been secured, ethical approval will be obtained from the National Healthcare Group's Domain Specific Research Board.

11.14 In Summary

Figure 11.4 Overview of MRC Framework and how the conducted studies integrate with the MRC framework



Footnotes: The MRC framework is referenced from this recent publication (“A new framework for developing and evaluating complex interventions: update of Medical Research Council Guidance.” BMJ 2021; 374: n2061)(276)

The current study protocol for the definitive randomized trial builds upon my prior work, including the feasibility study, pilot study, and single-session study. These studies have informed this work and helped refine the intended methods for this study. Without the conduct of these prior studies and risk assessment analysis, the premature execution of the definitive randomized trial might fail, as the methods might not be pragmatic enough and applicable in a real-world setting. In planning this protocol, I followed the Medical Research Council's (MRC) guidelines for designing complex interventions (239). Figure 11.4 provides an overview of the most recent MRC guidelines for developing and evaluating complex interventions and how the conducted studies to date integrate with the guideline's recommendations.

As depicted in Figure 11.4, a series of studies were conducted to determine the nature of the intervention to be adapted. The adapted intervention was then tested using feasibility and a pilot study, and a series of further studies aimed to refine the intended methods. A well-conceptualized study with prior studies refining the intended methods is essential to avoid the situation where only negative findings or non-significant results are derived from the study. Numerous examples in the literature demonstrate how investigations into attention bias modification among individuals with opioid use disorders failed to achieve any significant results. For instance, Charles et al. reported no changes in attentional biases among both users and healthy controls (59). As previously mentioned, only a single study involving methadone-maintained individuals compared ABM intervention against treatment as usual and found a significant reduction in attentional biases from baseline to post-test among those who received the bias modification intervention (88). The authors also reported that their participants who received ABM intervention increased their motivation to change, reduced their methadone dosing, and had fewer relapses. To date, no other studies have attempted to investigate what has been set out in this protocol.

Given the required sample size, our study's recruitment is expected to take at least 27 months for completion. Figure 11.4 is a grant chart summarising the timelines for this proposed randomised trial. Twenty-seven months has been provided for recruitment, and 36 months has been provided for the entire study.

Figure 11.5 Grant chart summarising the timelines for this proposed randomised trial.

Months												
Activities	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th
Modification of Apps												
Translation of Forms												
Application for Ethics												
Setting up Study Site												
Enrolment & Recruitment												
	13th	14th	15th	16th	17th	18th	19th	20th	21st	22nd	23rd	24th
Enrolment & Recruitment												
	25th	26th	27th	28th	29th	30th	31st	32nd	33rd	34th	35th	36th
Data Analysis												
Preparation of Manuscripts												

Several researchers have examined the significant endpoints of relapse rates, or the amount of substance used by participants after they complete the intervention, and subsequently followed up at various time points. Ideally, this endpoint would be useful for this definitive trial. However, there is a need to balance the legal issues in Singapore. The "Misuse of Drug" legal statutes require healthcare professionals to report any individual with clinical information or samples indicating substance abuse. This contrasts with other legal statutes overseas, such as in the United States, where physicians are not obligated to disclose information and maintain doctor-patient confidentiality (277). Measuring relapse rates is challenging due to several reasons. Firstly, there is a dilemma regarding mandatory reporting of individuals who relapse. Secondly, there is a risk of reporting bias given the severe legal penalties for reporting illicit drug use. Individuals might downplay or not report their relapse, which can lead to an underestimation of relapse rates.

This study is the first study to investigate a personalised attention bias modification intervention for opioid use disorder and how varying stimulus intervals for attentional bias modification can change the magnitude of attentional bias across the intervention. The findings from this randomised trial will be useful for developing future attentional bias modification interventions.

Chapter 12 Discussion and Conclusions

This closing chapter comprises six sections. Section 12.1 presents and summarises the key findings from each of the reviews and studies. Section 12.2 discusses the main findings arising from each of the studies. Section 12.3 highlights the strengths and limitations of this work. Section 12.4 focuses on the clinical and research implications arising from this work. Section 12.5 outlines the contribution of this research to the academic literature, as well as the limitations of this study. Finally, Section 12.7 discusses the impact of this research on my development as a clinician-scientist.

12.1 Summary of Key Findings

This dissertation details the preparatory work for a definitive randomized trial that aims to evaluate the effectiveness of a novel mobile co-designed attention bias modification intervention for individuals with opioid use disorders. The research involved systematic reviews and content analyses to support the existence of attentional biases in addictive disorders and mobile gamified interventions. Based on the MRC's guidelines for complex interventions, a feasibility study and a pilot study were conducted to refine the trial methodology (276). A co-design study was also performed to ensure the intervention aligned with patients' needs and scientific evidence. Due to COVID-19's impact on the pilot study, an additional study was carried out to refine the intended definitive randomized trial's methods. This research was necessary because there were no prior studies on attentional biases and its modification in an Asian population. The differences in participants' nature and pharmacological management in the local context make the generalisability of prior randomized trials among western cohorts uncertain.

Chapter 2 systematically synthesizes the literature on attention bias and bias modification in individuals with opioid, cannabis, and stimulant use disorders, which were selected due to their high prevalence in Singapore. Two systematic reviews were conducted to summarize the evidence for cognitive biases in these disorders.

Chapter 3 describes how technological advances have transformed the delivery of attention bias modification interventions. A systematic review and content analysis of the literature on mobile cognitive bias modification interventions were conducted, revealing that only three of the eight identified published studies were related to

addictive disorders, all of which reported mobile bias modification effective. However, among the 17 commercial applications identified, only five targeted addictive disorders, and only one of the scientifically validated applications was available commercially. The findings highlight the need for closer collaboration between academics and developers.

Chapter 4 presents a literature review of gamified cognitive bias modification interventions and content analyses of commercially available gamified cognitive bias modification applications on Google Store, which were integral to the preparatory work prior to the co-design workshops. Only four studies investigating gamified interventions have been published, with two reporting the effectiveness of the gamified application. The most common gaming elements integrated into scientifically validated applications were animations, sound effects, point-scoring systems, time pressure, and levels. The content-analytical review of commercial applications demonstrated that the most common gamification elements adopted were digital rewards and the provision of feedback. These strategies guided the discussion during the co-design workshop to identify gamification features that would enhance motivation to train and reduce attrition.

Chapter 5 systematically reviews the visual probe paradigms utilized in published studies for opioid, cannabis, and stimulant use disorders. It is noteworthy that there was significant variability in the task paradigms used, as well as in the level of detail reported. This variability in task paradigms underscores the importance of reporting task parameters in detail for future research to ensure result reproducibility. The understanding gained from this review of task paradigms has helped to inform the conceptualization of a mobile attention bias modification intervention.

Chapter 6 outlines a feasibility and acceptability study conducted among inpatients with opioid, cannabis, and stimulant use disorders at the National Addictions Management Service (NAMS). The study was conducted according to the MRC's framework for complex interventions, and it was deemed feasible, with a 75% recruitment rate and 11 of 30 participants completing all planned interventions. Most participants found the interventions easy to use and interactive and reported an increase in confidence in managing their addiction problems. However, 60% of participants were not motivated

to use the application for the recommended time. Only 14 of the 30 participants had baseline biases that could be modified, and those with positive biases were found to have previously abused more substances. Amongst these 14 participants, only 11 (or 36.7%) have had positive baseline biases that reduced with the intervention. Opioid users completed an average of 3.5 sessions of the bias modification intervention. The feasibility study confirmed that the recruitment methods were appropriate, and participants adhered to the interventions. It also demonstrated that my research could be conducted alongside the ward's existing rehabilitation program. However, the absence of baseline biases might be due to the use of medications during detoxification or the nature and timing of the visual probe task stimuli.

The qualitative comments from the feasibility study have also highlighted the need to consider the patient's perspective. This approach is relatively consistent with the increased recognition of participatory action and design research methods. PDR is defined as a qualitative research method involving key stakeholders to ensure that the research will be relevant and acceptable. In Chapter 7, PDR methods were applied to help refine the previously conceptualised mobile attention bias modification intervention. There are several reasons as to why PDR methods are needed to be considered for attention bias modification interventions. Firstly, the visual probe paradigm requires an individual to perform onerous repeats of the trials, which usually reduces motivation to train. Secondly, PDR methods allow participants to consider methods to improve their motivation to train. Thirdly, PDR could also be utilised in exploring participants' perspectives on gamification to determine whether gamification helps improve motivation. The application of PDR methods is one of the main novelties of this research, as prior to our work, no studies have attempted to personalise an attention bias modification intervention.

Three workshops involving healthcare professionals, both inpatients and outpatients, were conducted. The healthcare professionals and patient participants reported the stimulus presentation too rapid. Their preference was for a lengthier stimulus presentation interval at the start of the intervention and the stimulus interval to decrease as the intervention continued. Patient participants recommended personalisation of the included images. Some patients were cautious about the inclusion of gamification. The most common gamification elements recommended by both groups were that of

feedback, levels, and rewards. Patient participants reported safety concerns should the intervention be administered to individuals in early recovery (i.e., the stimulus images triggering cravings and leading individuals to a relapse). These findings are novel in the field of attention bias modification. In future conceptualisations of the intervention, the stimulus presentation for attention bias modification should thus be lengthier. Studies should also consider presenting both at a short and long stimulus interval to measure initial orientation and delayed disengagement. Future research should also consider having patient participants rate images for relevancy before including them. For gamification, the techniques could be considered. However, there remains a need to exercise caution in implementation, given that patient participants were concerned about the potential to generate an addiction to games.

Chapter 8 described the protocol for the randomised pilot study, comparing the co-designed intervention with the conventional intervention amongst individuals with opioid use disorder. Conducting a pilot study was critical, as it helped identify and eliminate problems that might jeopardise the success of the definitive randomised control trial. Targeting biases amongst individuals suffering from opioid use disorder was essential, given that previous reviews have highlighted the presence of strong biases despite individuals being maintained on opioid substitution therapy. Thus, this pilot study aimed to determine whether the definitive study's intended process (i.e., the recruitment of participants, randomisation into two separate arms and the administration of the intervention) would work. The plan was to screen a total of 60 participants and to allocate 30 participants each to either of the interventions. However, only eight participants were recruited before the onset of the COVID-19 pandemic, which curtailed further recruitment. Only three of the recruited participants presented with baseline biases and all these three participants were randomised to the co-designed intervention. None of the participants completed all the planned interventions. A risk assessment revealed high risks relating to subject recruitment, high attrition of subjects, insufficient funding, exceptional or unexpected delays and limited impact of the findings.

To mitigate the risks identified in Chapter 8, those of participant recruitment and attrition, Chapter 9 describes a new computational method (Trial-level Bias score) that

has been recently investigated in the literature, as a new method for computing attentional biases, and for demonstrating that attentional biases are not a static trait, but one that varies temporally across the trials. The reliability of TL-BS has been investigated in other studies, and the utilisation of this method could potentially identify more individuals with baseline biases. Chapter 9 highlights how this new method has been applied to the findings arising from the feasibility and pilot studies, and demonstrated that with the new method, it allowed for the re-classification of some individuals with previous negative baseline biases (as detected by the mean bias score) to having positive baseline biases. In Chapter 9, the temporal variation in attentional biases was also demonstrated for one participant (from the pilot study). This is a novel finding, as to date, no published studies have reported the variation of biases across the trials in a cohort of opioid-using individuals.

Chapter 9 concludes with a study that compared the TLBS method against the conventional mean bias score method. The TLBS method allowed for the reclassification of 3 participants who had negative baseline biases (by the mean bias score method), but the overall percentage of individuals with positive baseline biases did not change. Despite these findings, this study has demonstrated the feasibility of a more robust method for the calculation of attentional biases. Chapter 9 concludes with a discussion of the reliabilities of the TLBS method and highlights how other issues relating to general variability in reaction time and how individual characteristics might affect the computation. There remains a need for future studies to refine the TLBS method, taking these into consideration.

Chapter 10 describes the conduct of a single-session attention bias modification study which aims to overcome the two main limitations of the previously disrupted pilot study, that of (a) the absence of baseline biases leading to few participants being randomised and (b) the high attrition rates across the sessions of the intervention. The evaluation of a single-session approach also showed that among those with positive biases, 72.7% of them managed to successfully retrain their biases following just a single-session of bias modification. This demonstrates the preliminary potential of a single-session approach in the acute reduction of the underlying attentional biases. These findings are integral in refining the intended methods of the definitive randomised trial. From my findings, the TLBS method could be used in the definitive

study, as it is superior to the mean bias score method in terms of reliabilities; and it would make sense to have participants undertake a single session of bias retraining first, and then compare the reduction in attentional biases magnitude against repeated interventions. My findings have demonstrated that some individuals only require a single session of bias modification, while others might need further sessions for their attention biases to be reduced.

Chapter 11 described the protocol for a definitive randomised controlled trial comparing the effectiveness of the co-designed intervention with that of the conventional intervention using a three-session approach. Apart from comparing the effectiveness of the different interventions, it was intended to compare between a single session versus a three-session multi-session attention retraining approach. A three-session approach was planned for, as based on our feasibility study, participants completed an average of 3.5 sessions; and the findings, as aforementioned in Chapter 10, demonstrated that some individuals might need more than a single session. The prior studies have informed the conceptualisation of the protocol, to ensure that the significant risks to the conduct of the study will be mitigated. The data from the feasibility, pilot and single session study also informed the required sample size, in that a total sample of 222 participants with 111 per group is required to determine the superiority of the co-designed intervention, as compared to the conventional intervention. The rate of recruitment from the prior studies also suggests that the definitive trial will take between 27 to 36 months for completion. This has enabled us to draft a budget to seek external sources of competitive funding to finance this study. An estimated total funding of \$884,200 is required for the conduct of the randomised trial. The preliminary findings that we have obtained will be integral in justifying the funding required.

12.2 Discussion of Key Findings

In 2017, the only published reviews of attention bias modification were that of Christensen et al. and Cristea et al. (35, 89). The former review examined individuals with different addictive disorders but did not conduct a systematic review of the literature. The latter only comprised studies involving participants with alcohol and tobacco use disorders. Thus, my completed reviews were the first to systematically

synthesise all the evidence for attention biases amongst people with opioid, cannabis, and stimulant use disorders.

Since the conclusion and publication of my reviews, other reviews have also provided additional evidence for biases in these disorders. For example, in MacLean et al.'s review, the authors reported strong attentional biases among individuals with opioid use disorders. In their recent meta-analysis, O'Neill et al. have furthered our work by including 14 articles with a total of 1271 participants with cannabis use disorders (cannabis users, $n = 1044$; controls, $n = 107$) (278). These authors reported that individuals with cannabis use disorders have more significant attentional biases (278). These recent reviews have provided additional justification of the importance of assessing and modifying attentional biases. One of the main limitations of review 1 was that the effectiveness of attentional bias modification interventions could not be synthesised due to there being a paucity of interventional studies. A recent review by Hietmann et al. confirms this lack of interventional studies (150). They have considered a total of 18 studies, with most of the studies involving participants with alcohol and nicotine use disorders and three studies with participants with opioid use disorders. The authors reported evidence for multi-session attention bias modification for alcohol use disorder, whereas for opioid use disorders, only one study reported effectiveness. Thus, strong evidence supports this PhD work's rationale to evaluate the assessment and modification of attentional biases.

My second literature review in Chapter 3 revealed the disconnect between academics and developers, with most commercially available applications not being evidence-based. It also highlighted the difficulties academics face in commercialising their scientifically validated application. These findings are novel for the field of mobile cognitive bias modification interventions. In other fields, studies like Marshall et al., in their review of applications for anxiety and depression, have similarly reported that a low proportion of applications (3.4%) were evidence-based (279). Our findings also underscored the recommendations of Marshall et al. (279). These authors recommended that there should be more research into the effectiveness of mental health applications and that clinicians should exercise caution when recommending health applications. The work of Cox et al., which was the only study that have evaluated a commercially available application, should guide future research into cognitive bias modification

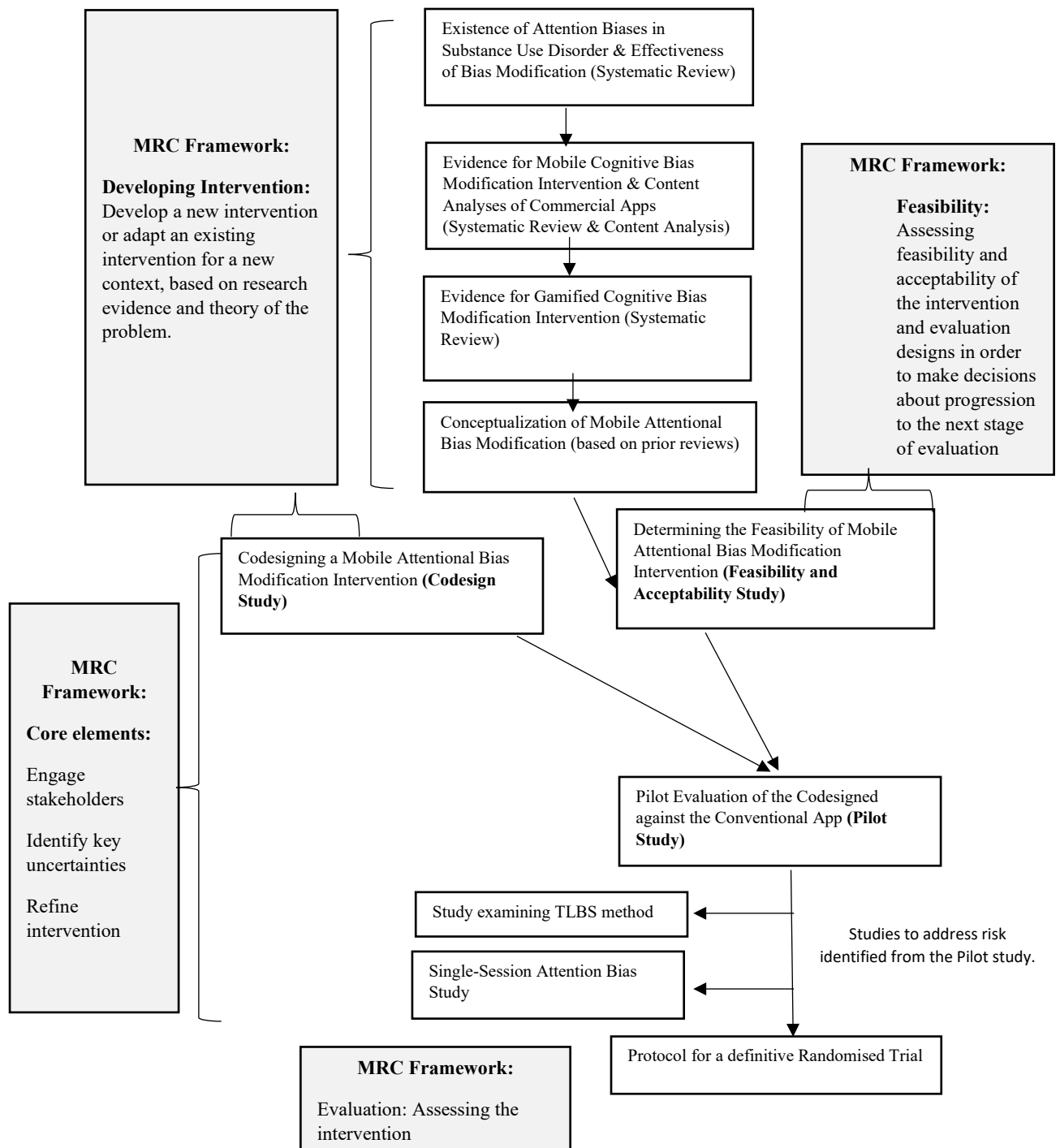
interventions in terms of how they evaluate their application and made it commercially available (170). Investigations of the utility of smartphone technologies in delivering cognitive bias modification interventions are justified. These technologies make it unnecessary for individuals to be confined to a laboratory to receive the intervention and facilitate the generalisability of training. Since the publication of the review, other researchers have investigated the effectiveness of these mobile technologies. For example, Laurens et al. examined a total of 1,082 individuals, who used an alcohol avoidance training application for 3 weeks, with 2 training sessions per week (280). The authors reported that 79% of the participants were adherent, and the intervention significantly reduced alcohol consumption (280). Similarly, Flaudias et al. also investigated the utility of a tablet-based application (281). They reported that those individuals who received attention bias training significantly reduced attentional biases (281). Most of the investigations have been confined to the investigation of alcohol use disorder. Given the initial positive findings from these studies, they provide further evidence justifying the investigation of mobile technologies for other substance use disorders.

Review 3, Chapter 4, investigates the utility of gamification in cognitive bias modification interventions, and the findings generated have helped guide the application of funding and the discussion of the co-design study (study 6). The completed review was the first to explore the commonalities in gamification techniques adopted amongst gamified cognitive bias modification interventions. Whilst there has not been further research in the published literature regarding gamified attention bias modification interventions at the time of this review, other recent studies have provided evidence of the potential of gamification. Litvin et al. compared a gamified application with a conventional cognitive behavioural therapy application and a waitlist control (282). They reported increased adherence and improved symptomatology amongst individuals assigned to the gamified application. The fact that gamification could increase adherence and reduce attrition is important, as cognitive bias modification interventions are known to be highly repetitive, such that motivation to train can decrease over time. Gamification could thus be a viable solution to this.

Study 1 (Feasibility and acceptability study, Chapter 6) was one of the key studies undertaken in this doctoral work. As aforementioned, this PhD work plan was based on

the MRC's framework for complex interventions. Figure 12.1 illustrates how the studies conducted within this PhD were aligned with the MRC's guidelines for complex interventions. Moreover, Study 1 examined attention bias assessment and modification in an inpatient sample of participants at NAMS, which is the first-time attention bias research has been undertaken in Singapore. The importance of conducting feasibility studies in advance of the definitive study has been recognised by other researchers in the field, such as Manning et al., who conducted an open-label pilot trial of feasibility and acceptability for a combined approach of bias modification and working memory training (283). Evidence from feasibility studies is integral in the planning of definitive studies. In our case, the successful conduct of Study 1 has helped in providing data regarding recruitment, adherence, attrition, and eligibility rates that were essential in planning the pilot and the definitive trials. Similarly in Manning et al.'s latter study, their feasibility study guided the sample size calculations (283). In addition, as the investigation of attentional biases amongst our patients was the first study of its kind, the success of the feasibility study contributed to progression to a pilot study (202).

Figure 12.1 Overview of MRC Framework and how the conducted studies integrate with MRC framework



Study 2 (Co-design study, Chapter 7) explored healthcare professionals' and patients' perspectives to refine the mobile attention bias modification intervention. Study 2 was the first of its kind in the field of cognitive bias modification interventions and

addressed some of the limitations with prior works. For example, Field et al. only investigated and recommended the personalisation of the stimulus images to improve the resultant reliability of the visual probe task (61). In more recent works by Manning et al. (2020, 2021, the authors described how their approach bias modification intervention was personalised, but the personalised features were limited to having participants select stimulus images that were relevant for themselves and having notifications within the application to remind individuals to complete specific assessments (284,285). Only recently did researchers like Manning (2022) consider the importance of personalising other features of their approach bias modification intervention for individuals with alcohol use issues (285). It is clear how our initial study set the stage for these subsequent studies and is instrumental in influencing researchers to consider the importance of the personalisation of cognitive bias modification interventions. In study 2, healthcare professionals and patients provided input not only regarding the images, but also in relation to the design of the intervention and the stimulus timing intervals for the bias modification task. Participants also selected gamification elements that they felt were appropriate for the task. The eventual application has been conceptualised and described in Zhang et al.'s paper on the needs of patient participants (235). Our co-design approach is pragmatic and resembles the approach used by Marjolein et al. (286). They employed co-design to develop an application that was culturally tailored and incorporated appropriate behavioural change techniques. The needs of Singaporean patients might differ from Western individuals; thus far, no study has investigated this. We cannot assume that all elements of an attention bias modification intervention that has been evaluated amongst a Western population would necessarily appeal to, and be effective in, our population.

Study 3 (Pilot Study, Chapter 8) describes the conduct of the pilot study, which aimed to refine the processes and methods for the definitive study. Although the study could not be completed due to the onset of the COVID-19 pandemic, the study has enabled the performance of a risk assessment, allowing for improved planning of the definitive randomised trial. The realities of such sudden, acute disruption have questioned how resilient conventional planned research methodologies are (278).

Study 4 (Single-Session Attention Bias Modification, Chapter 9 & 10) describes the application of a new computational method for the computation of attentional biases,

and the investigation of a single-session attention bias modification approach. The application of the TLBS method to compute attentional biases and to demonstrate the temporal variation in attention biases in individuals with opioid use disorder, is a novel finding, as no prior studies have attempted to do so. The findings arising from Study 4 augments the recent findings regarding the reliabilities of the TLBS method for addictive disorders (255). Similarly, the investigation of a single-session approach towards bias modification for individuals with opioid use is novel. It was important to conduct this additional study, as it allows for the evaluation and assessment of whether the intended research approach (which will subsequently be used in the definitive RCT) will be actionable and implementable. This is in-line with the RE-AIM framework that was introduced in Chapter 6. The conduct of this additional study is also in-line with the MRC framework, that emphasises the need for the identification of key uncertainties and the refinement of the intended intervention.

Study 5 (Chapter 12, Protocol for Definitive RCT) has been developed based on all the findings yielded to date to achieve a robust trial design. Based on the recruitment rates obtained in the prior studies, 36 months will be needed to conduct randomised trial's conduct. It is also evident that a relative sizeable funding is necessary for the conduct of this trial, and hence this cannot be undertaken in the current duration and with the limited funding in this PhD work.

12.3 Strengths and Limitations

The key strength of this body of work is that the intervention for this vulnerable population (individuals with addictive disorders) was conceptualised based on both the existing evidence and local patient participants' input. Additionally, this body of work was the first to incorporate a co-design process that resulted in the developing a personalised, novel, gamified attention bias modification intervention. The co-design process sought to optimise the stimulus images and the nature of the interventional task. This is an improvement over the prior work in this field, which only sought to optimise the nature of the images included in the stimulus set.

One of the challenges in Singapore pertains to the recruitment of individuals with addictive disorders for research, given the legalities involved about the mandatory reporting of individuals to the governmental and regulatory bodies, should they self-

report or if there is the presence of any clinical evidence of abuse of substances. In spite of such challenges, we have managed to achieve good recruitment numbers for most of the planned studies, albeit for the pilot study, which recruitment was disrupted in view of COVID-19. This was in part aided by the fact that all participants were informed of this legality issue during their orientation to our clinical service at NAMS.

In this body of work, the recommendations of the MRC framework on the development and evaluation of complex interventions were adhered to. In this framework, feasibility and pilot studies are recommended before the actual definitive trial. These preliminary studies helped to ensure that factors that might result in the trial being unsuccessful were minimised. Whilst the planned pilot study cannot be completed, a risk assessment was performed (Chapter 8), and it helped identify all the potential risks that might affect the definitive study in the future. The risks identified allowed for the conduct of subsequent studies (Chapter 9 & 10) which helped further to refine the intended methods of the definitive randomised trial and ensure that the overall intervention is pragmatic and could be implemented. We have managed to execute and conduct all the necessary preparatory studies to guide the plan for the definitive randomised trial.

The findings from each stage of this research program have been published in reputable international journals. In Section 10.5, I outlined how these papers have contributed to academia. The fact that the findings have all been peer-reviewed and published confirms the scientific rigour of this doctoral work. Already, some of these published works have also been cited by other academics. This helps to justify the impact and the contribution of my studies.

Alongside the many strengths of the research, there were also several limitations. Indirect measures of attentional biases, that of the visual probe tool, had to be used instead of direct measures, given the cost and complexity of direct measures, which make them impractical in the clinical setting. For the feasibility study, a small number of participants with alcohol use disorders were recruited, given that a proportion of individuals do have other medical comorbidities, particularly withdrawal seizures. The co-design study would be beneficial if both healthcare professionals and patient participants were jointly present in a single workshop. Unfortunately, given ethical considerations, this approach was not possible. The ethical board was concerned about

the power differential if both healthcare professionals and patient participants were in the same workshop and were concerned this might influence participants' response. In the synthesis of the findings from the co-design study, the perspectives from healthcare professionals and patient participants had to be integrated. I was unable to reperform the pilot study when the COVID-19 pandemic improved, given the expiry of the funding. Although the funding agency allowed for extension given the COVID-19 pandemic, the pandemic was too protracted and there were also other challenges to restart the study within the study, which render it impossible.

12.4 Research Implications

Further evaluative work will be necessary to determine whether the co-designed application is indeed more effective than the conventional intervention (i.e. the conduct of the definitive randomised trial). If proven effective, this will warrant further evaluation amongst patients with other substance disorders. There needs to be future work comparing the effectiveness of a single-session versus a multi-session bias retraining approach, and identifying individual characteristics that differentiate between whether someone needs just a single session, or require more protracted interventions. Future work should also determine the generalizability of the application when used in an 'individual' naturalistic environment, ideally using ecological momentary analytical methods, whereby individuals are tasked to take the intervention when they are deemed to be of high risk. Much of my current work focuses on the use of the application in a controlled environment. In Zhang et al.'s perspective article, I have highlighted the associations between bias modification and neurobiological changes (56). It is important for future research to better examine the biological underpinnings of bias modification by examining the dynamic changes in the brains of individuals following bias modification interventions. Future research should also consider following up individuals over time, to determine if there are sustained changes in outcomes relating to abstinence.

12.5 Clinical Implications

The completed reviews and studies have provided evidence for the existence of attentional biases in a Singaporean sample of individuals with addictive disorders. The existence of these automatic, unconscious biases could be a mediating factor responsible for an individual's lapse and relapse into their pre-existing condition. This

might bring about a paradigm shift in psychological treatment in that, bias modification intervention could be considered as an adjunctive treatment to conventional psychosocial therapies. This therapy helps in the remediation of cognitive biases, which conventional psychosocial therapies do not address. The fact that these interventions could potentially be delivered remotely, and without guidance by a therapist, also facilitates individuals' access to the intervention.

12.6 Contribution to Current Research

This body of work makes extensive contributions to addiction psychiatry and digital health, which is reflected by the high number of publications throughout the PhD journey. Table 10.1 provides an overview of the papers that have been published to date, the journals in which they have been published, the impact factor of the journals and, finally, the citations to date (according to Web of Science) for each of these published papers. Publication in open-access journals was a priority, given the launch of the Plan S mandate in 2018, which required scientists and researchers who benefit from state-funded research to publish their works in open-access repositories or journals that are available to all by 2021 (287). It is evident that my work has impacted the research community, given the number of publications and the corresponding citations. Some of the publications have also been reviewed by leading authors in the field, such as Wouter Boendermaker (Netherlands), Marilisa Boffo (Netherlands) and Reinout Wiers (Netherlands).

Table 12.1 Overview of published papers based on this doctoral research.

Title	Journal Published in & Year	Impact Factor & Rank of Journal	Total Citations (by February 2023)	Peer-review Reviewers
Attention bias in individuals with addictive disorders: systematic review protocol (112)	JMIR Research Protocols (2018)	0	7	Carol Choo Jiemin Zhu
Attention and cognitive bias modification apps: review of the literature and commercially available apps (181)	JMIR mHealth and uHealth (2018)	4.301, Q2 (Health Informatics)	21	Daniel Leightley Cendrine Robinson Robert Leeman
A systematic review of attention biases in opioid, cannabis, stimulant use disorders (113)	International Journal of Environmental Health and Public Health (2018)	2.468, Q1 (Public, environmental & occupational health), Q2 (Public Health, Environmental and Occupational Health)	12	Anonymous
Mobile phone cognitive bias modification research platform for substance use disorders: protocol for a feasibility study (191)	JMIR Research Protocols (2018)	0	3	Wouter Boendermaker Marilisa Boffo
Enhancing the quality and utility of content analyses for addictive disorders (288)	International Journal of Environmental Health and Public Health (2018)	2.468, Q1 (Public, environmental & occupational health), Q2 (Public Health, Environmental and Occupational Health)	12	Anonymous
A review of gamification approaches in commercial cognitive bias modification gaming applications (289)	Technology and Healthcare (2018)	0.787 (Q3, Health Informatics)	5	Anonymous
Web-based cognitive bias intervention for psychiatric disorders: protocol for a systematic review (153)	JMIR Research Protocols (2018)	0	1	Isabella Choi Montse Ferrer
Gamified cognitive bias interventions for psychiatric disorders: protocol of a systematic review (290)	JMIR Research Protocols (2018)	0	6	Wouter Boendermaker Marilisa Boffo
Gamified cognitive bias modification for psychiatric disorders (291)	JMIR Mental Health (2018)	3.54, Quartile ranking not available	13	Lies Notebaert Stephan Zipfel P Chand
A smartphone attention bias intervention for individuals with addictive disorders: protocol for a feasibility study (292)	JMIR Research Protocols (2018)	0	3	Roger Ho Bach Tran Reinout Wiers

Recent advances in attention bias modification for substance disorders (56)	International Journal of Environmental Health and Public Health (2018)	2.468, Q1 (Public, environmental & occupational health), Q2 (Public Health, Environmental and Occupational Health)	18	Anonymous
Cognitive biases in cannabis, opioid, and stimulant disorders: a systematic review (125)	Frontiers in Psychiatry (2018)	3.161 (Q1, Psychiatry and Mental Health)	9	Domenico De Berardis Azienda Usi Teramo Robert F Leeman
Incorporating participatory action research in attention bias modification intervention for addictive disorders: perspectives (293)	International Journal of Environmental Health and Public Health (2019)	2.468, Q1 (Public, environmental & occupational health), Q2 (Public Health, Environmental and Occupational Health)	7	Anonymous
Variations in the Visual Probe Paradigm for Attention Bias Modification for Substance Use Disorders (184)	International Journal of Environmental Health and Public Health (2019)	2.468, Q1 (Public, environmental & occupational health), Q2 (Public Health, Environmental and Occupational Health)	1	Anonymous
A smartphone attention bias app for individuals with addictive disorders: Feasibility and Acceptability Study (212)	JMIR mHealth and uHealth (2019)	4.301, Q2 (Health Informatics)	9	Carol Choo Frederike Fellendorf Najmeh Khalili-Mahani
Co-designing a mobile gamified attention bias modification intervention for substance use disorders: Participatory Research Study (235)	JMIR mHealth and uHealth (2019)	4.301, Q2 (Health Informatics)	7	Roger Ho Lies Notebaert Charlotte Magnusson Katherin Blondon
Co-designing a mobile gamified attention bias modification intervention: research protocol (234)	BMJ Open (2019)	2.376, Q1 (Medicine)	0	Anonymous
Web-based cognitive bias intervention for psychiatric disorders: Scoping Review (294)	JMIR Mental Health (2019)	3.54, Quartile ranking not available	8	Geronimo Jimenez Tzu Tsun Luk Sary Beidas
Making sense of negative findings from mobile attention bias modification interventions for individuals with addictive disorders: quantitative feasibility study (295)	JMIR mHealth and uHealth (2019)	4.301, Q2 (Health Informatics)	1	Roger Ho Tim Klose
Gamified M-Health attention bias modification intervention for Individuals with Opioid Use Disorder: Protocol for a Pilot Randomized Study (296)	International Journal of Environmental Health and Public Health (2019)	2.468, Q1 (Public, environmental & occupational health), Q2 (Public Health, Environmental and Occupational Health)	1	Anonymous

The insights gained from this current work has been applied to other related research areas. Through a collaboration with a team at James Cook University, Singapore, we have applied the same application, albeit with modifications, and conducted a mixed-method study amongst undergraduates with tobacco use disorders. The preliminary findings from my current work have been used as a basis for a study to investigate emotional biases amongst children with attention deficit/hyperactivity disorder. This project secured \$10,000 from the National Healthcare Group Serious Game Grant. Within NAMS, we have also undertaken further scoping reviews to demonstrate the existence of attentional biases in individuals with behavioural addictions.

12.7 Impact of Research on Researcher

Before the commencement of my PhD, I worked as a psychiatrist with a keen interest in research in the realms of digital health (E-health & M-health). Whilst I have published extensively, my publications were limited to proof-of-concept papers, technical notes and review as it was challenging to perform in-depth research on a topic or disease condition given the lack of funding and resources. My PhD study has allowed me to explore and examine my topic of interest in-depth and to refine my skills at performing reviews – including scoping, literature, and systematic reviews. Focusing on digital interventions, I have had the opportunity to improve my skills in conducting a content analysis of applications. I was also able to conceptualise from scratch both a feasibility and a pilot study, and I have learned how to not only conceptualise a study but also plan the logistics and conduct risk assessments. I have had the opportunity to learn entirely new skills, particularly in qualitative research methods, and to conduct a co-design research study. In view of the challenges posed by the pandemic, I was also forced to be innovative and pragmatic in re-conceptualising some of my intended research. I have also learnt how to conceptualise, plan for and conduct studies that are necessary in developing a complex intervention. As evident from Table 12.1, I have managed to publish most of my work, and this has helped me increased my visibility in the field of attention and cognitive bias modification, and this has led to new opportunities for collaborations, both locally and globally.

As an addiction psychiatrist, I have always been perplexed by the multiple relapses that an individual with addictive disorders experiences. This PhD work has allowed me to investigate a potential factor that can mediate these relapses, and I am encouraged that my findings demonstrate that attentional processes could be a contributing factor. I have planned future research (as described in Chapter 11) to further evaluate the intervention, and I hope that the intervention could be an adjunctive treatment modality to conventional psychological interventions.

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Perspective

Recent Advances in Attention Bias Modification for Substance Addictions

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Abstract: Research on attentional bias modification has increased since 2014. A recent meta-analysis demonstrates evidence for bias modification for substance disorders, including alcohol and tobacco use disorders. Several pharmacological trials have shown that pharmacological agents can attenuate and modify such attentional bias. The pharmacological trials that have appeared to date have produced mixed results, which has clinical implications. Developments in Internet and mobile technologies have transformed how attention bias modification is currently being achieved. There remains great potential for further research that examines the efficacy of technology-aided attention bias interventions.

Keywords: attention bias; attention bias modification; substance abuse; addiction; E-Health; M-Health

1. Overview of Prior Literature Review

Field et al. [1] and Cox et al. [2] have each highlighted the presence of attentional biases in substance use disorder and evaluated the clinical importance of attentional biases in their review and opinion articles. Attention biases are unconscious processes that typically cause individuals with substance use disorder to automatically orientate their attention towards substance-related cues in their naturalistic environment, with subsequent difficulty in disengaging from these cues [3]. Attentional biases are evaluated by a variety of measures. Most commonly, attentional biases are assessed using reaction time tasks, such as the Stroop task or the Visual Probe task [4]. In the Stroop task, participants are required to name the color of both the neutral and the drug-related word. The differences in the reaction time provide evidence for the presence of attentional biases. Similarly, for the visual probe task, participants are required to respond to a probe that replaces either a neutral or a substance-related image. The presence of attentional bias is demonstrated when participants demonstrate a faster reaction time responding to the probe that replace substance-related images [4].

Based on the dual-process model, it has been proposed that the chronic use of substances will increase the automatic processing of substance-related cues [5]. The dual-process model also proposed that these automatic tendencies tend to be coupled with inhibitions in normal cognitive control processes [5]. In a narrative review by Field et al. [1], attentional biases were of importance as they could predict the potential for relapse in individuals. However, the authors did not recommend that attentional bias modification should be included as part of the conventional treatment program,

as the evidence about efficacy was mixed [1]. Instead, Field et al. [1] highlighted a need for larger clinical trials to be conducted to generate more conclusive evidence. They also recommended that future research should focus on individuals, who are at high risk of relapse. These individuals have higher temptation and motivation to use the drug, with attentional biases possibly being enhanced in this context.

While Field et al. [1] highlighted that there is mixed evidence for attentional bias, Cox et al. [2] reviewed several attentional bias programs, including the alcohol attention control training program (ACTP) [4]. They reported that the attentional bias program is efficacious for re-training attentional bias, reducing craving, and enhancing self-efficacy and perceived self-control in a sample of harmful drinkers. Cox et al. [2] also reported the efficacy of attentional bias modification for drug-related attentional bias, such as attentional bias to opiate cues, in a sample of drug abusers, who were undergoing methadone maintenance therapy. As described in Cox et al. [2], attentional re-training typically involves an intervention that helps to retrain bias away from substance-related cues. For example, the visual probe task would involve having probes to replace the neutral rather than the substance-related stimuli [6]. These prior studies based on evidence arising from individual studies conducted before 2014, have already demonstrated the potential of targeting attentional biases amongst substance use individuals.

2. Objectives of Current Perspective Article

Since 2014, there have been further advances in the field of experimental psychology, with more research conducted on attentional bias modification. Attentional bias in addictive disorders has now been extensively investigated in a variety of addiction disorders [6,7]. Thus, the main objective of the current perspective article is to provide an overview of the literature related to attentional bias modification for substance use disorders. Secondly, it reviews how technological advances have aided in the delivery of attentional bias modification interventions. Thirdly, it reviews the effect of pharmacological agents on attentional biases. Finally, it describes the authors' perspectives on the clinical and research implications of attentional bias modification.

3. Existing Evidence for Attentional Bias Modification

To date, attentional bias modification interventions have been evaluated for a variety of addiction disorders, ranging from substance addiction to behavioral addiction. A prior meta-analytical study has synthesized the evidence for cognitive bias modification based on randomized trials published until 2015 [8]. The review examined 25 randomized controlled trials: 18 involved participants with alcohol use disorder and 7 involved participants with tobacco use disorder. In the review, the visual probe task was used in all twelve studies that specifically targeted attentional biases [8]. It should be noted that the meta-analysis objective was to review cognitive bias modification; hence, the authors have included other studies that targeted other biases, such as approach biases and interpretative biases [8]. Nevertheless, the prior review reported that cognitive bias modification was effective in the reduction of cognitive bias (Hedges' $G = 0.60$) [8]. However, there does not appear to be a relationship between the reduction in bias and the consequential reduction in cravings, which are thought to lead to the improvements in addiction outcomes [8]. Cristea et al. have provided two reasons as to why there was no association between bias reduction and improvements in craving. Firstly, it is possible that bias modification has effectively reduced bias, but this reduction in biases did not translate directly to affecting the objective clinical outcome. Secondly, it could be that more time is needed for the changes in biases to be reflected as changes in symptoms [8]. Jones et al. [9] undertook a review of all currently published meta-analyses on cognitive bias and reported that cognitive bias modification programs consistently targeted bias with effect sizes of 0.52–0.81. This review highlighted that the long-term efficacy of cognitive bias modification was only evident in studies with participants that have a substance addiction disorder [9]. Impulsivity has been proposed to be a mediator of attentional bias, and this has been examined in a prior meta-analytic study by Coskunipar and Cyders [10]. In the

prior meta-analysis, a total of 13 studies that explored the relationship between substance-related attentional bias and impulsivity were analyzed. A significant but small effect size was found between that of impulsivity and attentional bias [10]. The presence of impulsivity would cause individuals to have heightened attentional biases [10].

Apart from the existence of further studies evaluating the effectiveness of bias modification, the advances in experimental psychology has also led to the creation of newer methods for bias assessment. Leeman et al. [4] highlighted newer approaches in their critical review, such as eye movement tracking. This has been successfully utilized in other studies for the assessment of biases [11,12]. Apart from eye movement tracking, electrophysiological measures have been used in the assessment and the characterization of the changes following attentional bias modification. In their recent study, Zhao et al. [3] collated electrophysiological data from individuals abstaining from taking opiates, who were administered a dot-probe task. Their results demonstrated that abstaining individuals still had biases towards substance-related cues, with electrophysiological data suggesting that there was an overall shorter P1 latency, larger N1, N2, and P2 amplitudes, and a shorter latency and amplitude for P3 [3]. The data from these electrophysiological measures demonstrate the increased involvement in certain brain regions, such as the dorsal posterior cingulate cortex, superior parietal lobule, and inferior frontal gyrus [3]. In their study using electrophysiological measures, Pravaz et al. [13] also demonstrate that there were changes in the late positive potential as attentional bias was modified. Recent fMRI studies have also demonstrated that attentional bias is associated with activation in the following regions of the anterior cingulate cortex, dorsolateral prefrontal cortex, insula, nucleus accumbens, and amygdala [14–16].

In summary, the current evidence highlights that attentional biases are present in substance addictions. These attentional biases are amenable to modification using conventional interventions for attentional bias modification. While attentional biases were reduced following bias modification, the reduction in attention bias was not associated with improvement in other symptoms, such as cravings. The advances in the methods of assessing attentional biases and analyzing the involvement of neural circuitry have several implications for further research.

4. Pharmacological Drugs on Attentional Bias

Dopaminergic neurotransmission has also been responsible for unconscious attentional processes. In their systematic review, Luijten et al. [17] synthesized the evidence-related pharmacological intervention for attentional bias in substance use disorders, which includes stimulant, opioid, and cocaine-dependent individuals. The evidence showed that medications that modulate dopamine do affect the strength of attentional biases [17]. In the studies included in this systematic review, the pharmacological agents used were amisulpride (D2/D3 receptor antagonist), pramipexole dihydrochloride (D2/D3 receptor agonist), haloperidol (D2/D3 receptor antagonist), methylphenidate (dopamine reuptake inhibitor), D-cycloserine (partial glycine-site NMDA agonist), and acute tyrosine or phenylamine depletion. The measurements of attentional biases were conducted using conventional paradigms, such as the dot-probe task or the Stroop task. There was a reduction in attentional biases after the acute administration of these pharmacological agents [18]. However, these findings are confined to acute effects following a single dose of a particular medication. There were no longer-term studies conducted to demonstrate that attentional bias would diminish following longer-term administration of dopamine modulating agents [17].

While the dopaminergic neurotransmission potentially could account for these unconscious attentional processes, other neurotransmitter systems have been implicated, such as the noradrenaline system and the glutaminergic neurotransmission system. Atomoxetine [19], a pharmacological agent modulating noradrenaline reuptake, has been shown to be efficacious in reducing attentional biases to cocaine-related cues. It is postulated that the administration of atomoxetine increases noradrenaline levels, particularly in the prefrontal cortex. The increase in the noradrenaline levels is associated with

increased conscious inhibitory control. Despite the promising findings, it should be noted that the study evaluated only the acute effects of a single dose of atomoxetine.

Liu et al. [20] evaluated the effect of the selective serotonin reuptake inhibitor of escitalopram on attentional bias in a sample of cocaine-dependent individuals. The study by Liu et al. was based on the evidence generated from a preclinical study, which suggests that agonists of the 5-HT_{2C} receptor could affect attentional biases [18]. The dosage of escitalopram administered was in the range of 10–20 mg and subjects were followed up for a total of 28 days [20]. The selective serotonin reuptake inhibitor has been shown to be effective in reducing attentional biases only in the acute phase, which was determined by the reduction in attentional bias from baseline that occurred five hours following the administration [20]. The continued administration of escitalopram did not produce any significant changes in attentional biases from baseline when Stroop testing was re-administered subsequently. To our knowledge, Liu et al. [20] is the only study to date that has administered a course of the pharmacological agent over an appropriate follow-up period. The acute effects of escitalopram on attentional biases might be due to the increased activation of the 5-HT_{2C} receptors, while the lack of a reduction in attentional biases following chronic administration might be accounted for by adaptive changes in post-synaptic receptors [20]. Liu et al. [20] also pointed out that the chronic administration of escitalopram might have resulted in desensitization of the 5-HT_{1A} auto receptors; hence, the prolonged administration of escitalopram did not result in further increases of serotonin levels.

The findings from these studies demonstrate that pharmacological agents are helpful in the modulation of attentional biases when these medications are given acutely. No studies have determined whether there will be further reduction in attentional biases if dopaminergic or other medications are administered for a longer duration. The evidence arising from Liu et al. demonstrates that the chronic administration of serotonergic medications does not alter attentional biases. There are clinical and research implications arising from these results, which will be discussed subsequently. The findings from the current studies also highlight that researchers seeking to evaluate attentional bias and the effectiveness of bias modifications need to consider the pharmacological agents that the sample individuals are already on, as it might confound the results of the psychological intervention.

5. E-Health & M-Health Based Attentional Bias Modification Interventions

The introduction of digital technologies into healthcare has revolutionized various healthcare practices. E-health refers to the use of Internet-based technologies, telephone, and text-based messaging to support health interventions [21]. M-health refers to how smartphone and their accompanying applications are used as health care interventions [21]. Such technologies are being used in medical and surgical disciplines. In the latter setting, these technologies have changed the delivery of interventions for attentional bias modification [22]. Conventionally, attentional bias modification interventions, which involves training individuals to gain control over their automatic responses, were delivered in a controlled environment, such as a laboratory. Nowadays, interventions can be delivered remotely. In their study, Wiers et al. [22] evaluated an automated cognitive bias modification program for problem drinkers that was delivered using the Internet. In this study, the approach and avoidance biases were targeted as part of their online cognitive bias intervention. Approach and avoidance biases are similar to that of attentional bias as they are all unconscious processes and tend to cause individuals to experience a lapse or relapse [22]. Wiers et al. observed a reduction in drinking across all the groups, including the group that has received only control training [16]. Despite the findings of the study, Wiers et al. showed the potential of delivering attentional bias modification programs using the Internet [22]. However, one of the main limitations of such a mechanism of delivery would be that of attrition [22]. In the study conducted by Wiers et al., it should be noted that half of the recruited participants were not commenced on the intervention and another half of the sample dropped out during the intervention [22].

Web-based attentional bias modification programs have also been evaluated in adolescents with anxiety and depression, with demonstrable efficacy of the web-based program in reducing both anxiety

and depressive symptoms [23]. The study also reported high attrition rates from their web-based interventions [23]. To tackle attrition, other researchers have introduced gamification elements into existing conventional attention bias modification tasks. In their recent study, Boendermaker et al. [24] described how they introduced serious game elements into a conventional visual probe modification task for individuals with alcohol use disorder. In their design, they modified the conventional visual probe task to resemble that of a slot machine game, including in-game credits and rewards [24]. Despite the introduction of gamification elements, it did not affect attrition and did not increase the motivation in participants to complete the tasks, as participants in all training conditions felt that the tasks became boring over time. In a prior study by Boendermaker et al. [25], gamified version of cognitive retraining was compared to that of placebo and regular training in a sample of participants with alcohol use problems. The authors reported that despite there being no changes in bias or drinking behavior, the addition of gaming elements did help to increase the motivation to train.

Other studies have also described how smartphone devices have been utilized in the delivery of attentional bias modification intervention [26,27]. In the study by Clarke et al., a smartphone device was used to deliver attention bias modification for individuals suffering from insomnia. They reported that bias modification was helpful in reducing the arousal symptoms and improving the overall sleep quality [26]. Yang et al. [27] reported the feasibility of delivering cognitive bias modification for individuals with social anxiety disorder using smartphone device. Hence, it is clear from the existing literature that technological advances are increasingly incorporated in interventions for attentional bias modification, although there needs to be further work to determine the efficacy of these interventions. The fact that gamification could help to increase motivation for training in some attention bias interventions does imply that this remains an area for further research.

6. Clinical and Research Implications

There are clinical and research implications that arise from recent advances in attentional bias modification. The findings from the meta-analysis demonstrate that attentional biases could be subjected to modification. Targeting attentional biases is pertinent as according to the dual-process theoretical model, the repeated usage of an addictive substance would increase the automatic processing of substance-related cues, including attentional biases and automatic approach tendencies for substance-related cues [1]. Furthermore, these automatic processes are thought to suppress the normal cognitive control processes [1]. Targeting attentional biases help to address one of the key factors that could result in individuals having a lapse or relapse. Furthermore, these biases are not typically targeted in conventional psychological therapies, such as cognitive behavioral therapy. Based on the review by Cristea et al., it appears that attentional bias modification has been well-studied for alcohol and tobacco use disorders. Even though this review searched for trials involving other substance use disorders, such as cannabis, opiate, and amphetamine, it appears that no randomized trials were found for their synthesis. Hence, this warrants further review to synthesize the evidence for attentional bias and evaluate the effectiveness of attention bias modification for other substance disorders.

In our literature review, we have not managed to identify studies involving bias modification in individuals with dual diagnoses. However, in the clinical context, it is common for individuals to present with comorbidities or with dual diagnoses. To date, researchers have largely focused on samples with an isolated diagnosis or disorder. It is important for there to be further research evaluating the efficacy of attentional bias modification for individuals with dual diagnoses and comorbidities.

The advances in assessment of attentional biases also imply that researchers are no longer confined to a single measure, which was previously reaction time, in the determination of attentional biases. More recently, electrophysiological measures have been used to demonstrate the presence of attentional biases. Thus, it is pertinent for researchers who are planning further studies in this area to consider both an indirect and direct measure, which can potentially improve the accuracy of detection of attentional biases. Direct measures, such as electrophysiological measures, are ideal for demonstrating

the neural circuits that are affected and potentially altered using bias modification. Direct measures could also inform clinicians of real-time changes in neural circuitry or changes in brain activation following each administration of bias modification. It would be crucial for future research to examine how technology-aided delivery of an attention bias modification task could be coupled with another direct objective measure, such as electrophysiological measurements.

Furthermore, given how repetitive the task might be, it will be wise to consider pairing attentional bias modification intervention with motivational interventions [28]. In the protocol by Boffo et al., the authors have suggested the inclusion of motivational interviewing, as it is believed that motivational interviewing could help to support the individual in making changes to his/her behavior [28]. In addition, there appear to be mixed findings arising from pioneering work involving gamification for attention bias intervention. To some extent, this might imply that there remains a need for some elements of face-to-face contact, but it also implies that there needs to be further research to select the most appropriate gamification strategy for attention bias interventions.

More research is needed to evaluate web-based interventions to establish their efficacy. There are advantages to web-based interventions, as individuals would not need to be confined to a particular environment to receive the interventions for attentional bias modification. Moreover, the advances in technology might also allow for users to partake in these interventions immediately when they are at risk of relapse.

The findings from the pharmacological trials to date show that pharmacological agents are only efficacious in the acute reduction of attentional biases. While a diverse range of pharmacological agents has been evaluated, there remains a need for further studies evaluating the longer-term efficacy of pharmacological agents that modulate dopaminergic and other neurotransmitters. Current findings are important clinically as if these agents are useful in the chronic reduction of attentional biases, they could be considered for usage to prevent lapse and relapse in individuals. However, the usage of these pharmacological agents needs to be carefully considered due to their high propensity for inducing side effects. This includes extra-pyramidal side effects, amotivation, and apathy for medications, such as haloperidol. To minimize these side effects, it would be ideal if there were similarly efficacious psychological interventions for attention bias modification for which participants could be recruited. Researchers do need to take into careful consideration the pharmacological agents that individuals are on when they are evaluating attentional bias interventions, as some of these medications are potential confounders.

7. Conclusions

In conclusion, there remains a need for further research synthesizing the evidence and effectiveness of attention bias modification for other substance disorders. It is also important for future research to evaluate the efficacy of attentional bias modification for individuals with dual diagnoses. Future research should also consider pairing an indirect measure with a direct measure for the assessment of biases. Motivational interventions and gamification strategies need further evaluation to determine their effectiveness in helping to increase intrinsic motivation of participants undertaking bias modification interventions. Studies should also evaluate web-based bias interventions to determine their efficacy. Future pharmacological trials should evaluate whether chronic administration of pharmacological agents is effective in reducing attentional biases.

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Protocol

Attention Bias in Individuals with Addictive Disorders: Systematic Review Protocol

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Abstract

Background: Globally, substance disorders, particularly that of opiate use, cannabis use, and stimulant use disorders, are highly prevalent. Psychological treatments are an integral aspect of intervention, but a proportion of individuals still relapse despite having received such an intervention. Recently, the dual-process theory proposed that the unconscious processes of attention biases are responsible for these relapses. Prior meta-analyses have reported the presence of attention bias in alcohol and tobacco use disorders. More recent research has examined attention bias and its effectiveness in opiate use, cannabis use, and stimulant use disorder. The evidence syntheses to date have not examined whether attention bias is present in these disorders and could be subjected to manipulation. This is important information and would support the introduction of psychological interventions for attention bias for such patients. Such psychological interventions would help individuals maintain their abstinence and minimize the risk of relapse.

Objective: This paper aims to undertake a systematic review to synthesize the existing evidence for the presence of attention bias in all the disorders mentioned above, and to determine the clinical efficacy of attention bias modification.

Methods: A systematic review will be conducted. A search will be conducted on the respective databases up till 2017. Selection of the studies will be determined by the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. Quality assessment of the included studies will be assessed using the Cochrane Risk of Bias tool. A narrative synthesis will be conducted, with a meta-analysis considered only if there are sufficient studies for statistical analysis.

Results: The results of the systematic review will be available 12 months after the publication of this protocol.

Conclusions: This review is important as it will support the introduction of psychological interventions for attention bias for such patients. Such psychological interventions would help individuals maintain their abstinence and minimize the risk of relapse.

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KEYWORDS

attention bias; substance addiction; systematic review

Introduction

Background

The recent statistics from the United Nations Office on Drugs and Crime reported that a quarter of a billion individuals experimented with drugs in 2015, and 29.5 million individuals are currently diagnosed with a substance disorder [1]. The most commonly abused drugs include cannabis, opioids and amphetamines [1] with a prevalence of 3.8%, 0.7% and 0.77%, respectively [1]. Drug usage and dependence is also associated with comorbidities, such as that of retroviral diseases and hepatitis C. Among the 12 million individuals who have used drugs intravenously, 1.6 million individuals have acquired a retroviral disease and another 6.1 million individuals have acquired hepatitis C [1]. In response to this huge problem, the World Health Organization and the United Nations Office on Drugs and Crime have been working jointly in the formulation of various policies, and to improve the existing levels of care in low- and middle-income countries [2].

The treatment options for drug abuse are both pharmacological and nonpharmacological. Psychosocial treatments complement and augment the effectiveness of pharmacological treatments, and prior reviews have reported the effectiveness of a combination treatment for opioid use disorders [3]. A variety of psychological approaches are used, such as contingency management and cognitive behavioural therapy (CBT). While therapies such as CBT have been demonstrated to be efficacious in the treatment of cannabis use disorder [4], other studies have reported that despite its effectiveness, at least 40%-50% of individuals relapse within a year of successful treatment, and 70% of individuals relapse within three years [5]. Pharmacological options for the treatment of addictive disorders are varied; for cannabis and amphetamine disorders, these are limited, whereas for opioid use disorders, opiate substitution therapies (eg, methadone and buprenorphine) can be used [6]. Current evidence supports the use of symptomatic medications in the management of individuals who are acutely intoxicated, such as benzodiazepines for its sedative properties, and antipsychotics for individuals experiencing psychotic symptoms [7]. Recent research has addressed the use of gabapentin in the treatment of cannabis withdrawal, but further trials are necessary to determine its efficacy [7].

The observed high relapse rates into substance usage suggest that current psychosocial interventions do not completely address the issues leading to either lapse or relapse. The dual process model of addiction [8,9] has been posited to explain the lapse and relapses; this model proposes the involvement of two disparate processes, the reflective and the automatic process [8]. The reflective process involves conscious decision-making, and this has been the target of CBT treatment. Automatic processes refer to that of attentional bias [10], which are unconscious processes that lead individuals to focus on substance-related cues in their naturalistic environment and, having done so, experience a corresponding difficulty in disengaging from cues [10]. Such an automatic process increases the salience of substance-related cues and could potentially draw abusers towards substances. Attention bias could be

assessed using indirect measures, like that of Stroop test or a Visual Probe task, or the use of direct measures through eye movement tracking [10]. Indirect measures have the potential to be incorporated into an attention bias modification task, to help individuals cope with automatic processes that increase their intrinsic risk for relapse [11].

To date, there have been several studies that have evaluated the efficacy of attention bias modification paradigms for addictive disorders. Cristea et al [12] undertook a meta-analysis of attention bias modification for alcohol and tobacco disorders and found no significant effect of cognitive bias modification on craving and addiction outcomes, even though there was a moderate effect on cognitive bias. Their findings are important as they demonstrate the presence of cognitive bias. In addition, attention bias modification was effective against such biases. Unfortunately, Cristea et al's [12] meta-analysis was unable to demonstrate significant changes in secondary outcomes, but this could be because more follow-up time is required before a change in symptomatology is detectable. This review was further limited by the high risk of bias amongst the studies included and its focus being limited to alcohol or tobacco. Christiansen et al's [13] review had a wider target, including individuals who were using alcohol, tobacco, cocaine and cannabis. They attempted to appraise the existing evidence to determine whether attention bias assessed in treatment settings are predictive of relapse and whether modifying attention bias can help improve outcomes. Their review found mixed evidence. This study, however, had a number of limitations: the intrinsic methodological weaknesses of the included studies, the lack of clarity about inclusion and exclusion criteria, the time frame during which the search was conducted, and using search results from only PubMed and Scopus.

To date, there has been research that has examined attention bias and determined the effectiveness of attention bias modification in other addictive disorders, like opiate use disorder [14], cannabis use disorder [15] as well as amphetamine or stimulant use disorder [16]. However, there has been no evidence synthesis of these studies. There is a need to synthesize the information about attention bias and bias modification among opiate use, cannabis use and stimulant use disorder. This gap needs addressing urgently as these substances are being increasingly utilized globally. It will also be pertinent to determine the efficacy of attention bias modification interventions among these disorders.

Review Aims

The primary aim of this systematic review is to synthesize the current evidence with regards to attention bias among opioid use, cannabis use and stimulant use disorders. As a secondary aim, it will determine the efficacy of attentional bias modification interventions, including attentional bias reduction, cravings score and addiction outcomes. These will be correlated with the methodology that is being utilized in attention bias assessment and modification.

We will undertake a systematic review to synthesize the existing evidence for the presence of attention bias in the disorders mentioned above, and to determine the clinical efficacy of attention bias modification. The studies will be selected by

independent assessors and screened against our inclusion and exclusion criteria. A risk of bias assessment will be conducted to assess the quality of the included studies.

If there are sufficient studies, a meta-analytical review will be conducted to determine the effect size of attention bias modification intervention for opioid use, cannabis use and stimulant use disorders.

Methods

Search Strategy

To identify the relevant articles, search terminologies as outlined in [Textbox 1](#) will be used. The search terms will be combined using the Boolean operator “OR” and the search terms between two disparate concepts will be combined using the Boolean operator “AND”.

A comprehensive search will be conducted on the following databases: PubMed, MEDLINE, Embase, PsycINFO, Science Direct, Cochrane CENTRAL and Scopus. If full-text access is not available, the original authors will be contacted for their articles. Proceedings from scientific meetings and conference abstracts will also be included.

Inclusion and Exclusion Criteria

Only articles written in English will be included. The inclusion criteria are as follows: (a) attention bias assessed using a validated measure (such as that of Stroop test or Visual Probe/Dot-Probe Task); (b) participants in the studies must have a primary diagnosis of opiate use, cannabis use or stimulant use disorder; and (c) the study design must be a randomized trial. Studies will be excluded if (a) they have not included a validated measure for the assessment of attention bias (such as Stroop Test or Visual Probe/Dot-Probe Task); (b) participants in the studies have been diagnosed with another mental health disorders as their primary disorder (eg, depression as the primary disorder and substance use disorder as the secondary diagnosis); (c) studies involved a pharmacological intervention in which medications were utilized to determine their effects on attention bias; and (d) the randomized trial involved a cross-over design (given the high risk of bias associated with a cross-over design).

Condition or Domain Being Studied

This systematic review focuses on substance use disorders, and in particular, opioid use, cannabis use and stimulant use disorder.

Participants

Participants must be diagnosed with a substance use disorder, that of opioid use, cannabis use or stimulant use disorder, as the main or primary disorder. Participants may include individuals from the general population or a treatment-seeking cohort, and can be adolescent or adult.

Intervention / Exposure

The intervention administered to participants is either that of a Stroop or Visual Probe/Dot-Probe attention modification task.

Comparison with Placebo Group

Individuals may be compared with individuals who have received a placebo training or sham training interventions or individuals who have received only normal routine care.

Outcome

For the primary aim, the outcome will be the presence of attention bias as measured using a validated assessment tool. Attention bias is deemed to be present if participants are noted to have a longer reaction time spent on drug-related stimuli as compared to neutral stimuli.

For the secondary aim, the outcomes will be: a) reduction in the mean reaction time following the attention bias modification intervention; b) score reductions on validated craving measures (either a single-dimensional score, or a visual analogue scale or a multidimensional score such as that of the obsessive-compulsive craving score); and c) addiction outcomes, such as the mean time to relapse or the time maintained in abstinence.

Data Extraction, Sorting and Selection

The search strategy will identify articles that may have potential relevance. Selection of relevant publications will be conducted independently by two authors (MWBZ and JY). Articles will be first screened based on their title and abstract. Those shortlisted will be evaluated against the inclusion and exclusion criteria. Any disagreement between the two reviewers will be resolved through a discussion with the third author. An electronic form will be utilized to record the reasons for the inclusion and exclusion of each article. The current systematic review protocol will adhere to the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols [17].

The following data and information will be extracted from each article, recorded on a standardized electronic data collation form and cross-checked by the second author:

1. Publication details: author(s) and study year.
2. Study design and methodology: study design, sample size (intervention and control group), types of sample (treatment seeking or individuals in general population), country in which study was conducted, demographics of sample (mean age, age range, proportion of males and females), diagnosis of participants (opioid use, cannabis use or stimulant use disorder), methodology in which diagnosis is made.
3. Attention bias assessment and modification methodology: types of attention bias tools utilized (Stroop test or Visual Probe task).
4. Outcomes of interest: craving scores (as assessed using a validated questionnaire or toolkit), addiction outcomes (time to next relapse, amount of substances used), effect size (Cohen's *d* or Hedges' *g*) for attention bias modification procedure.

Textbox 1. Search terminologies.

("attention bias" OR "approach bias" OR "avoidance bias" OR "cognitive bias") AND ("addiction" OR "substance" OR "drug" OR "abuse" OR "Dependence" OR "Alcohol" OR "Drinking" OR "Opiates" OR "Heroin" OR "Cannabis" OR "Marijuana" OR "Stimulants" OR "Amphetamines" OR "Cocaine")

Quality Assessment

For the risk of bias assessment, the Cochrane Risk of Bias tool [18] will be used.

Strategy for Data Integration and Synthesis

For the systematic review, we will synthesize and report whether attention bias was present and how its presence was determined. We will also synthesize the findings of the studies narratively and report whether attention bias modification was effective.

If there are sufficient studies for each of the conditions, a meta-analysis will be conducted to synthesize statistically the pooled effect size for attention bias modification for opiate use disorder, cannabis use and stimulant use disorders. For the meta-analytic study, the statistical analysis will be performed using Comprehensive Meta-Analysis Version 2.0 based on the random-effects model. The random effects model assumes that there are varying effect sizes between the studies, due to the underlying differences in study designs and intrinsic heterogeneity of the sampled populations. The statistical analysis will compute the pooled effect size to determine the clinical efficacy of attention bias modification and to identify potential moderators (both categorical and continuous variables) that could account for the heterogeneity in the effect size computed. Between-study heterogeneity will be assessed with the I^2 statistic, which describes the percentage of variability among effect estimates beyond that expected by chance. As a reference, I^2 values of 25% are considered low, 50% moderate and 75% high in heterogeneity. Meta-regression analysis will be conducted to identify demographic variables that could contribute to the heterogeneity and the effect size computed. The regression coefficients and the associated Z and P values will be reported. Subgroup analysis will be undertaken to investigate the effects of categorical variables on the effect size obtained. For the meta-analysis, Egger's regression test will be conducted to determine if publication bias is present. If there

is significant publication bias, the classic fail-safe test will be performed to determine the number of missing studies that will be required for the P value of the publication bias to be higher than .05.

Results

We expect that the review will be completed 12 months from the publication of this protocol. We will report the results based on the identified outcomes as specified above.

Discussion

We are aware of the prior reviews investigating the efficacy of attention bias modification among substance use disorders, but these have been limited by the inclusion of select studies involving cohorts who have either alcohol use or tobacco use disorders. As there is a proliferation of research examining attention bias and bias modification among other highly prevalent substance use disorders, particularly that of opiate use, cannabis use and stimulant use disorders, there is a need to synthesize the evidence for attention bias and attention bias modification for these disorders. It is important to establish that attention bias is present in these disorders, and that it could be amenable to modification using conventional paradigms such as the Stroop testing or Visual Probe task.

The findings of this proposed review will have important clinical implications. Should attention biases be found among individuals with opioid, cannabis and stimulant use disorder, clinicians will need to review their treatment strategies. Rather relying on a single modality of therapy to modify conscious control, they will need to augment the conventional psychological interventions with one that targets attention bias. The current review will also determine which indirect method of bias modification is more efficacious for bias modification in substance using cohorts.

Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavioural therapy

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Review

A Systematic Review of Attention Biases in Opioid, Cannabis, Stimulant Use Disorders

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Abstract: *Background:* Opiates, cannabis, and amphetamines are highly abused, and use of these substances are prevalent disorders. Psychological interventions are crucial given that they help individuals maintain abstinence following a lapse or relapse into substance use. Advances in experimental psychology have suggested that automatic attention biases might be responsible for relapse. Prior reviews have provided evidence for the presence of these biases in addictive disorders and the effectiveness of bias modification. However, the prior studies are limited, as they failed to include trials involving participants with these prevalent addictive disorders or have failed to adopt a systematic approach in evidence synthesis. *Objectives:* The primary aim of this current systematic review is to synthesise the current evidence for attention biases amongst opioid use, cannabis use, and stimulant use disorders. The secondary aim is to determine the efficacy of attention bias modification interventions and other addictions related outcomes. *Methods:* A search was conducted from November 2017 to January 2018 on PubMed, MEDLINE, Embase, PsycINFO, Science Direct, Cochrane Central, and Scopus. The selection process of the articles was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. A qualitative synthesis was undertaken. Risk of bias was assessed using the Cochrane Risk of Bias tool. *Results:* Six randomised trials were identified. The evidence synthesized from these trials have provided strong evidence that attentional biases are present in opioid and stimulant use disorders. Evidence synthesis for other secondary outcome measures could not be performed given the heterogeneity in the measures reported and the limited number of trials. The risk of bias assessment for the included trials revealed a high risk of selection and attrition bias. *Conclusions:* This review demonstrates the potential need for interventions targeting attention biases in opiate and cocaine use disorders.

Keywords: attention bias; cognitive bias; addiction; opioids; cannabis; stimulants

1. Introduction

The United Nations Office on Drugs and Crime (UNODC) reported that, in 2015, at least 29.5 million individuals were afflicted with a substance use disorder globally [1]. Opiates, cannabis, and amphetamines are highly abused [1]. Substance use disorders are associated with multiple comorbidities. Treatment of substance use disorders involve both pharmacological and psychological approaches [2]. Pharmacological options remain limited, with only opiate substitution therapies

available for opioid use disorder in some countries. The main pharmacological options for cannabis and stimulant use disorders are limited to the use of symptomatic medications, such as benzodiazepines for agitation, or antipsychotics for psychotic symptoms [3]. Psychological interventions are crucial given that they help individuals maintain abstinence following a lapse or relapse into substance use. Psychological interventions commonly used include cognitive behavioural therapy for relapse prevention, contingency management, and more recently, mindfulness-based relapse prevention [2]. A prior review which examined 34 randomised controlled trials involving a total of 2340 alcohol and substance use individuals reported that cognitive behavioural therapy was useful, with an effect size of 0.45 (Cohen D) [4]. Cognitive behavioural therapies for substance use disorder typically equip individuals with skills to help them deal with both internal and external triggers, cognitive distortions, and decision delay skills relating to substance use. While therapies such as cognitive behavioural therapy have proven to be effective, other studies [5] have reported that 40–50% of individuals do relapse within a year of successful treatment, and 70% of individuals relapse within three years. The high relapse rate following a moderately effective intervention is of concern and suggests that interventions may not have adequately addressed all the issues leading to either a lapse or relapse.

Advances in experimental psychology has led to the “dual-process” model of addiction, which proposes there being an imbalance between the impulsive (limbic) system and the reflective (pre-frontal cortex) system [6–8]. Examples of these “dual-process” models include that of the incentive-sensitization theory [9], which suggests that through classical conditioning, a substance stimulus would increase in salience and result in increased motivation to acquire that substance (Robinson & Berridge, 1993 as cited in [9]). Therapies like cognitive behavioural therapy targets typically targets the reflective system. As aforementioned, the predominance of the impulsive (limbic) system and its associated biases might predispose individuals to a relapse. Biases common in addictive disorders include that of attention bias, which refers to the tendency for substance-related cues to selectively capture individuals’ attention in their naturalistic environment [9–11] and that of approach and avoidance biases, which refers to automatic tendencies to reach out for substance related stimuli (Wiers, R.W. 2013) [12]. To date, several studies have looked for attention biases in addictive disorders and the effectiveness of bias modification [12,13]. Cristea et al.’s (2016) [12] meta-analytic review involved studies that included participants with alcohol or tobacco use disorders, and reported that bias modification was effective, with an effect size (Hedges G) of 0.60. However, the changes in biases did not result in improvement in any other outcome measures, such as that of cravings. Although Cristea et al.’s (2016) [13] review provided evidence for the presence of biases in addictive disorders and the effectiveness of bias modification, the review was limited to only these two forms of substances of abuse. The included studies also had a high risk of bias. Christiansen et al. (2016) [14] on the other hand included in their review studies with participants who were using alcohol, tobacco, cocaine, or cannabis. Christiansen et al.’s (2016) [14] study included participants with a range of addictive disorders and demonstrated the presence of attention bias in these disorders. They reported that the evidence for the association between attention bias and relapse to be mixed and reported that the differences in the tasks and the limited sample size of the included studies could have potentially accounted for their findings. Whilst Christiansen et al.’s (2016) [14] review included participants with a range of addictive disorders, this review had limitations, in that the inclusion and exclusion criteria were not clearly specified and the time frame in which the search was conducted was not specified. Furthermore, the databases searched included only PubMed, Scopus, and prior published reviews, but not PsycINFO and MEDLINE.

Substance disorders, such as that of opioid, cannabis use, and stimulant use, have been highly prevalent, based on the recent reports released [1]. The estimated annual prevalences for these disorders in 2015 were of 3.8%, 0.7%, and 0.77%, respectively [1]. In 2015, there have been an estimated 183 million, 35 million, and 37 million past-year users of cannabis, opioids, and amphetamines, respectively, and the numbers of these users far supersede that for other substances, such as that for ecstasy (22 million past-year users). Given this, further research involving these three highly

prevalent disorders is of importance. Taking into consideration the limitations of the previous review and the number of new studies published that have evaluated bias modification for these highly prevalent disorders, there is thus a need for an updated systematic review to synthesise the information from these studies. The primary aim of this current systematic review is to synthesise the current evidence with regard to attention bias amongst opioid use, cannabis use, and stimulant use disorders. The secondary aim is to determine the efficacy of attention bias modification interventions including attentional bias reduction and other addictions related outcomes.

2. Methods

In our current review, we adhered to the plan as set out in our published protocol [15]. To achieve the objectives of the current review, a search was conducted from November 2017 to January 2018. The following databases were searched from inception—PubMed, MEDLINE, Embase, PsycINFO, Science Direct, Cochrane Central, and Scopus. The following search terminologies were used, such as (“attention bias” or “approach bias” or “avoidance bias” or “cognitive bias”) and (“addiction” or “substance” or “drug” or “abuse” or “dependence” or “opiates” or “heroin” or “cannabis” or “marijuana” or “stimulants” or “amphetamines” or “cocaine”).

2.1. Inclusion and Exclusion Criteria

Articles written in English language were included. Articles were also included if they fulfilled the following inclusion criteria: (a) attention bias which was assessed using a validated measure; (b) participants in the studies must have a primary diagnosis of opiate use, cannabis use, or stimulant use disorder; and (c) the study design is a randomised trial. Articles were excluded if (a) they did not include a validated measure for the assessment of attention bias; (b) participants in the study were diagnosed with other psychiatric disorders as the primary diagnosis (for example, Depression or Anxiety Disorders); (c) studies involved a pharmacological intervention in which medications were utilised to examine their effects on attention bias; or (d) the randomised trial involved a cross-over design. For (d), these randomised trials were excluded due to their high risk of bias.

Considering the limitations of prior reviews, only randomised trials were included for the current review.

2.2. Selection of Articles

Selection of relevant articles were conducted independently by two authors (Melvyn Zhang and Jiangbo Ying). Articles were first screened based on their titles and abstracts. Articles that were shortlisted were then evaluated against the inclusion and exclusion criteria. In the event of any disagreements with regard to the screening of the articles based on their titles and abstracts, or if there was no consensus whether to include or exclude the article, this would be discussed and resolved with the author (Guo Song).

The selection process was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [16].

2.3. Statistical Analysis

2.3.1. Extraction

The following data and information was extracted from each article and recorded on a standardised electronic data collation form: (a) Publication details (author(s) and study year); (b) Study design and methodology (Study design, sample size, types of sample, country, demographics of sample, diagnosis of participants, methodology in which diagnosis is made); (c) Attention bias assessment and modification methodology; (d) Outcomes of interest (e.g. craving scores, addiction outcomes, effect size for attention bias modification procedure).

2.3.2. Data Analysis and Synthesis

Due to the diversity of the outcome measures reported, meta-analytical synthesis was not feasible and a qualitative synthesis was undertaken instead.

2.3.3. Quality Assessment

The Cochrane Risk of Bias tool was used for the risk of bias assessment. Risk of bias assessment was conducted for the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.

3. Results

Based on our pre-defined search strategy, a total of 7814 citations were identified from the databases; 537 duplicated articles were excluded, 7277 records were screened, and 7192 citations were excluded as they were of no relevance to the topic of interest. A total of 85 full-text articles were downloaded for further evaluation against the inclusion and exclusion criteria. Seventy-nine citations were excluded as they did not fulfil the inclusion criteria, leaving six articles for the eventual qualitative synthesis. Figure 1 provides an overview of the study selection process. Table 1 provides an overview of the characteristics of the included studies. Half of the identified articles involved cohorts of individuals with opiate use disorder and the other half of the identified articles included cohorts with cocaine use disorder.

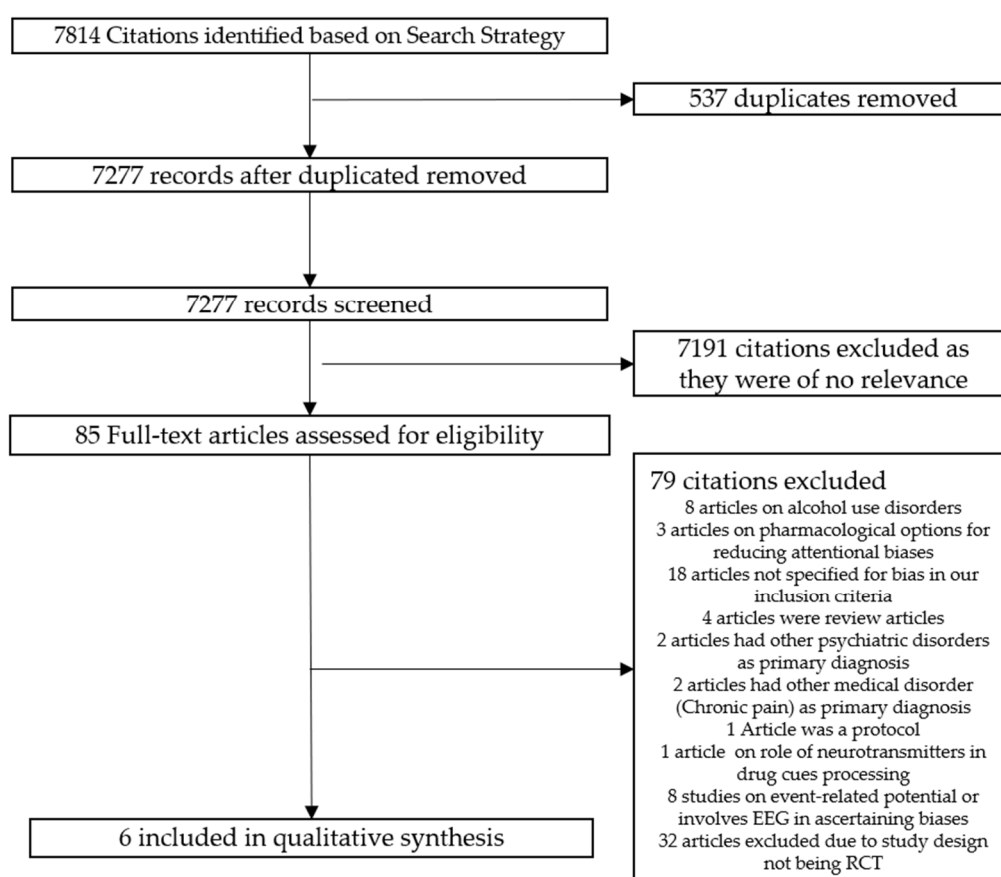


Figure 1. Flowchart for the Selection of Articles.

Table 1. Characteristics of Included Studies ($n = 6$).

Study	Study Design	Sample Size	Types of Sample	Demographics of Sample	Country	Diagnosis of Sample	Method of Diagnosis	Attention Bias Method	Outcomes
Franken, I.H. et al. (2000) [17]	Randomised trial	21 heroin-dependent participants 30 control participants	Participants with heroin dependence were recruited from an inpatient treatment centre Participants in the control group were recruited among clinical and administrative staff in the clinic	71.4% males (heroin-dependent) 83.3% (control group) Mean age 31.5 years (heroin-dependent) Mean age 34.8 (control group) Mean self-reported duration of heroin dependence was 93.9 months	Netherlands	Heroin Dependence	Based on the DSM-IV criteria for heroin dependence	Drug Stroop task	Higher overall reaction time for heroin participants as compared to control participants Mean pre-experimental craving was 13.8, mean post masked Stroop was 7.19 and mean post unmasked Stroop was 15.2
Lubman, D.I. et al. (2000) [18]	Randomised trial	16 methadone-maintained opiate addicts 16 age-matched control	Heroin addicts were recruited from local drug services Staff from these services were recruited as controls	Opiate group: mean age 31.4, Male to Female 11:5 Control group: mean age 31.7, male to female 8:8	United Kingdom	Heroin Dependence	ICD-10 and DSM IV	Pictorial Probe Detection Task	Faster reaction times to probes that replaced drug stimuli, indicative of the presence of an attentional bias
Marissen, M. et al. (2006) [19]	Randomised trial	110 Participants assigned to either cue exposure therapy or placebo psychotherapy	Abstinent heroin addicts who were admitted voluntarily to an in-patient drug-free therapeutic centre in the Hague	89% males, mean age 34 years old Average age of onset of heroin usage was 21.4 years, most have used heroin for 9.3 years	Netherlands	Heroin Dependence	DSM-IV criteria for heroin dependence	Emotional Stroop Task	Pre-treatment attentional bias predicted relapse at three months follow-up Reduction of attentional biases in both experimental conditions
Montgomery et al. (2010) [20]	Randomised trial	32 regular cocaine users and 40 non-users	Student Population at Liverpool John Moores University and the general population in the surrounding areas	Mean age for cocaine users assigned to placebo 19.29, assigned to alcohol 20.23 Mean age for non-users assigned to placebo 19.59, assigned to alcohol 20.0 13 male in cocaine use group 19 male in non-cocaine use group	United Kingdom	Cocaine dependence	Questionnaire	Visual Probe and Modified Stroop task	Cocaine participants who received alcohol had increased attentional bias for cocaine pictures The cocaine Stroop revealed no differences between cocaine users and non-users, and no effects of alcohol in either group
Mayer, A.R. et al. (2016) [21]	Randomised trial	37 participants assigned to either attentional bias modification therapy (ABMT) or control therapy	Not mentioned	ABMT group: 14 male, and 5 female, mean age 37.4 Control group: 10 male and 8 female, mean age 38.9	United States	Cocaine dependence	Structured clinical interview for DSM-IV	Visual Probe task	Presence of attentional bias Attentional bias not subjected to modification by ABMT
DeVito, E.E. (2017) [22]	Randomised trial	38 in treatment as usual plus computer-based CBT (CBT4CBT) 41 in treatment as usual	Recruited from community-based outpatient clinic	46% female, mean age 42.2	United States	Cocaine use disorder	DSM-IV	Computerized drug Stroop test	Stroop testing revealed that participants who have had a longer duration of cocaine abstinence during treatment (3+ weeks) have greater reductions in Drug Stroop effect. Engagement with CBT4CBT intervention also led to a reduction in Drug Stroop effect

3.1. Overview of Studies

Of the six identified randomized trials, only one study [21] investigated specifically attention bias modification on attention bias. Franken, I.H. et al.'s (2002) [17] study involved having participants undertake a supra- and subliminal Stroop task for the assessment of attention bias. Similarly, in Lubman, D.I. et al.'s (2000) [18] trial, the pictorial probe task that was used for the assessment of attentional bias. Marissen, M. et al.'s (2006) [19] trial investigated the effects of cue exposure therapy, instead of attention bias modification on attention biases. In the remaining two cocaine trials, one trial (Montgomery et al.'s (2010)) [20] evaluated the effects of alcohol administration on attentional biases. DeVito, E.E. et al. (2017) [22] in their study evaluated the effects of computer-based CBT (Cognitive Behavioral Therapy), as it is believed that CBT could strengthen cognitive control processes.

3.2. Characteristics of Three Studies for Opioid Use Disorders

The three randomised trials that included individuals with opiate use disorders recruited these individuals from either an inpatient treatment unit, local drug and treatment services, or individuals who admitted themselves into a drug and rehabilitation therapeutic unit for treatment. The sampled individuals were all from treatment seeking individuals. With respect to demographics, the mean age of the included participants was in their thirties, and all three involved a predominantly male cohort. The diagnosis of the individuals was all ascertained using psychiatric assessments, based on either the DSM-IV criteria or the ICD-10 diagnostic criteria. Two out of the three trials utilised Stroop-based task in the assessment of attention bias (Franken, I.H. et al., 2000; Marissen, M. et al., 2006) [17,19].

3.3. Primary and Secondary Outcomes Reported in Three Studies for Opioid Use Disorders

All three trials reported the presence of attention biases in individuals with opioid use disorders. Franken, I.H. et al. (2000) [17] reported that individuals with opioid use disorder had longer reaction time for cues as compared to controls, and Lubman, D.I. et al. (2000) [18] also reported that individuals tend to demonstrate faster reaction times for probes that replaced drug-related stimuli. There were varied secondary outcomes reported in each of the included studies. Franken, I.H. et al. (2000) [17] reported that bias modification led to a decrease in the cravings measure. Marissen, M. et al. (2016) [19] reported that baseline attention biases were predictive of subsequent relapses at three months follow-up. Marissen, M. et al. (2016) [19] also reported that cue exposure therapy did not lead to a significant reduction of attentional biases as compared to placebo psychotherapy.

3.4. Characteristics of Three Studies for Stimulant Use (Cocaine) Disorders

Only two out of the three trials provided information about the source of their participants. There was diversity in that Montgomery et al.'s (2010) [20] trial, recruited a student sample, whereas DeVito, E.E.'s (2017) [22] trial recruited participants from the community-based clinics. The mean age of the sample also varied, ranging from a mean of 19.29 years to that of 42.2 years. Males did not predominate in the trials. It is important to note that the diagnosis of cocaine dependence was established using a questionnaire for Montgomery et al.'s (2010) [20] trial, whereas the diagnoses for the remaining trials were ascertained by mean of the structured clinical interview and the DSM-IV criteria. Both visual probe task and Stroop task were used in the ascertainment of attention biases.

3.5. Main Outcomes Reported in Studies for Stimulant Use (Cocaine) Disorders

All three trials reported the presence of attention biases in individuals with cocaine use disorders. Similarly, the three trials also involved interventions to modify attentional biases. Montgomery et al. (2010) [20] demonstrated that attention biases towards cocaine stimuli were heightened when alcohol was administered, whilst DeVito, E.E. (2017) [22] reported that attentional biases reduced with the intervention. Notably, Mayer, A.R. et al. (2016) [21] reported in their trial that attention bias modification was not effective in reducing biases. In the three included randomised

trials, only Mayer, A.R. et al. (2016) [21] evaluated the efficacy of attention bias modification. DeVito, E.E. (2017) [22] evaluated the potential of computer-based CBT in enhancing executive cognitive control processes and reducing attentional biases.

Using the search strategy, we were unable to identify any randomised trials for cannabis use disorders.

3.6. Quality and Risk of Bias Assessment

We conducted a risk of bias assessment of the included studies using the Cochrane Risk of Bias tool. Review Manager 5 (RevMan5) (Cochrane Collaboration, 2014) [23] was used to prepare both Figures 2 and 3. Figure 2 provides an overview of the overall risk of each type of biases for all the studies. The percentages of low, unclear, and high risk of biases were automatically computed by RevMan5. Figure 3 provides an overview of our assessment of the risk of biases in each study.

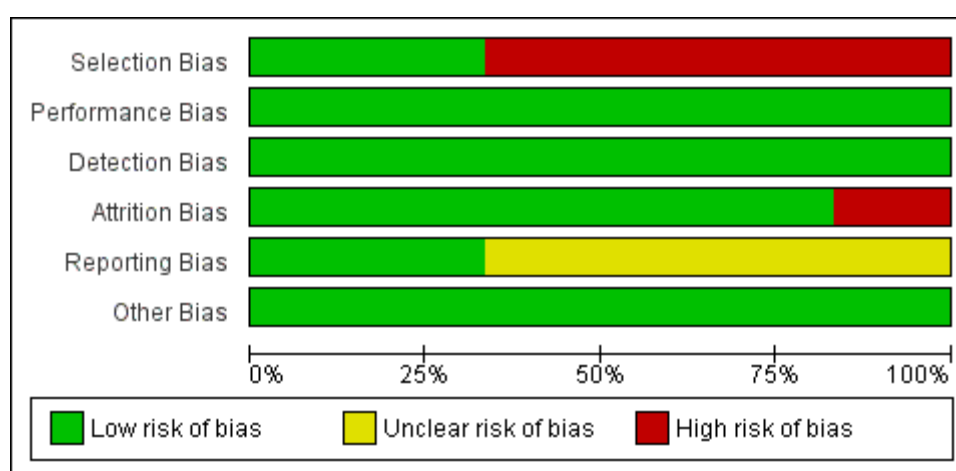


Figure 2. Risk of Bias Assessment for included studies.

	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias
Devito EE et al. (2017) [22]	−	+	+	−	+	+
Franken IH et al. (2000) [17]	−	+	+	+	?	+
Lubman Dr et al. (2000) [18]	−	+	+	+	?	+
Marissen M et al. (2006) [19]	+	+	+	+	?	+
Mayer AR et al. (2016) [21]	+	+	+	+	?	+
Montgomery et al. (2010) [20]	−	+	+	+	+	+

: Low Risk of Bias;
 : Unclear Risk of Bias;
 : High Risk of Bias

Figure 3. Risk of Bias assessment for each of the included studies.

Across all six studies, there was demonstration of high risk in both selection bias and attrition bias. Franken, I.H. et al.'s (2000) [17] study was graded as being high risk for selection bias due to the nature of its recruitment (inpatient treatment centre for participants and clinics for controls) and the discrepancies in the level of education, with controls having higher levels of education. Similarly, Lubman, D.I. et al.'s (2000) [18] trial included heroin participants who were noted to have significantly lower intelligence quotient and higher levels of anxiety and depression as compared to the controls. Selection bias was also present in Montgomery et al. (2010)'s [20] study, in that cocaine users had significantly higher scores on the AUDIT (Alcohol Use Disorder Identification Test) as compared to the non-users. DeVito, E.E. (2001) [22] study also rated high on the risk of selection bias as only participants with Stroop data at pre and post assessment were included. DeVito, E.E.'s (2001) [22] trial also had a high risk of attrition bias, as out of the original 101 participants recruited, data computation and analysis were only performed on an eventual sample of 61.

4. Discussion

Our current review has managed to identify more randomized trials than Cristea et al. (2016)'s [13] prior meta-analytical review for opioid and cocaine use disorder. Six randomised trials were identified to be included in the current systematic review, with three trials involving participants with opioid use disorder and three trials involving participants with cocaine use disorders. The evidence synthesized from these trials have provided strong evidence that attention biases are present in opioid and stimulant use disorders. There was similarity in the demographics of the participants of the three trials with opioid use disorder, in that the sample were treatment-seeking individuals, predominantly male, and the diagnosis was ascertained based on psychiatric assessments. Across all six trials, attention bias was reported to be present, despite the different methods of assessment with either the use of Stroop test or Visual probe task. Across the six trials, there remained no consensus that attention bias modification was effective. Evidence synthesis for other secondary outcome measures could not be performed given the heterogeneity in the measures reported and the limited number of trials. The risk of bias assessment for the included trials revealed a high risk of selection and attrition bias.

Our current review, by synthesizing the evidence from randomized trials, has provided evidence that attention biases are present in both opiate-use disorders and stimulant (cocaine) use disorders. The current findings complement and expand on the findings that Cristea et al. (2016) [13] previously reported. As aforementioned, their meta-analytical review included 24 studies that involved alcohol use and tobacco use participants. Even though the prior review made use of a search strategy that included keywords such as “cannabis, marijuana, cocaine, heroin, opiates, amphetamines”, randomized trials were not identified and hence evidence synthesis was limited to alcohol and tobacco addiction only. We acknowledge that in Christiansen et al.'s (2015) [14] review, they have identified more studies than in our review. They have identified three studies involving heroin-dependent participants and five studies involving cocaine-dependent participants. However, as aforementioned, the authors did not specify their inclusion and exclusion criteria and failed to utilize a systematic review approach and this limits the quality of the evidence synthesized. Nevertheless, their findings help to demonstrate that attentional bias are present in these disorders and are evident across a variety of study designs. In summary, our results fulfill the gaps in knowledge of Cristea's prior meta-analysis and add on to the evidence synthesized in Christiansen et al.'s (2015)'s review [14]. Attention biases are present in opioid and cocaine use disorders, and this finding is of clinical importance, as if attentional biases are present, specialized interventions could be devised to help retrain these automatic biases.

The results arising from the opioid trials demonstrate the presence of attention biases in individuals who were maintained on opiate substitution therapy (Lubman, D.I. et al., 2000) [18]. The presence of attention biases amongst individuals maintained on opiate substitution therapy implies that, whilst pharmacological interventions might help in the stabilization of lifestyle and minimization of harms associated with illicit usage, psychological interventions such as attention

bias modification needs to be considered as augmentative treatment, to help address the automatic processes that might result in a relapse. Franken, I.H. et al. [17] proposed in his review that drug-related stimuli is known as “cognitive intermediates” prior to a lapse or relapse, given that such salient stimuli activates unconscious processes leading to one having increased attention, but also leaving the individual with fewer resources available to apply learned coping strategies. Hence, there is clearly a need for attention bias modification to be considered for individuals with addictive disorders. There has also been increased recognition of this need, as evidenced by Heitman’s et al. (2017) [24] proposed protocol, in which they attempted to investigate both the effectiveness and cost-effectiveness of an online, Internet-based attention bias modification delivered in complement to usual intervention for individuals with alcohol or cannabis use disorders. Whilst there was a prior study (Hullu et al., 2017) [25] that evaluated combined cognitive bias modification and cognitive behavioural therapy, there remains, to our knowledge, no similar published studies or protocol for substance use disorders. A consideration of the integration of both modalities of therapy is crucial, given that cognitive behavioural therapies typically target the top down or reflective conscious decision-making processes, whilst bias modification targets the bottom-up or unconscious processes that could be responsible for lapse and relapse.

Amongst the studies identified for the current synthesis, only one study evaluated attention bias modification. The remaining studies evaluated other forms of intervention, including that of cue-exposure therapy and computerized cognitive behavioral intervention. Given this, this limits the evidence synthesis for the overall effectiveness of bias modification. Notably, most of the included studies were studies that merely evaluated for the presence of attention biases using mainly the Stroop task (in four studies). The remaining studies evaluated for attention biases using the visual probe task. Since different interventions were used, it is hard to compare whether the different tasks used (Stroop versus the visual probe) did have an effect on the overall results.

There are many strengths of this current review. We have comprehensively searched through the literature for randomized trials involving highly prevalent addictive disorders. Our current review identified more trials than Cristea et al.’s (2016) [13] review for opioid and stimulant use disorders. This is because we have searched through additional databases, namely that of MEDLINE, ScienceDirect, and Scopus, and the search was conducted up until 2017. Through our extensive search strategy, we managed to include trials that have been conducted among participants with highly prevalent substance use disorders, specifically that of cocaine use disorder. The findings arising from the current review help to provide evidence for the presence of attentional biases in other addictive disorders, and this is important clinically. It is important for clinicians to recognize that automatic processes such as attention biases could predispose individuals with opioid and cocaine use disorders towards a lapse or relapse. Clinicians need to recognize that for the chronically addicted individuals, psychological interventions such as cognitive behavioural therapy for relapse might not be adequate and there is a potential role for augmenting that treatment with attention bias modification. We managed to perform a risk of bias assessment to assess the quality of the trials that were included. We have adhered to our planned protocol and used a predefined search strategy and have adhered to the specified inclusion and exclusion criteria.

Despite the strengths, there are also several limitations. In our current review, we only included six trials. Our main limitations pertain to the fact that there might be other studies that have been published and were evaluated for the presence of attentional bias and the effectiveness of attentional bias modification but were excluded due to their study designs. We have not in our current review included the articles that Christiansen et al. (2015) [14] included in their prior review, as the prior review included studies with different study designs. We have originally considered in our review only randomised trials for inclusion in order to enhance the quality of the evidence derived by the synthesis [26]. There are intrinsic advantages with regard to considering only randomised trials. Trials involving randomisation remove the inherent chance of confounding, and the double-blinded process also helps in the minimisation of biases (Shrier, I. et al., 2007) [26]. However, Shrier, I. et al. (2007) [26]

previously articulated the need to consider the inclusion of other trial designs as the additional information derived could help in clinical reasoning and provide a solid foundation for causal inferences. Similarly, Peinemann, F. et al. (2013) [27] also opinionated that the consideration of the types of studies to be included is dependent on the clinical question that needs to be answered. Thus, for our current review, the main clinical question relates to whether attentional biases are present in highly prevalent substance use disorders, and whether these biases could be modified, and to look at its effect on other secondary outcome measures. As such, restricting the inclusion criteria to include only randomised trials would result in a significant number of observational studies being left out, as demonstrated by Christiansen et al. (2015)'s [14] review. Moreover, whilst attention biases are widely studied for alcohol and tobacco use disorders, attention bias and bias modification for stimulant use, cannabis use, and opiate use disorders are less well characterised. Also, given that many of these substances are considered illicit globally, it is potentially difficult for researchers to conduct randomised trials, given the ethical and legality concerns associated with a randomised trial. Given the high risk of bias in some of these randomised trials, especially for attrition and selection bias, randomisation has potentially not minimized the risk of confounders. Hence, the quality of the evidence synthesised from these limited randomised trials might not be superior in comparison to a review that considered the inclusion of a variety of study designs. Hence, in retrospect, to better answer the research and clinical question, a consideration of different study designs might yield more evidence for attentional bias modification in this emerging field, instead of limiting just to randomised trials. In addition, our review is limited as it did not include any studies involving participants with cannabis use disorder, which is a highly prevalent disorder globally. Lastly, we were limited to a qualitative synthesis of the data extracted from each of the studies, and a meta-analytical synthesis was not appropriate due to the heterogeneity in the outcomes reported.

5. Conclusions

The findings from our current review demonstrate the presence of attentional biases in two highly prevalent addictive disorders, that of opiate use and cocaine use disorders. Due to the heterogeneity in the secondary outcomes reported, the current review is unable to provide evidence pertaining to the effectiveness of bias modification, and the effect that bias modification has on other secondary outcomes. Nonetheless, this review is important as it demonstrates the potential need for interventions targeting attention biases in opiate and cocaine use disorders. Future research should consider the inclusion of other study types to better synthesise the evidence for attention bias and bias medication in these highly prevalent addictive disorders.

Author Contributions: Z.M., D.S.S.F., and H.S. conceived the current review. Z.M. and J.B.Y. extracted the data. S.G. helped to resolve any conflicts between Z.M. and J.B.Y. in the selection of the articles. Z.M. wrote the initial draft, and T.W. and H.S. helped in the initial revisions. All authors contributed to the final draft of the manuscript prepared for submission.

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Cognitive Biases in Cannabis, Opioid, and Stimulant Disorders: A Systematic Review

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Background: Opiates, cannabis, and stimulants are highly abused and are prevalent disorders. Psychological interventions are crucial given that they help individuals maintain abstinence following a lapse or relapse into substance use. The dual-process theory has posited that while the repeated use of a substance leads to increased automatic processing and increased automatic tendencies to approach substance-specific cues, in addition to the inhibition of other normal cognitive processes. Prior reviews are limited, as they failed to include trials involving participants with these prevalent addictive disorders or have not reviewed the published literature extensively.

Objectives: The primary aim of this review is to synthesize the evidence for cognitive biases in opioid use, cannabis use, and stimulant use disorders. The secondary aim of the review is to determine if cognitive bias could be consistently detected using the different methods. Lastly, this review will narratively synthesize the evidence of possible associations between cognitive biases and other addiction-related outcomes.

Methods: A search was conducted from November 2017 to January 2018 on PubMed, MEDLINE, Embase, PsycINFO, Science Direct, Cochrane Central, and Scopus. Articles were included if participants had a primary diagnosis of opioid use, cannabis use, or stimulant use disorder. The selection process of the articles was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. A qualitative synthesis was undertaken.

Results: A total of 38 studies were identified. The main finding is the evidence that cognitive biases are present in the 38 studies identified, except for a single study on opioid use and stimulant use disorders. Cognitive biases were reported despite a variety of different methods being utilized. Synthesis of secondary outcome was not feasible, due to the varied outcomes reported.

Conclusions: Cognitive biases have been consistently observed in opioid use, cannabis use, and stimulant use disorders, despite a range of assessment tools being utilized in the assessment for these biases.

Keywords: attention bias, approach bias, cognitive bias, substance use, addiction

INTRODUCTION

Attention bias in substance use disorder refers to the preferential allocation of attention to substance-related stimuli (1), while approach biases refer to the automatic action tendencies to reach out for substance-related cues (1). Thus, this implies that for an individual with a substance use disorder, substance-related cues can grab the individual's attention (2). Previously theories such as classical conditioning or incentive-sensitisation theories, have provided explanations as to how these cognitive biases develop (2). More recently, the dual-process theory has posited that whilst the repeated usage of a substance leads to increased automatic processing and increased automatic tendencies to approach substance-specific cues, in addition, other normal cognitive processes are affected (3). The cognitive control process, which normally serves to inhibit this automatic behavior, is itself inhibited (3). This coupled with the increased dopamine in the cortico-striatal circuit, results in individuals having increased attention and automatic tendencies toward substances, precipitating a relapse. Cox et al. (4) highlighted the need for specific interventions to modify these automatic unconscious processes. Whilst the Stroop task has been routinely used for the assessment of cognitive biases, several other paradigms have been used to retrain attentional or approach tendencies, such as the visual probe or the approach/avoidance task (4, 5). The visual probe task, when used as a cognitive retraining intervention instead of an assessment intervention, involves pairing probes with a neutral stimulus 100% of the time, to retrain attentional biases away from substance cues (4). When the approach/avoidance task is used as a retraining tool, it involves the presentation of substance-related cues in the push-away format and neutral cues in a pull-closer format (5). To date, there has been some initial research conducted on substance use disorders, both in determining whether cognitive biases are present for specific addictive disorders and in the evaluation of the effectiveness of bias modification (6, 7).

Several reviews have examined the presence of cognitive biases in addictive disorders as well as the effectiveness of bias modification. Cristea et al. (1) undertook the first meta-analysis examining the effectiveness of bias modification for substance use disorders. Even though the authors included in their review search terminologies for a variety of addictive disorders, they only managed to identify and include studies that included participants with alcohol or tobacco use disorders. This review reported that bias modification for both cognitive biases was moderately effective, with an effect size of 0.60 (Hedge G) (1). Notably, the review found no association between the reduction in biases and other outcomes such as cravings. One of the major limitations of the review (1) was that it included participants who had either alcohol or tobacco disorders, with no studies being included that focused on other substances of abuse. High risk of biases was identified in the studies included, which might have affected the results synthesis. Whilst Cristea et al. (1) did not, in their meta-analytical review found any association between cravings and attentional biases, their findings are not unexpected. Field et al. (8) in their previous review sought to determine the relationship between cravings and attentional

biases. From the 68 studies that they have included, they reported the presence of a weak relationship between attentional biases and cravings ($r = 0.19$). Field et al. (8) have reported there being a larger association between attentional biases and illicit substances and caffeine, as compared to alcohol and tobacco. Christiansen et al. (9) attempted in their review to determine if there was an association between cognitive biases and relapse, and their study included participants with alcohol, tobacco, cocaine, and cannabis disorders. It was reported in the review that the assessment of cognitive biases did not predict relapse and that attentional bias modification did not reduce the future risk of relapse. Whilst the review by Christiansen et al. (9) included participants with a range of addictive disorders, the time frame was not specified, nor the inclusion and the exclusion criteria used in the selection of the articles. In addition, the database search was limited to that of PubMed, Scopus, and prior published reviews. Hence, there is a possibility that other relevant citations were missed and reduced the quality of the evidence synthesis.

The fact that the reviews to date are limited to certain substance disorders matters. The recent report released by the United Nations Office on Drugs and Crime (UNDOC) stated that in 2015, 29.5 million individuals had a substance use disorder (10), with an estimated 28 million healthy years of life lost due to drug use (10). Substances like cannabis, opioids, amphetamines, and prescription opioids are widely abused. In 2015, it was estimated that there were 183 million cannabis users, 35 million opioid users, and 37 million amphetamine and prescription stimulant users (10). For the management of substance use disorders, there are limited pharmacological options. Symptomatic medications, such as benzodiazepines or antipsychotics, are routinely prescribed for patients to control acute intoxication symptoms following cannabis or stimulant use. There remain no medications that are approved to help individuals maintain abstinence following cannabis or stimulant use. Psychological interventions can help individuals maintain abstinence following a lapse or relapse (11). Psychological interventions routinely used include cognitive behavioral therapy, contingency management, and more recently mindfulness-based relapse prevention (11). A prior review provided evidence that cognitive behavioral therapy is effective for substance use disorders, with an effect size of 0.45 (Cohen D) (12). However, despite this effectiveness of cognitive behavioral therapy, 40–50% of individuals still relapse within a year of successful treatment and another 70% of individuals relapse within 3 years (13). The high relapse rate following a moderately successful intervention suggests that it has not adequately addressed all the issues leading to a lapse or relapse. Cognitive behavioral therapy mainly addresses the cognitive control issues and fails to address the unconscious processes responsible for relapse. Consequently, further studies have been conducted evaluating the effectiveness of cognitive bias modification for individuals with different types of substance use disorders.

Given the limitations of previous reviews and the recent review by (14), together with recent studies that have evaluated cognitive biases in substance disorders that are highly prevalent (opioid, cannabis, and stimulant use disorders), there is a need

for a systematic review to synthesize the information from these studies. The primary aim of this review is to synthesize the evidence for cognitive biases in the following substance use disorders: opioid use, cannabis use, and stimulant use disorders. If biases are consistently present, this will help to guide future research involving bias modification. The secondary aim of the review is to determine if cognitive bias could be consistently detected using the different methods. Lastly, this review will narratively synthesize the evidence of possible associations between cognitive biases and other addiction-related outcomes.

METHODS

A search was conducted, on the following databases (PubMed, MEDLINE, Embase, PsycINFO, Science Direct, and Scopus), from inception through to January 2018. The following search terminologies were used: (“attention bias” OR “approach bias” OR “avoidance bias” OR “cognitive bias”) AND (“addiction” OR “substance” OR “drug” OR “abuse” OR “dependence” OR “Opiates” OR “Heroin” OR “Cannabis” OR “Marijuana” OR “Stimulants” OR “Amphetamines” OR “Cocaine”).

Inclusion and Exclusion Criteria

Only articles that were written in English language were included. Articles were included if participants had a primary diagnosis of opioid use, cannabis use, or stimulant use disorder. Articles were excluded if participants had other psychiatric disorders as a primary disorder, or if the study involved a pharmacological intervention in which medications were used to examine their effects on cognitive biases. All types of study design were included.

Selection of Articles

Two authors (MZ and JY) independently selected the relevant articles. Articles were initially screened based on their titles and abstracts. Articles that were shortlisted were then further evaluated against the inclusion and exclusion criteria. If the reviewers disagreed, this was resolved through a discussion with another author (GS.). The selection of the articles for inclusion was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines.

Statistical Analysis

The following data were systematically extracted from each of the identified articles and recorded on a standardized electronic data collation form: (a) authors and study year, (b) study design and methodology (study design, sample size, types of sample, country, demographics of sample, diagnosis of participants, methods in which diagnosis was established), (c) cognitive biases assessment and modification methods, (d) outcomes of interest (presence of attention or approach biases, effectiveness of biases modification, other secondary outcomes reported such as craving scores or addiction outcomes).

As the reported outcome measures were heterogeneous, a meta-analytical synthesis was not feasible. The secondary outcomes reported varied by the studies, and even if there were similar outcomes reported, very often, a quantitative approach

(meta-analysis) was not feasible as no effect size or statistics were reported. Hence, a qualitative synthesis was undertaken instead. As both randomized and non-randomized studies were included, there remains no single risk of bias tool that could be applied across all the studies for quality assessment. Hence, quality assessment was not performed.

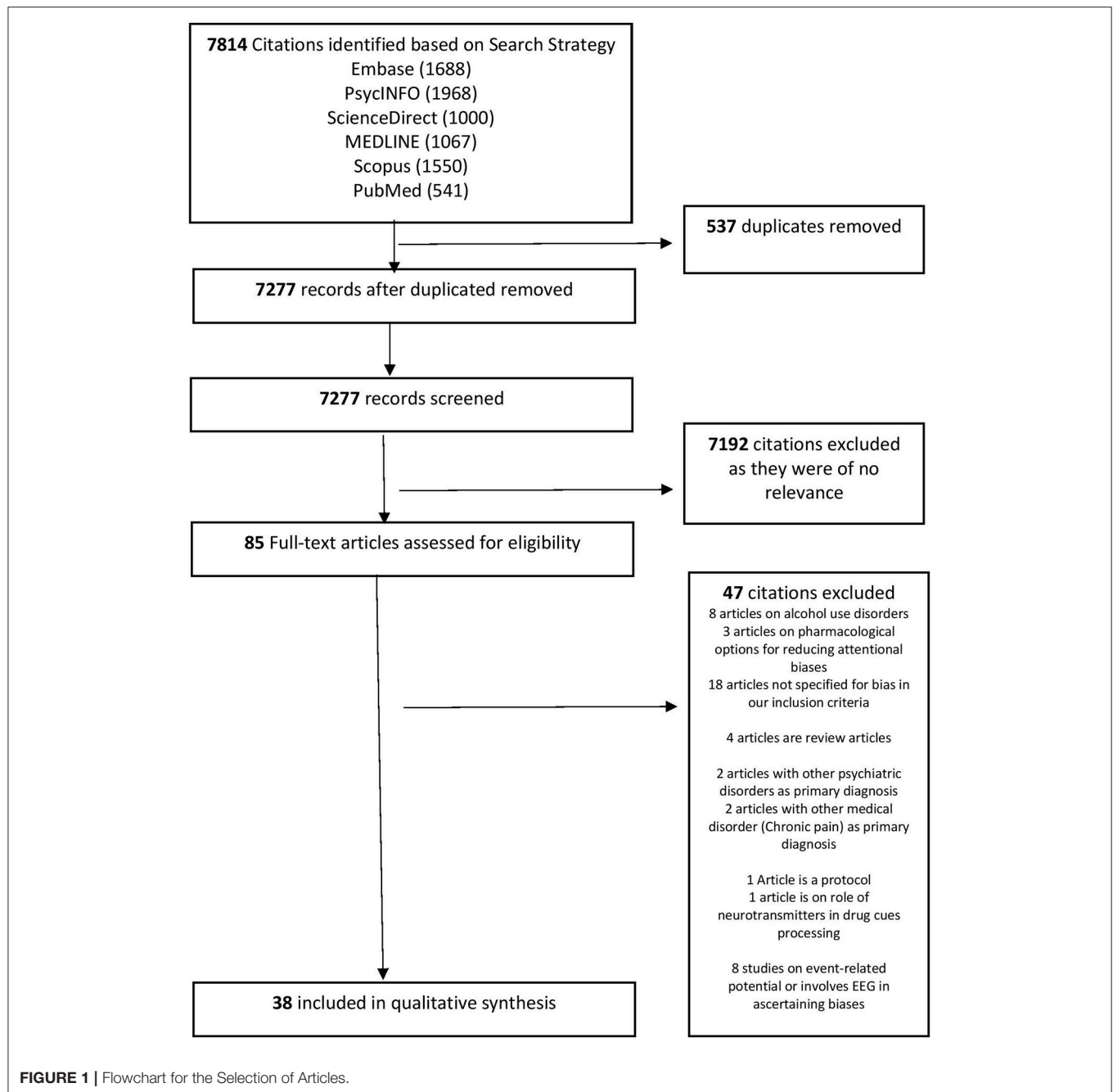
RESULTS

Based on our search strategy, a cumulative total of 7,814 citations were extracted from Embase, PsycINFO, Science Direct, Scopus, MEDLINE, and PubMed. Five hundred and thirty-seven duplicated articles were removed, leaving 7,277 citations. On further screening, 7,192 citations were removed as they were of not relevant. Eighty-five full-text articles were downloaded and evaluated against the inclusion and exclusion criteria. Forty-seven citations were excluded for reasons documented in **Figure 1**. Thirty-eight articles were selected for this qualitative synthesis. **Figure 1** provides an overview of the selection process of the articles for the current review. **Tables 1–4** provide an overview of the core characteristics of the included studies ($n = 38$).

Eleven articles involved participants with opioid use disorder, 16 articles involved participants with cocaine use disorder, nine articles involved participants with cannabis use disorder, and two articles involved samples of participants with different disorders (i.e., drug-dependent participants with either cocaine, cannabis, or opiate dependence; or participants with alcohol, cannabis, amphetamine, or GHB use disorders). Out of the 11 articles involving participants with opioid use disorder, three were randomized trials, seven were cross-sectional studies and one was a longitudinal study. Out of the 16 articles involving participants with cocaine use disorder, three were randomized trials, 11 were cross-sectional studies, one a pilot study and one a case-controlled study. Out of the nine articles involving participants with cannabis use disorder, two were case-control studies and seven were cross-sectional studies.

Characteristics of 11 Studies for Opioid Use Disorders

Three studies [Franken et al. (15), Marissen et al. (17), and Zhou et al. (21)], recruited participants in an inpatient treatment facility. The remaining studies ($n = 8$) recruited participants who were outpatients or who had attended a harm reduction program. Six studies [Bearre et al. (18), Fadardi et al. (19), Anderson et al. (22), Charles et al. (23), Ziaee (24), and Zhao et al. (25)] included participants who were receiving methadone substitution-based treatment. Apart from the study by Ziaee et al. (24), which failed to provide information about the gender ratios of the recruited cohort of individuals, all studies had predominantly male participants, and the mean age was between 30 and 45 years. Most of the included studies were conducted in Europe ($n = 6$), with the remaining studies conducted in the United States ($n = 1$), Iran ($n = 2$), and China ($n = 2$). The diagnosis of opioid use disorders was ascertained by means



of the Diagnostic and Statistical Manual (DSM) criteria for almost all of the studies. Only four studies [those of Bearre et al. (18), Fadardi et al. (19), Charles et al. (23), and Ziaee et al. (24)] failed to report how the diagnosis was ascertained. In the assessment of attention biases, the Stroop task was used in five studies; the visual probe task in two studies and the remaining studies used the visual probe task with concurrent eye tracking ($n = 1$), approach and avoidance task ($n = 1$), attentional visual search ($n = 1$), and flicker change blindness paradigm ($n = 1$).

Primary and Secondary Outcomes Reported in the 11 Studies for Opioid Use Disorders

Ten of the eleven reported the presence of biases in their sampled participants, except in Charles et al. (23) reported no baseline attentional differences between the healthy controls and opioid-dependent participants. Studies that assessed attention bias using the Stroop task reported an higher overall reaction time (15) among abusers, or enhanced attentional biases for drug-related stimuli especially among abusers (19) and that attentional

TABLE 1 | Characteristics of studies for opioid use disorders.

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
OPIOID USE DISORDERS									
Franken et al. (15)	Randomised trial	21 heroin dependent participants 30 control participants	Participants with heroin dependence were recruited from an inpatient treatment center Participants in the control group were recruited among clinical and administrative staff in the clinic	71.4% males (heroin dependent) 83.3% (control group) Mean age 31.5 years (heroin dependent) Mean age 34.8 (control group) Mean self-reported duration of heroin dependence was 93.9 months	Netherlands	Heroin Dependence	Based on the DSM-IV criteria for heroin dependence	Drug Stroop task	Higher overall reaction time for heroin participants as compared to control participants Mean pre-experimental craving was 13.8, mean post masked Stroop was 7.19 and mean post unmasked Stroop was 15.2
Lubman et al. (16)	Randomised trial	16 methadone maintained opiate addicts 16 age-matched control	Heroin addicts were recruited from local drug services Staff from these services were recruited as controls	Opiate group: mean age 31.4, Male to Female 11:5 Control group: mean age 31.7, male to female 8:8	United Kingdom	Heroin Dependence	ICD-10 and DSM IV	Pictorial Probe Detection Task	Faster reaction times to probes that replaced drug stimuli, indicative of the presence of an attentional bias
Marissen et al. (17)	Randomised trial	110 Participants assigned to either cue exposure therapy or placebo psychotherapy	Abstinent heroin addicts who were admitted voluntarily to an in-patient drug-free therapeutic center in the Hague	89% males, mean age 34 years old Average age of onset of heroin usage was 21.4 years, most have used heroin for 9.3 years	Netherlands	Heroin Dependence	DSM-IV criteria for heroin dependence	Emotional Stroop Task	Pre-treatment attentional bias predicted relapse at 3 months follow-up Reduction of attentional biases in both experimental conditions
Beaure et al. (18)	Cross-sectional study	60 participants	Recruited from a harm reduction program (methadone maintenance or needle exchange)	44 participants on methadone maintenance, 16 on needle exchange program Mean age 32 years, mean 7.07 months of heroin use	United Kingdom	Heroin dependence	Not mentioned	Flicker change blindness paradigm	Attention bias increase as the monthly frequency of heroin use increases
Fadardi et al. (19)	Cross-sectional study	53 drug abusers with 71 non-abusers as controls	Drug abusers were recruited from a local drug-use services clinic and were on methadone maintenance therapy Controls were students, academic staff and other personnel of Ferdowsi University of Mashhad and people from the local community who were visiting the university	Drug abusers: 100% male, mean age was 36.57 years Control: 54% male, mean age 26.62 years	Iran	Opiate abuse	Not mentioned	Persian Version of classic and addiction Stroop tests	Higher attentional bias for drug-related stimuli than non-abusers

(Continued)

TABLE 1 | Continued

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
Waters et al. (20)	Longitudinal study	68 heroin dependent inpatients	Addiction treatment center	85.3% Males Mean age 40.87 Age of first heroin use was 22.34 Total years of heroin use was 14.13	Netherlands	Heroin Dependence	DSM-IV criteria for heroin dependence	Drug Stroop task	Attentional biases to drug cues were elevated during temptation episodes
Zhou et al. (21)	Cross-sectional study	22 male abstinent heroin abusers 20 healthy males	Recruited from a legal rehabilitation center in Yunnan Province, China	All males Mean age 31.45	China	Opioid dependence	DSM-IV criteria for heroin dependence	Pull/Push task (Based on Approach/Avoidance Task rationale)	Abstinent individuals had higher tendencies to approach heroin-related stimuli, and avoidance tendencies toward heroin stimuli were reduced
Anderson et al. (22)	Cross-sectional study	17 opioid dependent patients 17 controls	Opioid dependent patients were from local methadone clinic Controls recruited from newspaper advertisements and flyer postings	Patients: mean age 44.4; male to female 9:8 Control: mean age 42.9; male to female 9:8	United States	Opioid Dependence	Structured clinical interview for DSM-IV (SCID-I)	Attentional Visual Search Task	Patients in treatment for addiction experience greater difficulty ignoring stimuli associated with non-drug reward.
Charles et al. (23)	Cross-sectional study	23 opioid dependent 21 healthy controls	Those prescribed with opioid substitution within the National Health Service	Mean age for Patient group (ABM-away) 43.91, (ABM-control) 45.17 Control group (ABM-away) 41.00, ABM-Control 38 Gender M:F for patient group ABM-away 10:1, ABM-control 10:2 Control group ABM-away 8:3, ABM-control 7:3	United Kingdom	Opioid Dependence	Not mentioned	Visual Probe Tasks	No baseline differences in attentional biases between control and patient group No change in AB following bias modification Treatment adherent patients who did not use illicit opiates on top of their prescribed opiates had statistically significantly greater attention bias away from substance-related stimuli

(Continued)

TABLE 1 | Continued

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
Ziaee et al. (24)	Cross-sectional	24 in experimental group received Drug Attention Control Training Program in addition to treatment as usual 24 in control group received only treatment as usual	Participants were drug abusers who were undergoing methadone maintenance therapy in a drug-abuse clinic	Mean age of experimental group was 33.17; mean age of control group was 38.75 The drugs that participants most commonly abused were opium, crystal and opium sap	Iran	Drug abuse and on methadone maintenance therapy	Not mentioned	Drug Stroop test	Experimental group showed reduction in attention bias for drug related stimuli, temptations to sue, doses of medicine, and number of relapses; increases on the Readiness to Change Questionnaire and 2 subscales of the Situational Confidence Questionnaire
Zhao et al. (25)	Cross-sectional	30 heroin dependents 39 healthy controls	Heroin dependents were from a methadone clinic Controls were service workers and security guards from a university	In heroin group: mean age 39.83, male to female 2:1 In control group: mean age 41.42, male to female 9:10	China	Heroin dependence	DSM-IV	Visual probe task with concurrent eye movement monitoring	Heroin group reacted faster to probes associated with substance-related pictures than neutral pictures, and they directed more initial fixations and maintained longer initial fixation durations toward substance-related pictures than neutral pictures.

TABLE 2 | Characteristics of studies for cannabis use disorders.

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
CANNABIS USE DISORDERS									
Field et al. (26)	Case control	17 regular cannabis users 16 non-users	Students and Staff at the University of Southampton	5 males, 12 females in the group of cannabis users Mean age of 22.4 years Median length of time cannabis smoked 3 years 4 males, 12 females in control group. Mean age 20.9 years.	United Kingdom	Cannabis	No mention of any diagnostic tools	Visual Probe Task	High levels of craving associated with significant attention bias for cannabis-related words
Field et al. (27)	Cross-sectional study	28 recreational cannabis users, including 15 in the "dependent" group and 13 in the "non-dependent" group	Students or staff at the University of Liverpool	6 female, 22 male Mean age was 21.9 years	United Kingdom	Cannabis Dependence	Scores on the Cannabis Severity Dependence Scale	Drug Stroop task	Significant attention bias in the cannabis group No association between attention bias and frequency of cannabis use or subjective craving
Field et al. (28)	Case control	23 regular cannabis users 23 non-user controls	Students and staff at the University of Liverpool	Cannabis users mean age was 23.04 Non-users mean age was 21.30 Gender ratio for Cannabis users: 14:9 (M:F) Gender ratio for non-users 8:15 (M:F)	United Kingdom	Cannabis abuse	Self-report usage of drugs	Visual Probe task with concurrent eye movement monitoring	Regular cannabis users had biases to maintain gaze on cannabis cues, and faster approach responses to cannabis cues
Cane et al. (29)	Cross-sectional study	17 marijuana-smokers 15 non-marijuana smokers	Students from the University of Kent	Not provided	United Kingdom	Cannabis dependence	Screening questionnaire	Drug Stroop task	Mean reaction time was significant for the marijuana group (Mean time for marijuana words was 984ms, neutral words was 895ms).
Cousijn et al. (30)	Cross-sectional study	32 heavy cannabis users and 39 non-using controls	Recruited through advertisements on the Internet and in Cannabis outlet (coffee-shops)	34% females for heavy cannabis users, mean age 21.2 37% female for controls, mean age 22.0	Netherlands	Cannabis dependence	Cannabis Use Disorder Identification Test and Structured Diagnostic Interview (MINI)	Approach and Avoidance Task	Heavy cannabis users had approach bias for cannabis as compared to controls. Approach bias was predictive of cannabis use at 6 months follow-up.

(Continued)

TABLE 2 | Continued

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
Cousijn et al. (31)	Cross-sectional Study	42 heavy cannabis users with intentions to use 45 heavy cannabis users shortly after cannabis usage	Recruited in five different cannabis outlets	82 males, 8 females Aged 18-59	Netherlands	Cannabis dependence	Cannabis Use Disorder Identification Test-Revised	Approach and Avoidance Task	Heavy cannabis users with the intention to use did not show a cannabis approach bias, whereas intoxicated cannabis users did show an approach bias regardless of image category. Moreover, craving was negatively associated with the approach bias, and no relationships were observed between the cannabis approach bias, satiation, prior cannabis use, and response inhibition
Cousijn et al. (32)	Cross-sectional study	27 heavy cannabis users 26 controls	All recruited via Internet advertisement and Amsterdam coffee shops	30% females in cannabis group, 38% females in control group Mean age 24.0 years in cannabis group Mean age 25.3 years in control group	Netherlands	Cannabis dependence	Cannabis Use Disorder Identification Test-Revised	Classical and Cannabis Stroop test	Cannabis smokers as compared to control group have stronger attentional bias for cannabis word Within the group of cannabis users, those who were clinically recognized as dependent showed a stronger attentional bias than the heavy, non-dependent users. Cannabis users who displayed reduced cognitive control (as measured with the classical Stroop task) showed increased session-induced craving. Cognitive control did not appear to modulate the relationship between attentional bias to cannabis words (cannabis Stroop task) and cannabis dependence.
Metrik et al. (33)	Cross-sectional	93 participants	Recruited from community	34.4% female	United States	Cannabis dependence	SCID-IV-NP for assessment of cannabis dependence	Marijuana Stroop Test	Presence of Attention bias to marijuana words (mean time was 752.89) vs. control (721.88) $p < 0.001$
Vujanovic et al. (34)	Cross-sectional	12 adults with cannabis use disorders 13 controls	Recruited via local advertisements	8 female Mean age 31, range 22-45	United States	Cannabis use disorder	Screening test and structured clinical interview for DSM-IV Axis I disorder	Pictorial stimuli attention bias task	Cannabis use disorders group showed greater attentional bias to cannabis cues at the 125-ms probe time Cannabis use disorders group also reported greater perceived stress and post-task stress scores

TABLE 3 | Characteristics of studies for stimulant use disorders.

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
STIMULANT USE DISORDERS									
Franken et al. (35)	Pilot Study	16 cocaine dependence or cocaine abuse individuals	Addiction treatment department of a psychiatric hospital	13 males, 3 females Mean age was 26.4 years Mean cocaine abstinence was 184 days Mean age of first cocaine use was 18.6 years Mean years of regular cocaine use was 5.7 years	Netherlands	Cocaine abuse/dependence	DSM-III-R criteria for cocaine dependence or cocaine abuse	Reaction time experimental task	Attentional bias was present in patients with higher scores on the obsessive cocaine thoughts and higher craving scores.
Hester et al. (36)	Case control	23 cocaine users with 23 matched controls	Not available	23 non-drug using participants (7 female), mean age 39.4 years 23 active drug using participant (7 female, mean age 40.3)	United States of America	Cocaine dependence	Not available	Emotional Stroop Task	Mean reaction time for cocaine words for cocaine users (922.7ms), for controls (772.2ms). Significant attention bias for active cocaine users
Vadhan et al. (37)	Cross-sectional study	17 cocaine-dependent treatment seeking males 20 cocaine-dependent nontreatment seeking males	Recruited from two clinical treatment trials of combination pharmacotherapy and cognitive-behavioral relapse prevention therapy Non-treatment seekers were recruited from behavioral pharmacology studies	Mean age of treatment seekers was 42.2, mean age of nontreatment seekers was 40.4	United States	Cocaine Dependence	DSM-IV criteria, Structured Clinical Interview	Drug Stroop task	Treatment seeking participants have increased response latency when presented with cocaine-related words. Non-treatment seeking participants did not demonstrate this.
Hester et al. (38)	Cross-sectional Study	16 active cocaine users	No mention of source of recruitment, but participants were retained in the study if they had used cocaine in the past 72 h.	Mean age 41, Mean education 11.6 years	Australia	Cocaine dependence	Not mentioned	Working Memory task that manipulated attention by varying behavioral contents	Cocaine users had significantly poorer attentional control under high working memory demands, suffering both increased response times and reduced recall accuracy, with this effect more pronounced for cocaine stimuli
Montgomery et al. (39)	Randomised trial	32 regular cocaine users and 40 non-users	Student Population at Liverpool John Moores University and the general population in the surrounding areas	Mean age for cocaine users assigned to placebo 19.29, assigned to alcohol 20.23 Mean age for non-users assigned to placebo 19.59, assigned to alcohol 20.0 13 male in cocaine use group 19 male in non-cocaine use group	United Kingdom	Cocaine dependence	Questionnaire	Visual Probe and Modified Stroop task	Cocaine participants who received alcohol had increased attentional bias for cocaine pictures The cocaine Stroop revealed no differences between cocaine users and non-users, and no effects of alcohol in either group.

(Continued)

TABLE 3 | Continued

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
Liu et al. (40)	Cross-sectional study	37 cocaine-dependent subjects, 32 controls	Recruited from an ongoing neuroimaging study and via newspapers advertisements	Cocaine dependent subjects used cocaine for a mean of 13.64 years	United States	Cocaine dependence	Structured clinical interview for DSM-IV (SCID-I)	Cocaine Stroop Task	Cocaine-dependent subjects showed attentional bias to cocaine-related words, increased impulsivity, and poor inhibitory control compared with controls. The attentional bias was associated with inhibitory control in cocaine-dependent subjects but not in control subjects.
Tull et al. (41)	Cross-sectional study	30 cocaine dependent patients with PTSD, 30 cocaine dependent without PTSD	Residential substance use disorder treatment center	Mean age cocaine with PTSD was 44.57, cocaine without PTSD was 44.27 Male in cocaine with PTSD was 26.7%, in cocaine without PTSD 83.3%	United States	Cocaine Dependence	Not mentioned	Visual Dot probe task	Differences in attentional bias following script intervention (neutral or trauma script) Non-PTSD participants have greater attentional bias following neutral script than PTSD participants This effect was reversed following trauma script exposure, with PTSD participants exhibiting a greater attentional bias toward the location of cocaine imagery than non-PTSD participants.
Carpenter et al. (42)	Cross-sectional Study	25 individuals	Active cocaine users seeking treatment at Columbia University's Substance Treatment and Research Service	Mean age 37 years	United States	Cocaine dependence	Structured clinical interview for DSM-IV (SCID-I) and independent psychiatric examination	Drug Stroop	Attention bias toward cocaine related stimuli not demonstrated Stronger implicit beliefs about the positive effects of cocaine use prior to treatment were associated with poorer treatment outcome when an escalating voucher-incentive program was in place. An attentional bias for cocaine-related stimuli was associated with better treatment outcome when an escalating voucher-incentive program was removed. No association between cocaine use beliefs and treatment outcome was found when beliefs were measured with self-report instruments.
Marhe et al. (43)	Cross-sectional study	34 cocaine dependent inpatients	Recruited from an addiction treatment center	Mean age 38.7 85% males 11.4 years of using cocaine	Netherlands	Cocaine dependence	DSM-IV criteria for cocaine dependence	Cocaine Stroop test	Presence of attentional bias, with cocaine dependent patients responding slower to cocaine stimuli
Bardeen et al. (44)	Cross-sectional study	22 cocaine dependent patients with BPD 36 cocaine dependent patients without BPD	Community based residential substance use disorder treatment facility	26 females, mean age of 44.5 years	United States	Cocaine dependence	DSM-IV criteria for cocaine dependence	Dot-probe task	Males with BPD have higher attentional bias scores following a post trauma script intervention

(Continued)

TABLE 3 | Continued

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
Kennedy et al. (45)	Cross-sectional study	35 individuals	Substance abuse and treatment program	20 non relapsers, mean age 43.7 15 relapsers, mean age 43.0	United States	Cocaine dependence	Structured clinical interview for DSM-IV	Stroop tasks	Attention bias was present, with cocaine-dependent subjects having increased reaction time for personal drug use words (928.6ms) vs. neutral words (897.2) The level of attentional bias for cocaine-use words was not predictive of eventual relapse
Dias et al. (46)	Cross-sectional study	46 cocaine dependent subjects 41 healthy controls	Recruited by a variety of media advertisements	cocaine dependent group Mean age was 46.3 Control mean age was 40.0 cocaine dependent group %Male was 84.8%, Control %Male was 51.2	United States	Cocaine dependence	DSM-IV (SCID-1)	Eye-tracking cocaine attentional bias task	Presence of attentional bias toward cocaine cues as cocaine dependent subjects made more anti-saccade to cocaine cues
Mayer et al. (6)	Randomised trial	37 participants Assigned to either attentional bias modification therapy (ABMT) or control therapy	Not mentioned	ABMT group: 14 male, and 5 female, mean age 37.4 Control group: 10 male and 8 female, mean age 38.9	United States	Cocaine dependence	Structured clinical interview for DSM-IV	Visual Probe task	Presence of attentional bias Not subjected to modification by ABMT
Marks et al. (47)	Cross-sectional study	20 cocaine dependence 20 cocaine and alcohol dependent	Recruited through word of mouth and postings on community bulletin boards	Cocaine mean age 43.4 Cocaine alcohol mean age 43.4 6 females in each groups	United States	Cocaine and alcohol dependent	Structured clinical interview for DSM-IV	Eye-tracking cocaine attentional bias task	Cocaine dependent had attentional bias toward cocaine Cocaine-alcohol dependent has attentional bias toward both cocaine and alcohol.
Devito et al. (48)	Randomised trial	38 in treatment as usual plus computer-based CBT (CBT4CBT) 41 in treatment as usual	Recruited from community based outpatient clinic	46% female, mean age 42.2	United States	Cocaine use disorder	DSM-IV	Computerized drug Stroop test	Reductions in Drug Stroop Effect across treatment were associated with greater engagement with CBT4CBT-specific treatment components
Sharma et al. (49)	Cross-sectional study	Study 1 52 participants, 27 of which were regular marijuana users and 25 were not marijuana users Study 2 16 Anonymous participants	Recruited through social networks and known to be marijuana smokers or non-users Recruited from two local Narcotics Anonymous Fellowships	Mean age 31 years old 38 males 13 males, 3 females, with ages of 25 to 41	United Kingdom	Cannabis dependence Cocaine dependence	Self-report Self-report	Drug Stroop task	A slowdown in responding to the color of non-words that were paired with cocaine-related images compared with non-cocaine related images. The slowdown was also characterized as a carryover effect, with the largest effect occurring on trials following the addiction-associated non-word. No effects were found for marijuana images associated with non-words.

TABLE 4 | Characteristics of studies with heterogeneous sample of participants.

Study	Study design	Sample size	Types of sample	Demographics of sample	Country	Diagnosis of sample	Method of diagnosis	Attention bias method	Outcomes
MIXED COHORT									
Carpenter et al. (50)	Cross-sectional study	80 drug dependent individuals	All were illicit drug users enrolled in one of the six randomized trial combining coping skills relapse prevention and pharmacotherapy	62 males, 18 females 45 participants (cocaine), 25 participants (marijuana), 10 participants (heroin) Mean age 39.9 years	United States of America	Cocaine, Marijuana and Heroin dependence	DSM-IV dependence criteria Structured psychiatric interview	Drug Stroop Test	All groups had slower reaction times when presented with cocaine words.
Van Hamel et al. (51)	Cross-sectional	78 adolescents with substance dependence 64 healthy controls	Addiction care facility	Substance dependence group mean age 19.5 Control group mean age 19.0	Netherlands	Alcohol, Cannabis, Amphetamine or GHB Use disorder	Self-reported substance usage and severity of usage	Visual Probe task	Attentional bias for stimuli presented at 500ms and 1250ms. Higher severity of dependence, increased AB

biases to drug-related cues were heightened when abusers had temptation episodes (20). Studies that assessed attention bias using the visual probe task reported that the reaction time for abusers was faster when they had probes that replaced drug-related stimuli. The only study that paired the visual probe task with concurrent eye tracking (25) demonstrated that abusers not only have faster reaction time to drug-related probes, but also more initial fixations and maintained fixations on drug-related probes or images. For the approach and avoidance task, Zhou et al. (21) reported that former users of opioids have a greater tendency to approach heroin-related stimuli and a reduced tendency to avoid or push away these stimuli. The study using the flicker change blindness paradigm reported an association between the attention biases and the monthly frequency of heroin use. The study assessing attentional bias using attentional visual search showed that attention biases were present and that the presence of attentional biases would cause abusers to have heightened attention for other non-drug-related reward probes.

Four of the included studies reported other secondary outcomes following attention bias assessment and modification and provided evidence for the potential effectiveness of bias modification. Franken et al. (15) reported a reduction in the mean craving scores following masked Stroop intervention. The study by Ziaee et al. (24) found bias modification was associated with a reduction in several outcome parameters, including temptations to use, doses of medication, and number of relapses. Marissen et al. (17) reported findings similar to those of Ziaee et al. (24) concerning relapse, as Marissen et al. (17) found that baseline attentional biases could predict relapse at three months' follow-up. With regard to the effectiveness of the interventions, Marissen et al. (17) reported a reduction in attentional biases amongst individuals who received either cue exposure therapy or placebo psychotherapy. In contrast to the reductions in attentional biases were demonstrated by Marissen et al. (17) and Charles et al. (22) did not find any changes in attentional biases following their intervention.

Characteristics of 9 Studies for Cannabis Use Disorders

Four studies [Field et al. (26–28) and Cane e al. (29)] recruited students; the remainder (*n* = 5) recruited through advertisements or from cannabis outlets. No study recruited participants who were part of inpatient treatment or rehabilitation facility. The majority of the sampled participants were males. The mean age in years across all of the studies ranged from 20 to the early 30s. Seven of the studies were conducted in Europe, and the remaining two studies were conducted in the United States. There was heterogeneity in the method of ascertaining the diagnosis, with one study Field et al. (28) basing their diagnosis on self-reported information, four studies [Field et al., (27), Cane et al., (29), and Cousijin et al. (31, 32)] on questionnaires, and the remainder (Cousijin et al. (30), Metrik et al. (33), and Vujanovic et al. (34)] on structured interviews. In the assessment of biases, the Stroop task was used in four of the studies, and the remainder of the studies used the visual probe task (*n* = 1), or the visual probe task with concurrent eye tracking (*n* = 1), or the pictorial

attention bias task ($n = 1$), or the approach and avoidance task ($n = 2$).

Primary and Secondary Outcomes Reported in 9 Studies for Cannabis Use Disorders

All of the studies provided evidence for the presence of biases. For study that assessed attention bias using the Stroop task, it was reported that the mean reaction times for cannabis or marijuana stimuli were longer as compared to neutral stimuli (29). Stroop-based testing also helped in the differentiation of users who used varying amounts of cannabis (32), as it was reported that those who were clinically dependent had had a stronger attentional bias as compared to those who were non-dependent. The visual probe task and the visual probe task coupled with concurrent eye tracking provided both direct and indirect evidence of the presence of attention bias, as regular cannabis users exhibited biases in maintaining gaze on cannabis cues and increased reaction times for cannabis cues (28). Like that of the visual probe task, the pictorial stimuli attention bias task also reported the presence of attentional biases among cannabis users and these biases were most prominent when the probe was presented for 125 ms (which is shorter than the normal duration of 500 ms). For the studies that used the approach and avoidance task, one study reported the presence of an approach bias amongst heavy users (individuals who used cannabis on 10 or more days per month), whereas the other study did not report the presence of an approach bias in heavy users but found an approach bias for cannabis cues only amongst those users who were intoxicated at the time of testing.

There is mixed evidence for the association between attention bias and cravings. Field et al. (26) reported that the high levels of cravings were associated with attentional biases but in a later study, Field et al. (27) reported observing no association between attention biases and cravings. Cousijn et al. (31) also reported the lack of an association between approach biases and cravings. One study Cousijn et al. (30) reported approach bias to be a predictor of relapse.

Characteristics of the 16 Studies for Stimulant Use Disorders

Eight studies [Franken et al. (35); Vadhan et al. (37), Tull et al. (41), Carpenter et al. (42), Marhe et al. (43), Bardeen et al. (44), Kennedy et al. (45), and Devito et al. (48)] recruited a clinical or treatment-seeking cohort of participants, one study Montgomery et al. (39) recruited a student sample, and five studies [Hester and Garavan (38); Liu et al. (40), Dias et al. (46), Marks et al. (47), and Sharma et al. (49)] recruited a cohort of participants from the community. There was a predominance of males in those samples that reported a gender ratio. The mean age across the studies varied within the range of 20–45 years, with a single study Montgomery et al. (39) including an adolescent cohort (mean age 19 years old). Twelve of the included studies were conducted in the United States, four studies in Europe, and one study in Australia. The diagnosis of stimulant use disorder, most studies (12 out of 17 studies) used the diagnostic criteria, two

studies used a questionnaire or self-report, respectively, and the remainder of the studies did not provide any information as to how the diagnosis was ascertained. Eight studies utilized Stroop testing, one study used a reaction time experimental task, one study used a working memory task, four studies used the visual probe task, and two studies used the visual probe task with eye-tracking.

Primary and Secondary Outcomes Reported in Studies for Stimulant Use Disorders

All of the included studies reported the presence of biases except Carpenter et al. (42), which failed to demonstrate an attention bias in their sample of cocaine users. Two studies reported the severity of the underlying dependency to affect the resultant biases [Franken et al. (35) and Van Hamel et al. (51)]. Studies that assessed attention bias using the visual probe with eye-tracking to assess for attentional bias demonstrated that the cocaine-using cohort exhibited gaze preferences toward cocaine stimuli.

Concerning secondary outcomes, Franken et al. (35) reported that attentional bias was elevated in patients who had higher levels of cravings. Liu et al. (40) observed that attentional bias amongst cocaine users was associated with heightened impulsivity and poorer inhibitory control. Marks et al. (47) reported that there appears to be generalization of attentional bias for cocaine stimuli to that of alcohol stimuli. Mayer et al. (6) reported that there was no effectiveness of attention bias modification in reducing cocaine-related attentional biases.

Outcomes Reported in Studies With a Heterogeneous Sample

Two studies [Carpenter et al. (42) and Van Hamel et al. (51)] studied group with differing diagnosis. The studies included drug-dependent participants with either cocaine, cannabis or opiate dependence; or participants with alcohol, cannabis, amphetamines, or GHB use disorders. Both the Stroop test and the visual probe task were used in the assessment of attentional biases, and both trials demonstrated the presence of attentional biases.

DISCUSSION

This is perhaps the first review that synthesizes the evidence of cognitive biases in opiate, cannabis and stimulant use disorders. The main finding is the evidence that cognitive biases are present in the 38 studies identified, except for a single study on opioid use and stimulant use disorders. There were differences in the participants recruited for each disorder, with opioid use disorder studies recruiting mainly treatment-seeking individuals, who were either abstinent or maintained on opiate substitution therapy. The bias assessment methods used included the Stroop task, visual probe, eye movement tracking, approach and avoidance task, attentional visual search, and flicker change blindness paradigm. The findings for the secondary outcomes were narratively reported, but not synthesized due to their high heterogeneity.

Our main finding is the evidence that cognitive biases are present in opiate use, cannabis use, and stimulant use disorders. This finding is novel as there have not been any prior reviews of cannabis use disorders. In their meta-analysis, Cristea et al. (1) attempted to search for randomized trials for these substance disorders, but eventually only included trials that evaluated participants with alcohol or tobacco use disorders. Given this, the paper by Eberl et al. (5) only provided evidence that cognitive biases were present and could be subjected to modification among participants with either alcohol or tobacco use disorders. A review by Christiansen et al. (9) included participants with opiate use disorders (17, 42, 43) and participants with cocaine use disorders (17, 42, 43, 45, 52). Whilst the work by Field and Cox (2) provided evidence for the presence of cognitive biases in opiate and cocaine use disorders, the evidence synthesis was from a limited number of studies, given that the primary objective of the review was to ascertain the association between cognitive bias and relapse. In their critical review, Leeman et al. (53) provided evidence for the presence of attentional biases in cocaine use disorders. This review was limited only to the assessment of cocaine studies as the authors reported that prior studies have reported that individuals with cocaine use disorders have particularly robust cognitive biases and that, given the lack of effective treatment approaches, novel approaches such as bias modification need to be considered (53). It is clear that the current review addressed several gaps in the prior reviews, by synthesizing the evidence for cognitive biases in three highly prevalent substance use disorders (opioid, cannabis, and stimulant use disorders) through evaluating studies with different study designs. None of the prior reviews synthesized evidence for the presence of attentional biases for individuals with cannabis use disorders. Evidence synthesis for this is of particular importance, given that cannabis use has been increasingly globally (34), and an estimated 10% of regular cannabis users do eventually develop dependence. Also, apart from the risk of developing an addictive disorder, cannabis use has been associated with heightened risk for the development of other psychiatric disorders, such as psychosis, cognitive impairment, and potentially also amotivational syndrome. Thus, the identification of the presence of cognitive bias in individuals with cannabis use disorders signifies that there remains a need for interventions to deal with these unconscious processes. Also, cognitive bias assessment could also help in the differentiation of individuals who are clinically dependent on cannabis and those who are using cannabis recreationally, as it has been demonstrated that individuals who are clinically dependent have stronger attentional biases. Whilst our synthesized results demonstrate the presence of cognitive biases in all three addictive disorders, it should be noted that there were two outlier studies (23, 42). One of the studies (23) attributed this finding to the fact that the presentation of the opioid-related stimuli might have appeared to be novel to the control sample.

Our synthesis of the published literature demonstrated the presence of biases in individuals who receive opiate substitution therapy (16). The presence of biases among individuals maintained on opiate substitution therapy implies that whilst pharmacological interventions might help in the stabilization of

the lifestyle and minimisation of harms associated with illicit usage, it does not have any effect on factors that could still predispose individuals to a lapse or relapse (14). Drug-related stimuli have been proposed to be “cognitive intermediates” prior to a lapse or relapse, given that such salient stimuli activate unconscious processes, leading to one having increased attention, but also leaves the individual with fewer resources available to apply learned coping strategies. Hence, there is clearly a need for cognitive bias modification to be considered for individuals with addictive disorders. There has been increased recognition of this need, as evident by the protocol proposed by Heitman et al. (54), in which they attempt to investigate both the effectiveness and cost-effectiveness of an online Internet-based cognitive bias modification method that is delivered in addition to treatment as usual for individuals with alcohol or cannabis use disorders. Whilst there has been a prior study (55) that has evaluated combined cognitive bias modification and cognitive behavioral therapy, there remains, to our knowledge, no published studies or protocol for a similar study for substance use disorders. A consideration of the integration of both modalities of therapy is crucial, given that cognitive behavioral therapies typically target the top-down or reflective conscious decision-making processes, whilst bias modification could target the bottom-up or unconscious processes that are responsible for lapse and relapse occurrences.

The fact that cognitive biases could be detected by different tools negates the previous concerns raised about the reliability of the assessment tools. Biases were reported to be present despite there being a varied range of assessment tools that were utilized. The combination of indirect and direct measures used in the ascertainment of cognitive biases helped improve the evidence base, supporting the presence of these biases in all three disorders. Across all three disorders, a combination of both indirect and direct measures was used in the ascertainment of cognitive biases. Indirect measures, as aforementioned, refer to assessment tools such as the Stroop task or the visual probe task. In these indirect measures, participants are required to either name the color in which neutral and drug-related words are printed or respond to probes that replace either neutral or salient stimuli (53). Reaction time is measured and used as a surrogate in the determination of attentional biases. Direct measures provide better evidence of cognitive biases, given that eye movements in response to neutral or drug cues are used in the ascertainment of cognitive biases (12). Ataya et al. (56) previously investigated the internal reliability of the Stroop task and the visual probe task in the assessment of attention biases and reported that the modified Stroop task was more reliable as compared to the visual probe task, as it is a simpler task and is less likely to influence the reaction time that is being measured. Field and Christiansen (57) reported that the eye-movement measurement of cognitive bias does help to further mitigate against the concerns about reliability. Given that a variety of conventional indirect measures and direct measures were used for all the different disorders, we believe that this helps to better the quality of our synthesized evidence of the presence of cognitive biases in these disorders.

Notably, there was a single study Montgomery et al. (39) that has utilized different methods of cognitive bias assessment in the

same group of participants. Interestingly, the authors reported that there was an increase in attentional biases following the administration of the visual probe task. However, participants' response did not differ when the modified Stroop task was used. Montgomery et al. (39) explained the differences in their results by highlighting that the visual-probe task might be better in measuring visuospatial attention. The Stroop task might not be as sensitive in the measurement of visuospatial attention but is better in assessing for response inhibition and other cognitive processes. Whilst we have previously discussed the advantages of having both direct and indirect measures in the assessment of biases, the results arising from Montgomery et al.'s (39) study has other implications if only indirect measures are to be used. This might be in the context of web or mobile-delivery of cognitive bias modification intervention. As such, it is of importance for researchers to carefully consider which assessment tool might be most appropriate, depending on the stimulus that they present to participants, given that the visual probe task is better able to measure visuospatial attention, and the Stroop task better for response inhibition. Also, while the Stroop task has been found to be more reliable, the results arising from Montgomery et al.'s (39) study also highlights the need for researchers to consider other aspects of the intervention, that might affect whether the task is capable of detecting biases.

This review has several strengths. A comprehensive search through the literature identified studies for the highly prevalent addictive disorders. No other reviews have synthesized the existing evidence for biases and cannabis use disorders. There are however limitations. The inclusion of a mixture of study designs, including both randomized and non-randomized studies affects the quality of the evidence, given that non-randomized studies have the risk of confounding and other biases. We were unable to perform a risk of bias assessment, due to the diversity of study designs and there remains no single tool that could assess risk of bias across different study designs. Whilst we search for studies involving participants with stimulant use disorders, the studies included involved participants who were primarily using cocaine. It will be beneficial if studies involving participants who were using amphetamines be conducted and incorporate into future synthesis, particularly as there is an increasing global trend of amphetamine abuse and dependence. We are also limited to a qualitative synthesis of the data extracted

from each of the studies pertaining to attentional biases. Most of the studies included focus on the assessment of attentional biases in substance-using individuals, so evidence synthesis for the effectiveness of attentional or approach bias modification could not be undertaken. Secondary outcome measures had great heterogeneity, so we were unable to identify a common dataset for the synthesis.

CONCLUSIONS

Cognitive biases have been consistently observed in opioid use, cannabis use, and stimulant use disorders, despite a range of assessment tools being utilized in the assessment for these biases. The presence of attentional and approach bias signifies the importance of bias modification interventions. There remains a need for future research to explore the presence of attentional biases in other stimulant use disorders, such as amphetamine use disorders. It is also of importance for future research to evaluate the efficacy of bias modification for these highly prevalent disorders and to determine if reduction of these biases is associated with improvements in other addiction outcomes.

DATA AVAILABILITY

All available data have been included in the manuscript.

AUTHOR CONTRIBUTIONS

MZ, DF, and HS conceptualized and planned the current review. MZ and JY were involved in the literature search, extraction, and selection of the articles for inclusion in the current review. MZ wrote the initial draft of the manuscript and TW helped in the amendments of the initial draft. All authors were involved in the subsequent revisions and preparations of the manuscript prior to submission.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Review

Attention and Cognitive Bias Modification Apps: Review of the Literature and of Commercially Available Apps

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Abstract

Background: Automatic processes, such as attentional biases or interpretative biases, have been purported to be responsible for several psychiatric disorders. Recent reviews have highlighted that cognitive biases may be modifiable. Advances in eHealth and mHealth have been harnessed for the delivery of cognitive bias modification. While several studies have evaluated mHealth-based bias modification intervention, no review, to our knowledge, has synthesized the evidence for it. In addition, no review has looked at commercial apps and their functionalities and methods of bias modification. A review is essential in determining whether scientifically validated apps are available commercially and the proportion of commercial apps that have been evaluated scientifically.

Objective: The objective of this review was primarily to determine the proportion of attention or cognitive bias modification apps that have been evaluated scientifically and secondarily to determine whether the scientifically evaluated apps were commercially available. We also sought to identify commercially available bias modification apps and determine the functionalities of these apps, the methods used for attention or cognitive bias modification, and whether these apps had been evaluated scientifically.

Methods: To identify apps in the published literature, we searched PubMed, MEDLINE, PsycINFO, and Scopus for studies published from 2000 to April 17, 2018. The search terms used were “attention bias” OR “cognitive bias” AND “smartphone” OR “smartphone application” OR “smartphone app” OR “mobile phones” OR “mobile application” OR “mobile app” OR “personal digital assistant.” To identify commercial apps, we conducted a manual cross-sectional search between September 15 and 25, 2017 in the Apple iTunes and Google Play app stores. The search terms used to identify the apps were “attention bias” and “cognitive bias.” We also conducted a manual search on the apps with published evaluations.

Results: The effectiveness of bias modification was reported in 7 of 8 trials that we identified in the published literature. Only 1 of the 8 previously evaluated apps was commercially available. The 17 commercial apps we identified tended to use either an attention visual search or gamified task. Only 1 commercial app had been evaluated in the published literature.

Conclusions: This is perhaps the first review to synthesize the evidence for published mHealth attention bias apps. Our review demonstrated that evidence for mHealth attention bias apps is inconclusive, and quite a few commercial apps have not been validated scientifically.

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KEYWORDS

attention bias; cognitive bias; smartphone; mHealth; psychiatry; telemedicine; mobile applications

Introduction

Advances in experimental psychology have led to further research into cognitive bias modification. Cognitive biases refer to automatic attentional or interpretational tendencies toward certain stimuli [1]. Cognitive bias is an overarching term and includes other common cognitive biases, such as attentional biases, approach biases, and interpretative biases [2]. These unconscious processes are postulated to be involved in the psychopathologies of various disorders, including social anxiety disorder [3], alcohol use disorder [4], and tobacco use disorder [5]. Cognitive bias modification refers to the retraining of these automatic processes. For addictive disorders, theories such as the opponent process theory or the incentive-sensitization theory have been proposed to explain the causes of the vicious cycle of addiction [6]. However, more recently, the dual-process theory has postulated that, in addictive disorders, automatic processing of substance-related cues is increased, with a corresponding decrease in normal inhibitory control [7]. Thus, these automatic processes would cause an individual to relapse into substance use. While the dual-process model does not apply to other psychiatric disorders, other theoretical approaches have similarly proposed the presence of an enhanced threat-detection mechanism, and that this, in turn, results in socially anxious individuals to be hypervigilant toward threatening or anxiety-invoking stimuli [8].

Experimental psychologists have developed various attention bias assessment tools, such as the dot-probe task, visual-probe task, visual search task, and cognitive bias interpretations [6]. In addition to assessment, these tools are commonly also used for bias modification. For the visual-probe task and the dot-probe task, individuals are required to respond to a probe that replaces either a neutral image or a substance-related image, or for affective conditions, images depicting positive or negative emotional states. Attentional biases are assessed to be present if individuals demonstrate a faster reaction time in responding to probes replacing images associated with high salience [6]. Cognitive bias modification for interpretations involves presenting individuals with ambiguous scenarios and with word fragments that help to disambiguate the scenarios in a positive way [9]. In the visual search task, individuals are required to identify the positive smiling picture among a range of other pictures with a range of emotions [10]. To date, further research has examined the efficacy of bias modifications, and a recent meta-analytical study synthesized the evidence for substance use disorders [11]. In their meta-analysis of trials involving participants with tobacco or alcohol addiction, Cristea et al [11] reported that cognitive bias interventions had a moderate effect on cognitive bias (Hedges $g=0.60$), but there was no effect of bias modification on other outcomes, such as cravings [11]. Jones and Sharpe [1] in their review of meta-analyses found that there is more evidence for cognitive bias modification in ameliorating anxiety symptoms than in ameliorating depressive symptoms. Jones and Sharpe [1] also reported that the long-term efficacy was evident only in addiction trials. It is essential to note that studies included in these meta-analytical reviews were trials conducted within the controlled environment of a laboratory [1]. Conducting attention bias modification in a

laboratory setting reduces the risk of attrition to these highly repetitive tasks, but the results may not be replicable in a less-supervised clinical or community setting.

In parallel with the development of the above, there have been major advances in both eHealth and mHealth technologies in the 21st century. eHealth, or electronic health, refers to the use of Web-based interventions [12] and mHealth, or mobile health, refers to the use of mobile devices, such as smartphones and their accompanying apps, for health care [12]. In psychiatric practice, both eHealth and mHealth technologies have been adopted for the delivery of psychological interventions for conditions such as depression and bipolar disorders to monitor patients' mood state [13] and to reduce drinking among individuals with alcohol use disorder [14]. Advances in technologies have also transformed how conventional attention and cognitive bias modification tasks are being delivered. An evaluation of the efficacy of Web-based attention bias modification interventions by Wittekind et al [15] found that a Web-based approach and avoidance could retrain attention bias among individuals with tobacco use disorder and reported its efficacy in smoking reduction. In a study of individuals with social anxiety disorder, Sportel et al [16] compared the effectiveness of Web-based cognitive bias modification against conventional cognitive behavioral therapy and reported that both modalities of intervention were effective in reducing social anxiety symptoms. These studies highlighted the potential of Web-based bias interventions as an alternative to conventional laboratory-based attention bias modification. Given the proliferation of commercially available health apps and the increased recognition of the role of attention bias in medical and psychiatric disorders, more commercially developed apps that aim to manipulate attention bias are expected to become available. Studies have been published, such as that by Clarke et al [17], that have evaluated whether an attention bias modification task was helpful for individuals with insomnia.

We know of no reviews to date that have synthesized the literature to determine the existing evidence for mHealth-based bias modification interventions. Also lacking is an understanding of the common functionalities and methods of bias modification used in these commercially available apps. By analyzing in parallel both the apps offered in commercial app stores and the apps evaluated in published works on attention and cognitive bias modification, we can determine whether scientifically validated apps are available commercially and estimate the proportion of commercial apps that have been evaluated scientifically.

The primary objective of this review was to determine the proportion of attention or cognitive bias modification apps that have been evaluated scientifically. The secondary objective was to determine whether the scientifically evaluated apps were commercially available. In this review, we also sought to identify commercially available bias modification apps and determine the functionalities of these apps, the methods used for attention or cognitive bias modification, and whether these apps had been evaluated scientifically. The evidence from this review has important implications for clinical care, technological development, and research.

Methods

Phase 1: Identification of Attention and Cognitive Bias Modification Apps in the Published Literature

To achieve the primary objective, we initially searched PubMed and MEDLINE for articles published from 2000 through to September 24, 2017. We performed an updated search from April 14 through 17, 2018 on PubMed and MEDLINE and 2 additional databases, PsycINFO and Scopus. We selected the year 2000 because, before this date, few people had access to personal digital assistants and mobile phones. The search terms we used were “attention bias” OR “cognitive bias” AND “smartphone” OR “smartphone application” OR “smartphone app” OR “mobile phones” OR “mobile application” OR “mobile app” OR “personal digital assistant.” We included only English-language articles.

The inclusion criteria were that (1) cognitive bias modification must have been delivered using a mobile device (mobile phone, smartphone, or personal digital assistant), and (2) delivery was in the form of a specific app or game. We excluded articles that simply described how a Web-based intervention could run on a mobile device.

All the articles were initially screened based on their title and abstract by 2 independent authors (MZ and JY). Full copies of the shortlisted articles were then evaluated against the inclusion and exclusion criteria. Any disagreement between the 2 authors was resolved by discussion with the third author (GS). The rationale for inclusion and exclusion was captured on an electronic form, together with the following information: (1) publication details (names of the authors and the year of publication), (2) specific condition targeted, (3) description of the intervention, (4) method of delivery of attention bias or cognitive bias modification, and (5) main outcome and findings arising from the study.

Phase 2: Identification of Commercially Available Apps

We then conducted a manual cross-sectional search between September 15 and 25, 2017 on the apps stores iTunes (Apple Inc, Cupertino, CA, USA) and Google Play (Google LLC, Mountain View, CA, USA). The search terms we used were “attention bias” and “cognitive bias.” The manual search was supplemented in the same period with the use of a mobile app search engine, 42matters (42matters AG, Zurich, Switzerland), to search for all the available apps globally. If an app had both a free and paid version, we analyzed the paid version, as it is commonly recognized that paid versions have more functionalities; free versions of apps tend to offer only limited access to functionalities [18].

We extracted the following information from the identified apps and recorded it on a standardized electronic data collation form: (1) app name, (2) general description of the app, (3) method of attention or cognitive bias modification, (4) other functionalities, (5) range of total downloads, (6) app ratings, (7) reference

source, and (8) last date of modification. For the method of attention or cognitive bias modification, we recorded the tool that was being used (eg, visual-probe task, dot-probe task, or visual search).

To determine whether commercially available apps had been evaluated scientifically, we cross-checked the extracted commercial app against those apps that we had previously identified in phase 1. Also, we assessed any references that were cited in either the description or within the app for any scientific evaluation of the app. We contacted developers of the respective apps via email on November 5, 2017 for further information as to whether the app had been evaluated scientifically.

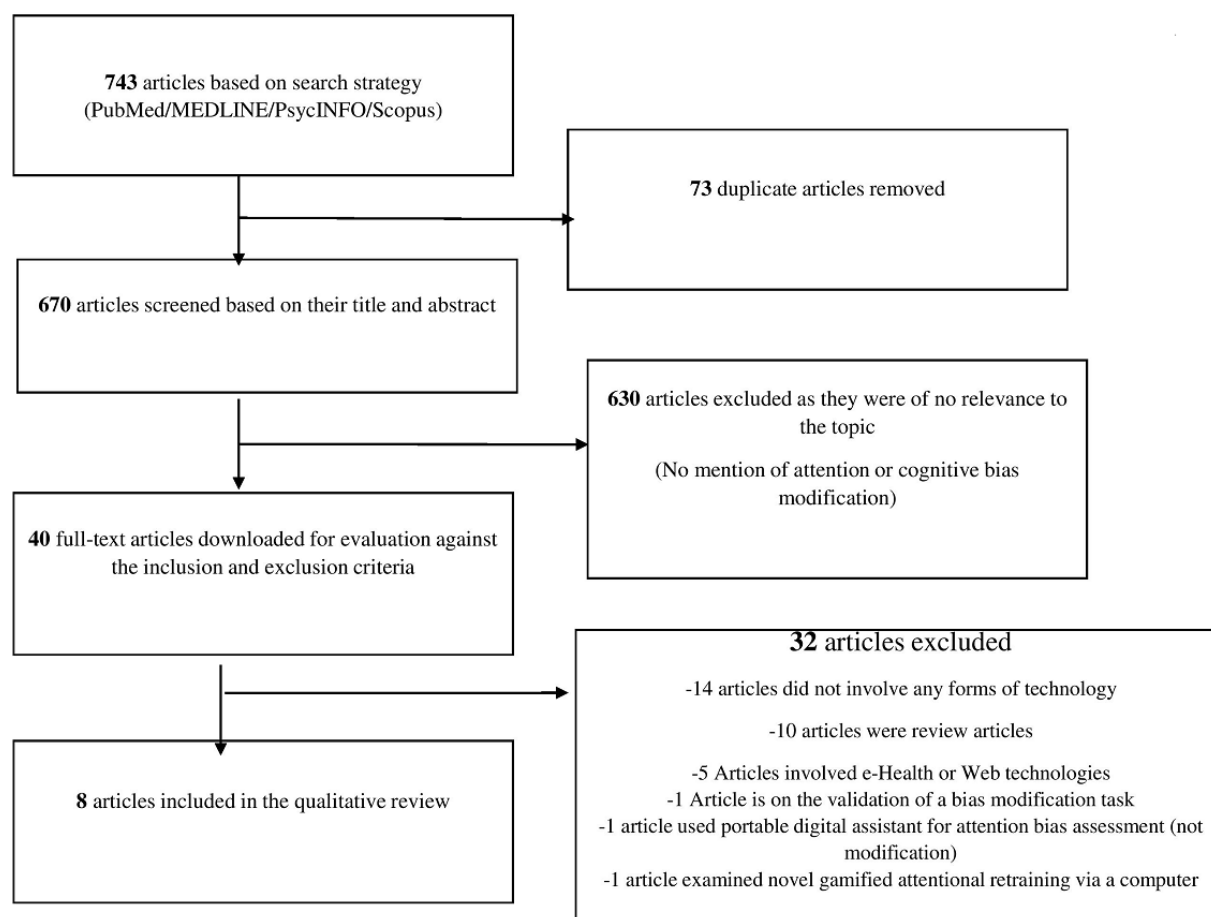
Phase 3: Availability in App Stores of Apps in the Published Literature

We manually searched the app stores (Apple iTunes and Google Play) for the apps with published evaluations (phase 1). We supplemented the manual search with a mobile app search engine (42matters) to extend the search. We downloaded and evaluated available apps and extracted the following information: (1) app name, (2) general description of the app, (3) method of attention or cognitive bias modification, (4) total number of downloads (if available), (5) app ratings (if available), (6) reference source, and (7) last date of modification of the app.

Results

Figure 1 provides an overview of the study selection process. Our initial and updated search identified 743 citations. Of these, 73 were duplicates, and we screened the 670 remaining articles by their title and abstract, leaving 40 articles. We then downloaded these for further evaluation against the inclusion and exclusion criteria, leaving 8 articles suitable for qualitative review.

The articles described mHealth apps for the delivery of attention or cognitive bias modification for following conditions: insomnia (n=1), social anxiety (n=1), anxiety disorder (n=3), alcohol use disorder (n=1), and tobacco use disorder (n=2). Table 1 [17,19-25] summarizes the main characteristics of the studies that we included. Nearly all of the trials used either the dot-probe or visual-probe task, except for 1 study that used cognitive bias for interpretation intervention, and another that did not specify the task applied. With regard to the outcomes, 7 studies reported effectiveness and only 1 reported no effect. Bias modification was found to be effective, as it helped improve symptoms of insomnia and cognitive symptoms of presleep arousal [17]; reduce subjective anxiety [20]; improve performance on stress task [21]; reduce attentional biases for cigarettes [22,25]; reduce the amount of alcohol consumed [24]; and reduce prenatal stress and anxiety [23]. However, Yang et al [19] reported that bias modification was not effective, as the bias scores among participants with social anxiety disorders were not reduced.

Figure 1. Flowchart of article selection.

Only 1 of the apps described in these articles was commercially available on the app stores (based on our phase 3 search).

In phase 2, we retrieved a total of 15 apps from Google Play and 2 apps from iTunes; 5 of the apps were available in both stores. The flowchart in Figure 2 shows the app selection process from the commercial stores.

We downloaded and further evaluated the commercial apps ($n=17$). Multimedia Appendix 1 summarizes the main characteristics of the commercially available attention bias or cognitive bias apps. Of 17 apps, 10 were free to download. Most of these apps claimed to target conditions such as stress ($n=7$), anxiety ($n=3$), tobacco ($n=3$), alcohol use disorders ($n=2$), and grief ($n=1$). One app (Bias Modification) did not specifically mention in the app description or in the app the targeted condition. Most used attention visual search in bias modification, with only 2 apps adopting the cognitive bias modification for interpretation method. A total of 4 apps used methods of bias modification that differed from visual probe, cognitive bias modification, and attention visual search tools. For the app Quitty, the bias modification task involved using a tobacco product as a projectile to hit other objects. For the apps Stop Smoking-Quit Smoking, Stay Sober, Stop Drinking, and

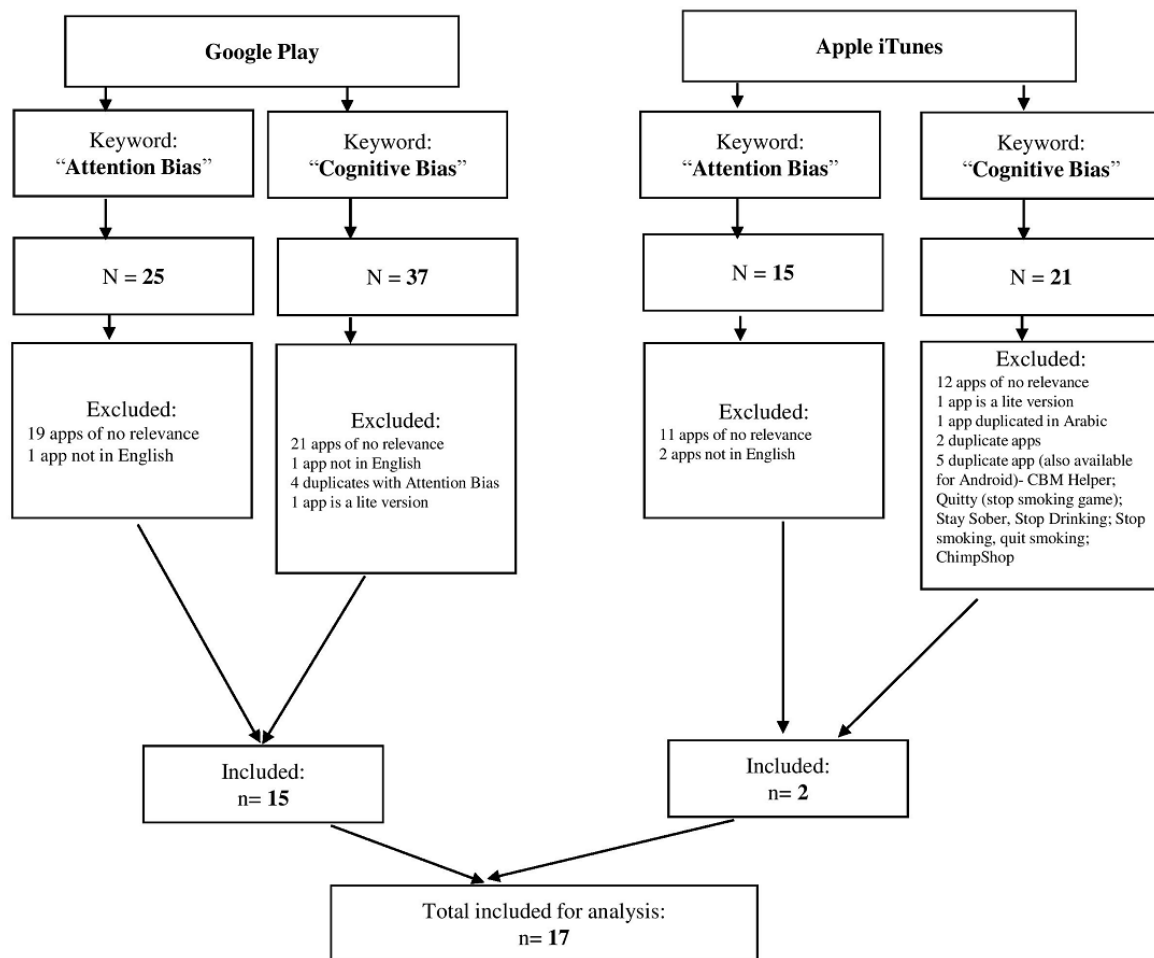
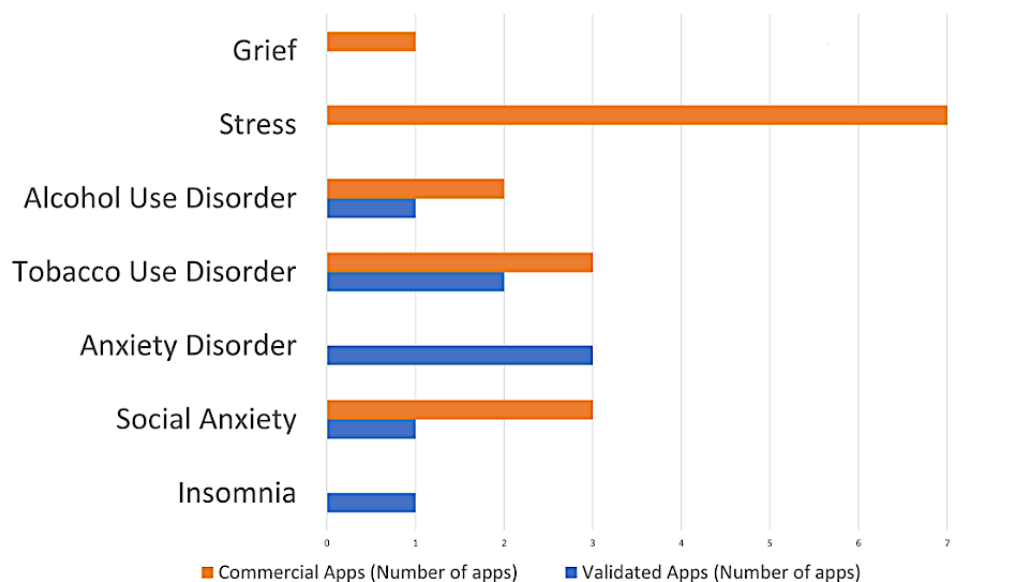
ChimpShop, the paradigm involved an avatar running through an environment, and bias was retrained by avoiding the substances. There were limited additional functionalities for most of the included apps, with 5 apps including questionnaires or other functionalities, such as the ability to customize images (Spot Smile, brighten your day app) or the addition of reminders (AntiAnxiety), to allow for customization of the app for the individual user. Only 4 apps attributed a reference source within the app, of which 1 has been previously evaluated (ChimpShop). On the Android platform, 2 of the apps had been downloaded between 10,000 and 50,000 times. After contacting developers to find out whether their apps had been evaluated previously, 3 replied, but none of the developers were able to offer evidence demonstrating that their app had been evaluated in a prior study (Quitty, Happytap, and AntiAnxiety).

Figure 3 provides a graphical overview of the target conditions for both validated scientific apps and commercial apps. Apps evaluated in a prior study targeted mainly tobacco use disorder and anxiety use disorder; while of the 17 commercially available apps, most targeted stress. Tobacco use disorder appeared to be a common disorder that both validated and commercial apps targeted, with a total of 2 and 3 validated and commercial apps, respectively.

Table 1. Overview of attention and cognitive bias modification apps in the published literature.

Reference	Condition targeted	Description of intervention	Method of ABM ^a	Main outcomes reported	Availability in commercial stores
Clarke, 2016 [17]	Insomnia	ABM task involving 48 word pairs comprising sleep-related threat words paired with nonthreat words.	Dot-probe task	The primary outcome measured was whether the delivery of attention bias task could help reduce symptoms of insomnia and cognitive symptoms of presleep arousal. Participants who received ABM training reported significantly lower presleep arousal and better overall sleep quality. Those assigned to the ABM condition also fell asleep faster and woke less often during the night (based on electro-physiological measures)	No
Yang, 2017 [19]	Social anxiety	CBM-A ^b task involving the presentation of 2 faces as stimulus. CBM-I ^c task based on the presentation of ambiguous scenarios. Attention and interpretation modification involving half the tasks for CBM-A and CBM-I.	Dot-probe task, CBM-I	The main outcome was to compare the effectiveness of 3 types of training program. Delivering cognitive bias modification via smartphone device is feasible. CBM-A and attention and interpretation modification was not effective as measured by the dot-probe attention bias scores.	No
Dennis, 2014 [20]	Anxiety	Gamified ABM app	Dot-probe task	The main outcome of the study was to determine whether the gamified ABM task could help reduce threat bias, anxiety, and the stress reactivity of trait anxious individuals, in a way similar to that of laboratory-based bias modification. The single session helped reduce subjective anxiety and stress reactivity. Long-training bias modification helped reduce threat bias and difficulties with disengagement.	No
Dennis-Tiwary, 2016 [21]	Anxiety	Gamified ABM app (Personal Zen)	Dot-probe task	Subjective anxiety and stress responses measured following the intervention showed that there was no difference in overall self-reported anxiety symptoms. However, behavioral performance improved during the stress task among female participants.	No
Kerst, 2014 [22]	Smoking	Attention retraining via personal digital assistant in natural environment	Modified visual-probe task	The main outcome examined was whether delivering attention retraining on a personal digital device in the natural environment could help reduce attention bias and overall cravings for smoking. Attention bias decreased in the intervention group and overall craving decreased in the intervention group.	No
Denis-Tiwary, 2017 [23]	Anxiety and stress	Gamified ABM app (Personal Zen)	Dot-probe task	Biobehavioral indices of prenatal stress and anxiety were reduced following the intervention.	No
Cox, 2015 [24]	Alcohol	Gamified ABM app (ChimpShop)	Not specified	The main outcome measured was the amount of drinking. The intervention reduced drinking in problematic drinkers by 60%.	Yes
Robinson, 2017 [25]	Smoking	Attention bias retraining	Visual-probe task	Attentional biases in smokers were reduced. Reduction in attention biases did not reduce craving or biological measures of smoking.	No

^aABM: attention bias modification.^bCBM-A: cognitive bias modification-attention.^cCBM-I: cognitive bias modification-interpretation.

Figure 2. Flowchart of the selection of apps from the commercial stores.**Figure 3.** Overview of conditions targeted by both commercial and validated apps.

Discussion

Principal Findings

We reviewed all the cognitive bias modification apps that we identified to be available commercially and those evaluated in the research literature. The effectiveness of mHealth attention bias modification was reported in 7 of 8 previous trials. Only 1 of 8 previously evaluated apps was commercially available. The 17 commercial apps we identified in phase 2 tended to use either an attention visual search or a gamified task. Despite some commercial apps indicating a reference source, we managed to find only 1 app that had been evaluated previously in the published literature. None of the developers who replied could offer further evidence that their app had been validated through prior research.

This review highlighted that the evidence for mHealth-based attention and cognitive bias modification is inconclusive, as we found only 1 trial [19] out of the 8 that reported no effectiveness for bias modification. Our findings are similar to those for Web-based attention bias modification, a precursor to mobile-based interventions. Notably, in psychiatry, Web-based attention bias modification interventions have been evaluated for addictive, depressive, and anxiety disorders [26-28]. For conditions such as tobacco use disorder, while some trials reported the effectiveness of approach and avoidance [15], others, such as Elfeddali et al [29], who administered an approach and avoidance bias modification intervention to 434 participants, reported that bias modification did not lead to a reduction in bias or in the absolute number of cigarettes smoked. Similarly, for anxiety disorders, some trials reported the effectiveness of Web-based interventions, but many reported that Web-based interventions had no effectiveness [30-34]. We postulate that the mechanism of delivery of bias modification could have resulted in some trials having negative results. Of significance, Jones and Sharpe [1], in their recent meta-analytical review of previously published meta-analysis, synthesized the evidence not just for effectiveness but also with regard to training locations. Jones and Sharpe [1] reported that most of their included studies recommended laboratory-based administration of attention bias modification interventions rather than remote administration. Web-based administration of attention bias modification is remote and less controlled than laboratory-based administration. Attention bias modification interventions do typically provide some form of guidance from a therapist at the onset of the intervention, as well as supervision during the intervention, in which the therapist offers feedback if too many erroneous responses are made.

Our review suggests that, while some trials evaluated attention bias apps, only 1 of these apps appears to have progressed to being commercially available. In contrast, there are a variety of commercially available apps without scientific evaluation. Given this, individuals are highly likely to download other nonvalidated apps instead of those that have been validated, after searching for attention or cognitive bias apps in the app stores. In our case, we identified only 1 app that had been scientifically validated, but the download rates of the app were low, and hence it is likely to have ranked low in the stores.

Similarly, Haskins et al [35], in their review of smoking cessation apps, reported that among the scientifically validated apps they found in commercial app stores, only 2 ranked among the top 50 apps in the store.

Haskins et al [35] also highlighted that the fact that the numbers of commercially available apps far exceeded the numbers of scientifically validated apps implies that current evaluation strategies are no longer appropriate, as mHealth interventions can be rapidly developed and implemented [35]. While we agree that there need to be alternatives to evaluate the scientific evidence of commercially available apps, we are cautious given that there are very limited tools available for the evaluation of commercial apps, such as the Mobile App Rating Scale [36] or the Silberg Scale [37]. We have in this research adopted a framework for such an evaluation, in that we attempted to search for commercial apps in the published literature and to search for any academic references in the app description and within the app itself. We also contacted the developers for further clarification. Our findings also suggest that there is a potential disconnect between academics and app developers. Our findings suggest that most commercial apps were developed independently by companies, based on the attributions of the references (as [Multimedia Appendix 1](#) shows). While the developers of 2 of the apps (ChimpShop and AntiAnxiety) reported some form of collaboration with an academic or academic institution, we found only a trial involving ChimpShop in this review. Clinicians and other health care professionals are rarely involved in app development due to several factors, including the lack of time and technical skills [38]. Even if clinicians or other health care professionals are involved, their role is limited to ensuring that a workflow is appropriate. Taking these factors into consideration, Zhang et al [39] previously recommended strategies that health care professionals can use in the development of cost-effective apps. The involvement of health care professionals and academic centers in the conceptualization of apps is advantageous, given that evidence-based methods can be incorporated into the planned app. Involving health care professionals is one method to help bridge the academic commercial divide. Another method would be to involve not only health care professionals, but also service users or patients themselves in the joint design and conceptualization of evidence-based apps. There has been more recent research recognizing the importance of such a codesign approach [40,41].

Strengths and Limitations

One of the major strengths of our study is that we identified both scientifically validated mobile attention bias modification interventions and commercially available attention bias modification apps. However, our study had several limitations. We do acknowledge that, while we searched comprehensively across several databases, we did not search databases such as Google Scholar for relevant published works. However, we believe that the 4 databases that we searched would have covered all the published articles, and a search of Google Scholar would have yielded few additional articles. The identification of apps was confined to the Apple and Google app stores. While these are the 2 most widely used app stores, it is possible that different apps might be available in other

stores, which we did not review. We acknowledge that we might have left out progressive Web apps from our search. We were unable to systematically search for progressive Web apps, as there was no webstore we could systematically search by keywords. Similarly, we searched only for English apps in our review. This might have excluded relevant apps on attention or cognitive biases that were not in English. We were not able to include apps in other languages, as we did not have the assistance of a translator in this study. Our search was confined to a total duration of a few weeks, which might have left out new apps, given how rapidly new apps are introduced into commercial app stores.

Implications

The most important clinical implication of this study is health care professionals' need for caution when recommending cognitive bias modification apps to their patients. Moreover, as mentioned above, some of these apps presented users with

self-assessment questionnaires. Hence, there is a possibility for some individuals to self-diagnose and take the intervention. It is very important to emphasize in any app conceptualization that an assessment by a medical professional is still important. Our work highlights the need for researchers to carefully consider the method of delivery of an attention bias intervention through an app and how the app could compare with the conventional delivery of such an intervention in a laboratory setting, as in this study we found apps that used unconventional methods of bias modification.

Conclusions

Our review highlighted that, while evidence for the effectiveness of mHealth attention bias apps is mixed, a variety of commercial apps are available, with most appearing not to have been evaluated. It is important for future research to take into consideration the findings of this study, in the design, implementation, and evaluation of mHealth attention bias apps.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Characteristics of attention bias in commercial apps.

[\[PDF File \(Adobe PDF File\), 43KB-Multimedia Appendix 1\]](#)

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Review

Gamified Cognitive Bias Modification Interventions for Psychiatric Disorders: Review

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Abstract

Background: Automatic biases, such as attentional biases and avoidance and interpretative biases, have been purported to be responsible for several psychiatric disorders. Gamification has been considered for cognitive bias modification, mainly to address the core issues of diminishing motivation to train over time, as bias modification intervention tasks tend to be highly repetitive. While a prior review has suggested how gamification strategies could be applied to such tasks, there remains a lack of systematic evaluation of gamified cognitive bias modification interventions in the literature.

Objective: The objective of this review is to understand the overall effectiveness of a gamified approach for cognitive bias modification and inform future research that seeks to integrate gamification technologies into existing conventional bias modification interventions.

Methods: To identify the relevant articles for our review, the following search terminologies were used: (“cognitive bias” OR “attention bias” OR “interpret* bias” OR “approach bias” OR “avoidance bias”) AND (“training” OR “modification” OR “practice” OR “therapy”) AND (“gamification” OR “game elements” OR “game” OR “gaming” OR “game mechanics”). PubMed, MEDLINE, PsycINFO, and Scopus databases were searched systematically for articles published after 2000. Articles were included if they described a gamified cognitive bias modification task and included participants with underlying psychopathological symptoms. Data were systematically extracted from the identified articles, and a qualitative synthesis was performed.

Results: Four studies evaluated gamified cognitive bias modification interventions. Two studies included participants with anxiety symptoms, one with affective symptoms, and one with alcohol problems. The conventional visual probe task paradigm was used in 3 studies, and the attentional visual search task paradigm was used in the last study. We found gaming elements incorporated to include that of animations, sounds, feedback, and a point-scoring system for response time and difficulty. Of the 4 identified studies, only 2 reported their gamified interventions to be effective.

Conclusions: Our review is the first to systematically synthesize the evidence for gamified cognitive bias modification interventions. The results arising from our review should be considered in the future design and conceptualization of gamified cognitive bias modification interventions.

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KEYWORDS

attention bias; cognitive bias; gamification; psychiatry

Introduction

Automatic biases are involved in the psychopathologies of several psychiatric disorders, including anxiety and alcohol and tobacco disorders [1-5]. Cognitive biases include attention, approach/avoidance, and interpretative biases, and these biases can be retrained. Modification of these automatic biases could be achieved with tasks such as the visual probe task (which involves the repeated pairing of probes with neutral stimulus) [6], approach/avoidance task (which involves presenting the salient stimulus in a push-away format) [7], or cognitive bias modification for interpretation (which involves training individuals to disambiguate ambiguous scenarios in a positive way) [8]. Prior reviews have synthesized the evidence for cognitive bias modification [9,10]. In a review by Cristea et al [9], 25 trials involving participants with alcohol and tobacco disorder were identified; bias modification was found to be effective for attentional and approach biases, with an effect size of 0.60. Jones et al [10] reviewed meta-analyses and reported that cognitive bias modification was effective for anxiety disorders with effect sizes ranging from 0.13 to 0.74, depressive disorders with effect sizes ranging from 0.35 to 0.85, and appetitive disorders (defined to include eating and addictive disorders) with effect sizes ranging from 0.003 to 0.36.

Most conventional cognitive bias modification interventions have been delivered in the laboratory, but in recent years, rapidly advancing Web technologies have been increasingly adopted. Wiers et al [11] administered a Web-based attention control training and approach bias retraining intervention for 136 participants with problem drinking and reported a reduction in drinking across all the intervention groups. Similarly, William et al [12] harnessed the potential of Web technologies for the delivery of an online cognitive bias modification training and reported it to be effective in reducing depressive and distress symptoms. In addition to Web technologies, mobile technologies are being used to transform the delivery of bias modification interventions. It has been reported that a mobile app could help in improving insomnia symptoms [13].

Just as technology has transformed the mechanism of delivery of cognitive bias modification intervention, advances in gamification have transformed the nature of conventional cognitive bias modification interventions. Gamification is defined as the use of game-design features in a nongaming context [14], and the term “serious games” refers to games that are designed and built specifically for education, training, or behavioral modification [15]. These technologies have been adopted in health care, and some have been evaluated. Currently, most of these gamified interventions are used in chronic disease rehabilitation and mental health [16], with the most common gamification technique being feedback. Lumsden et al [17] synthesized the evidence for gamification for cognitive assessment and training. The authors reported gamification helped improve engagement in the short and longer term and made the task more attractive. Other studies have found increased self-empowerment [16] and improved existing skills sets [16]. More recently, Lau et al [15] reported in a review that serious games could help improve psychiatric symptoms, with an effect size of 0.55.

Boendermaker et al [18] reviewed how gamification might help address one of the core challenges of conventional interventions, that of motivation to train; these tasks tend to be highly repetitive with a need for multiple training sessions. The article highlighted several potential gamification strategies and explored how they have been used in some studies. The gamification approaches used included the addition of gaming elements to existing tasks, transformation of a conventional task into a serious game, identification of an underlying theory of the intervention and development of a game, addition of a full gaming approach to a conventional task (both intrinsic and extrinsic combinations), and use of over-the-shelf entertainment games. While this review provides timely insight into how gamification strategies have been adapted for bias modification interventions, it was not a systematic review with a database search. Other research on the evaluation of a gamified variant of an attention bias modification task determined that a gamified intervention was effective for anxiety [19]. However, to date, there is no systematic evaluation of gamified cognitive bias modification interventions in the literature. This is needed to understand the overall effectiveness of a gamified approach for cognitive bias modification and inform future research that seeks to integrate gamification technologies into existing conventional bias modification interventions.

The primary aim of our research was to review gamification in cognitive bias modification for psychiatric disorders. Our secondary aim was to identify gamification elements used in cognitive bias modification interventions and evaluate the evidence for their effectiveness by assessing whether the gamified intervention resulted in changes in biases or improvement in secondary outcomes (eg, improvements in anxiety or depressive scores, reduction in the absolute amount of alcohol consumed) and if any motivational improvement was seen.

Methods

The methods for our systematic review are based on our protocol, published elsewhere [20].

Search Strategy

To identify relevant articles for the review, the following search terminologies were used: (“cognitive bias” OR “attention bias” OR “interpret* bias” OR “approach bias” OR “avoidance bias”) AND (“training” OR “modification” OR “practice” OR “therapy”) AND (“gamification” OR “game elements” OR “game” OR “gaming” OR “game mechanics”). PubMed, MEDLINE, PsycINFO, and Scopus databases were systematically searched for articles published after 2000; before 2000, there were limited computer-based interventions. When full-text access was not available, the original authors were contacted for their articles.

Inclusion and Exclusion Criteria

Articles were included if they described a cognitive bias modification intervention in the form of a gamified task and included participants assessed to have underlying psychopathological symptoms such as depressive, anxiety, or addictive symptoms. Articles were excluded if they were opinion

pieces, review articles, or design documentation, or described an intervention that used an existing over-the-shelf game. Only English language articles were included.

Screening, Data Extraction, Sorting, and Selection

All articles identified using the search strategy were downloaded and imported into a reference manager (Endnote X8, Clarivate Analytics). The articles were screened based on their titles and abstracts by two independent authors, MZ and JY. Full copies of the shortlisted articles were evaluated against the inclusion and exclusion criteria with any disagreement resolved by a discussion with the third author (GS).

For relevant articles, the following data were extracted:

- Publication details: authors, study year, and country in which the study was conducted
- Study design (observational or experimental design)
- Sample size
- Type of sample (treatment seeking or community sample)
- Demographics of sample (mean age, gender proportion)
- Psychopathological symptoms of participants and methods of ascertaining psychiatric symptoms
- Details of gamified cognitive bias modification intervention (mechanics of game-play and the conventional cognitive bias modification intervention that the gamified task was based on)
- Primary outcomes and secondary outcomes: effectiveness of gamified cognitive bias modification intervention and any changes in psychiatric symptoms

Data Integration and Synthesis

A qualitative synthesis of the evidence extracted from the articles was performed. Due to the heterogeneity in the outcomes reported, it was not appropriate to conduct a meta-analytical synthesis.

Results

Identified Studies

The predefined search strategy identified 1008 citations from 4 bibliographic databases; after duplicate articles were excluded, 970 records were screened and, of these, 962 were excluded as not relevant to the topic of interest. Eight full-text articles were downloaded for further evaluation against the inclusion and exclusion criteria. Four citations were excluded as they did not fulfill the inclusion criteria, leaving 4 articles for the qualitative synthesis. [Figure 1](#) provides an overview of the study selection process. For an overview of the characteristics of the selected studies, see [Multimedia Appendix 1](#).

Characteristics of Identified Studies

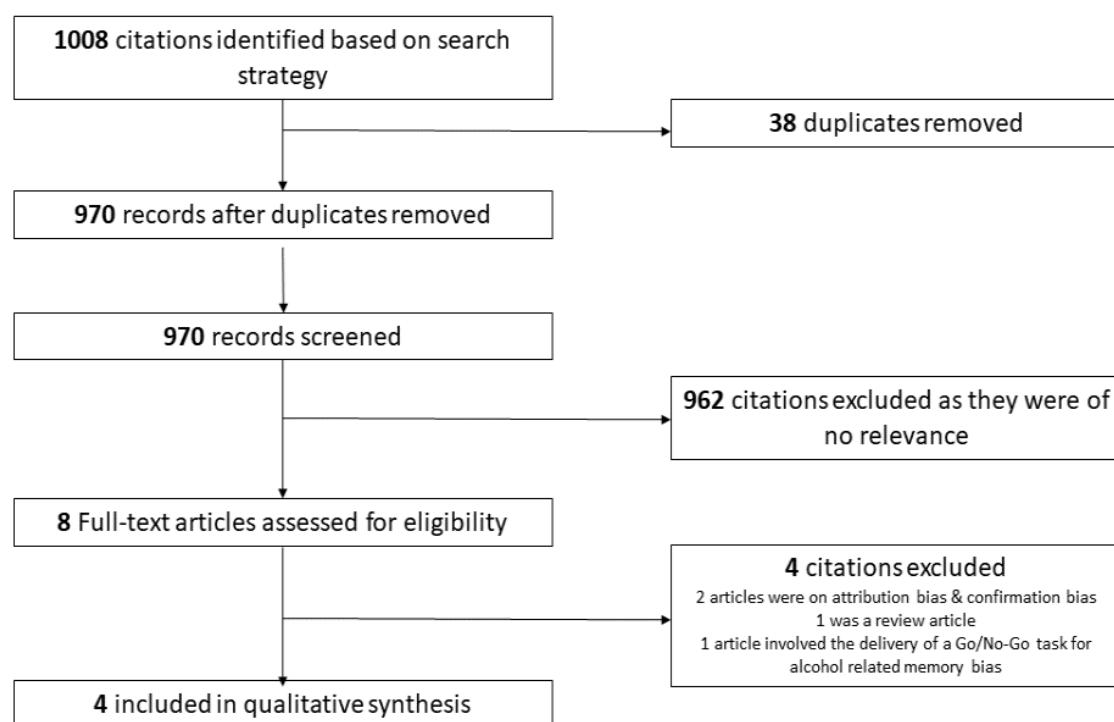
Two of the 4 studies identified involved participants with anxiety symptoms [19,21]. One involved participants with alcohol-related problems [4] and one, participants with affective symptoms [22]. All studies were experimental, randomized

controlled designs recruiting participants from universities with mean ages of participants 20 to 30 years. All studies were conducted in a western setting. Two studies came from the United States, one from the Netherlands, and another from Belgium. None of the studies used a structured clinical interview to ascertain symptomatology or diagnosis but relied on validated questionnaires (State-Trait Anxiety Inventory [19,21], Mood and Anxiety Symptoms Questionnaire [22], and Alcohol Use Questionnaire and Alcohol Use Disorders Identification Test questionnaire [4]). Three studies based their gamified intervention on the visual probe task and one on the attentional visual search task. Gaming elements integrated into these tasks included animations, sound effects, reward points, time pressure, and levels of complexity.

Characteristics of a Gamified Cognitive Bias Modification Intervention

Two studies [19,21] used the same app for their intervention, a gamified attention bias modification app based on the conventional dot-probe task. The gamification elements included that of animated characters, a system for points scoring, and sound effects. Two animated characters would appear on the screen simultaneously, both disappearing into a hole. One character would cause a path of grass to rustle behind and participants undertaking the intervention were asked to trace the path in the grass. Based on the author's description of the gamified intervention, 4 different sounds were played, and different rewards were given depending on participant accuracy and speed. The lowest pitch sound would be played and red jewel awarded for slow response or responses that were least accurate, a medium pitch sound would be played and purple jewel awarded for moderate speed and accuracy, and a high pitch sound would be played and gold jewel awarded if fast and accurate. There was also a feedback sound for incorrect responses. There were 2 variants of the gamified intervention: 25 minutes of training along with 20 minutes of rest or 45 minutes of training with no rest. Points accumulated as the intervention progressed, and feedback was given immediately on completion.

Pieters et al [22] used a gamified app for cognitive bias modification for anxiety symptoms, based on the conventional visual attention task. The game required participants to tap on smiling faces, with smiling faces making up 60% of the faces and disgust faces the remaining 40%. Once the participant tapped on the smiling face, the face bounced up for a short distance and become untappable for 0.5 to 1 second. Participants were instructed to prevent the smiling faces from falling down the screen by tapping on them. Points were awarded to incentivize game play. A point was awarded for tapping the smiling face the first time and 5 points awarded if the same smiling face was tapped a second time. There was negative scoring with the loss of 3 points if a smiling face was not tapped and fell off the screen.

Figure 1. Flowchart of the selection of studies.

Boendermaker et al [4] used a shot game for attention bias modification, based on the conventional visual probe task. The gamified intervention included a reward system, graphics, animations, sound effects, time pressure, and levels. Their game resembled a slot machine with a coin-based reward system. Like the conventional task, participants were required to identify the probe that replaced the position of the alcohol or neutral image. Participants won bonuses for responding rapidly and were given access to new levels in the game.

Three studies delivered the gamified cognitive bias modification intervention using a mobile device, and Pieters et al [22] used a computer.

Reasons for Gamification

Two studies described the reasons for inclusion of gamification. The intervention by Boendermaker et al [4] included gaming elements to potentially increase participant motivation to train via the intervention. The authors also sought to determine if the inclusion of gaming elements increased the effectiveness of the conventional visual probe task. Dennis et al [10] were interested in whether the inclusion of gamification changed the effects of the attention bias modification.

Primary and Secondary Outcomes

Of the 4 studies, 2 [19,21] reported the gamified variant of the cognitive bias modification intervention to be effective. Dennis et al [19] reported that the long-training attention bias modification task resulted in a reduction of threat bias and difficulties individuals had with disengaging from threat-related stimulus. There were also corresponding reductions in the subjective and observed anxiety and stress. Similarly, the authors of the second paper [21] reported that the single session of

gamified attention bias modification was effective in improving the performance of the attention bias modification task. However, the authors reported that significant results were observed among females only. Contrary to the findings of Dennis et al and Dennis-Tiway et al [19,21], Pieters et al [22] reported that their gamified intervention did not result in any reduction in attention biases or associated mood-related measures.

In the study involving participants with alcohol-related problems [22], the gamified variant of the cognitive bias modification task did not reduce attention bias and failed to achieve a decline in overall alcohol consumption. Of importance, the study by Boendermaker et al [4] was the only study that investigated the effects of gamification and motivation of participants in using the training task. Boendermaker et al [2] reported that motivation to train did not increase with the addition of gaming elements. In fact, participants assigned to receiving the gamified variant reported having lower motivation to continue the training task as compared to participants assigned to other conditions.

Discussion

Principal Findings

Our review is the first to systematically synthesize the evidence for gamified cognitive bias modification interventions. Of the 4 studies that evaluated a gamified cognitive bias modification intervention, 2 studies included participants with anxiety symptoms, one with affective symptoms, and one with alcohol problems. Gamified interventions were based on the conventional visual probe task in 3 studies and the attentional visual search task in the last study. The gaming elements

incorporated into the task included animations, sounds, feedback, and a point-scoring system for response time and difficulty. Two publications discussed their rationales for gamification, one sought to determine if gamification enhances motivation, and one to determine if the gamified attention bias modification was as effective as a conventional modification. Out of the 4 identified studies, 2 studies reported their gamified intervention to be effective. Of significance, these 2 studies used the same app and were from the same research group.

The 4 studies applied gamification across a variety of psychiatric disorders—anxiety and affective and addictive disorders. The conditions that gamified cognitive bias modification interventions target are like those targeted by conventional mobile-based cognitive bias modification interventions. The review by Zhang et al [23] evaluated the published literature and reported that out of 8 identified studies, at least 4 studies used a mobile intervention to target anxiety-related disorders (anxiety and social anxiety disorders). In their review of meta-analyses, Jones et al [10] included 5 meta-analyses that examined anxiety-related outcomes. Thus, anxiety conditions have been extensively investigated in the published literature. This could, therefore, explain why there have been more studies that have applied gamification techniques in increasing the inherent effectiveness of existing conventional training tasks.

All identified studies have based their gamified intervention on the conventional cognitive bias modification intervention, which is of importance, as the conventional cognitive bias modification intervention is the most commonly used task. Three studies were based on the conventional visual probe task and one on the attentional visual search task. In line with the recommended gamification techniques of Boendermaker et al [18], it appears that all 4 studies have used intrinsic integration with evidence-based training task as a basis, given that all 4 studies based their intervention on a conventional task and added gaming elements to that task. Adopting intrinsic integration makes tasks more engaging and might increase the inherent levels of motivation to continue training. Unfortunately, we found no evidence that the adoption of intrinsic integration led to increased motivation to train as only 1 study [4] included motivation to train as an outcome measure, and in that study, there were no improvements.

In keeping with the objectives of the review, we identified some of the common gaming elements that are incorporated in the published gamified interventions: animations, sound effects, point-scoring systems, time pressure, and levels. In their review, Hoffman et al [14] proposed a taxonomy of gamification strategies that could be applied for the evaluation of gamification strategies in apps. The authors used the taxonomy to evaluate stress management apps and found that feedback or performance-orientated strategies were frequently used in the 62 evaluated apps. Like the review of Hoffman et al [14], our findings demonstrated that performance-orientated gamification strategies are used for some of the gamified apps (time pressure and levels in the Boendermaker et al [4] study). Economic gamification strategies are more commonly used, with 4 studies

reporting the usage of a point system. The differences in our findings, as compared to that for stress management apps, is not unexpected. Prior research highlighted the importance for designers to carefully consider the gamification techniques used, depending on the nature of the app and how gamification could affect user interaction [14]. Thus, for cognitive bias modification interventions, incorporating feedback might be less feasible, as feedback usually involves a comparison to a set standard or others' performance. Digital rewards like points might be more tangible, both as an extrinsic motivator and as a surrogate indicator of how well one is performing on the task.

The existing evidence is inconclusive for gamified cognitive bias intervention effectiveness, as only 2 of the 4 studies reported positive findings, but several implications arise from our review. Why gamification is effective in some studies and not others must be determined to guide consideration of which gamification strategies to adopt in an intervention. User perspectives of what makes an app engaging and which strategies result in short and longer term engagement are important to consider in the design of gamified cognitive bias modification interventions. While only 4 studies were identified for this review, Zhang et al [23] found that there were 17 commercial cognitive bias modification apps in the app stores. It might be helpful to analyze the gamification features in commercial cognitive bias modification apps and see if certain gamification features are associated with higher rates of downloads, a surrogate measure of acceptability. Also, a qualitative analysis of the feedback that individuals provide for the gamified commercial apps might be helpful for developers or health care professionals who are creating a new gamified intervention.

Strengths and Limitations

A major strength of our review is that we systematically identified from the published literature gamified cognitive bias modification interventions and synthesized the evidence for their overall effectiveness. We also identified the gamification strategies that they have adopted. Our review will be of importance for future research seeking to design and evaluate gamified cognitive bias modification interventions, as it provides information about gaming elements that might affect whether interventions are effective. Despite the strengths, there are some limitations. In our review, we were limited to a qualitative synthesis because a meta-analytical synthesis was not appropriate given the heterogeneity in the studies and outcomes reported. Our synthesized results might have limited generalizability, as 2 studies used similar apps and tested the apps in a university sample.

Conclusions

By identifying gamified cognitive bias modification interventions in the published literature and synthesizing their evidence, our findings have helped bridge the gaps in previous reviews. The results arising from our review should be considered in the future design and conceptualization of gamified cognitive bias modification interventions.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Characteristics of included studies (n=4).

[\[PDF File \(Adobe PDF File\), 195KB-Multimedia Appendix 1\]](#)

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A review of gamification approaches in commercial cognitive bias modification gaming applications

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Abstract.

BACKGROUND: Cognitive biases are mostly automatic processes that result in individuals giving increased attention to threatening stimuli, with the difficulties in disengaging from these stimuli. Recent reviews have reported the presence for attention bias in several psychiatric conditions and provided evidence that such biases could be subjected to modification. Web-based and mobile based bias modification have mixed efficacy and gamification techniques proposed as a solution. There remains a gap in knowledge pertaining to the gamified applications for bias modification that are commercially available.

OBJECTIVE: An analysis of their gamification approach will help in identification of common gaming elements adopted for use.

METHODS: To identify commercial applications, a manual cross-sectional search was conducted between 1 and 11 November 2017 on the Google Play store. The following search terminologies were used: “Attention bias” and “Cognitive bias”. The classification of the gamification technique for both the published applications and commercial applications were based on the six approaches described by Wouter et al. [17] and the 17 gamification techniques described by Hoffman et al. [18].

RESULTS: A total of nine applications were included in the current review. Five out of the nine applications involved the addition of gaming elements to an evidence-based task, and three involved the usage of intrinsic integration while leaving the evidence-based task intact. Other common gamification strategies used are that of the inclusion of digital rewards ($n = 8$) and the provision of feedback ($n = 7$). The average number of gamification techniques across all the nine applications is 3.2.

CONCLUSIONS: Even though most commercial applications appear to have their basis on a validated gamification approach for the delivery of attention bias modification, there remains a need for further research in evaluating these applications clinically.

Keywords: Attention bias, cognitive bias, gamification, smartphone, M-health

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1. Introduction

The advances in experimental psychology has led to an increased recognition of cognitive biases. Cognitive biases refer to automatic processes such as automatic attentional or interpretational tendencies towards stimuli, that are of high salience [1]. For example, individuals with addictive disorders tend to be naturally drawn towards substance-related stimuli, whilst individuals with anxiety disorders tend to be naturally drawn towards threatening stimuli. Recent research has demonstrated that attention biases are present in a variety of disorders, ranging from that of addictive disorders to affective conditions, and these automatic biases could be subjected to modification. The Stroop task or the visual probe task are routinely used to assess for the presence of attention bias, and these tasks could also, in turn, be used as a mean for bias modification [2]. In the conventional visual probe task, the probe is associated with the threatening stimuli only 50% of the time, thus enabling a determination of the attention bias towards the threatening stimuli. When the task is adapted as an intervention, the probe is associated with the non-threatening stimuli 100% of the time, thus shifting the attention focus away from the threatening stimuli towards that of the neutral stimuli. By doing so, attention biases are being retrained. Prior meta-analysis has reported the efficacy of attention bias modification on attention biases in samples of individuals with either tobacco or alcohol use disorders [3]. More recently, a review of meta-analysis has similarly reported the evidence for attention bias in a myriad of psychiatric conditions [1]. There have also been published protocols seeking to evaluate the combined efficacy of conventional psychological therapy with attention bias modification [4]. While not much is known with regards to the later about the added effectiveness, the evidence to date highlights that there is a role to consider the modification of such biases, potentially as part of routine psychological treatment for various disorders.

The advances in technologies in the last decade have transformed various aspects of healthcare, including that of the delivery of cognitive bias modification interventions. Web-based attention bias modification has already been investigated for a variety of conditions, including that of addictive disorders [5,6], depressive disorders [7,8], social anxiety disorders [9,10] and obsessive-compulsive disorder [11,12]. M-health, or mobile health technologies, have also been utilised in the delivery of attention bias modification intervention. The main advantage of using M-health technologies relates to the mobility and portability of the intervention. M-health attention bias modification interventions have also been investigated for disorders ranging from that of insomnia [13] to that of anxiety disorders [14,15] and that of tobacco use disorders [16]. The evidence arising from either web-based or mobile-based studies appears to be mixed, with some studies reporting the intervention to be effective and others not. Jones and Sharpe [1] in their review have examined the impact of training locations, and have reported that laboratory administered interventions are more efficacious, given that administration of such interventions in the laboratory allows for greater supervision and control, as compared to remote administration. It is critical to recognise that cognitive bias modification tasks are highly repetitive and hence, there is an inherently high propensity for individuals to drop out, or not remain motivated to continue with the intervention [17].

Gamification has been proposed as a method that could help address the lack of motivation in the completion of such repetitive training tasks [17]. The integration of gamification technologies could potentially help in reducing the attrition rates from cognitive bias modification interventions. Gamification refers to the use of game-related elements in a non-game context, as an attempt to make the intervention more engaging. In their prior review, Boendermaker et al. [17] reported how six different gamification approaches could be used in enhancing the effectiveness of cognitive bias modification tasks. The approaches include the addition of gamification elements to existing conventional bias modification tasks;

the transformation of the conventional task into a serious game; identification of an underlying theory of an intervention and developing a game out of it; the addition of a full gaming approach to a conventional task; intrinsic and extrinsic combination and lastly, OTS (Over the shelf entertainment games). While Boendermaker et al. [17] have proposed several gamification approaches for bias modification tasks, other researchers have proposed a taxonomy of 17 common gamification approaches [18] and have examined common commercial stress management applications, to determine if they include elements of this approach. The most common approach applied in stress modification applications was that of the provision of feedback. Both the classification systems would be of value in the future analysis of smartphone applications which contains gamification elements.

The previous review [17] has highlighted several publications involving gamified versions of attention bias modification interventions delivered either using the Web or using a mobile device. For example, Boendermaker et al. [19]’s gamified version of a visual probe task (known as evaluating the shots) was reported to be effective in reducing alcohol-related attention biases, but not the overall alcohol consumption or the alcohol binges. Based on Boendermaker et al. [17]’s gamification classification, Boendermaker et al. [19] gamified task was based on the approach of “intrinsic integration with evidence-based task” as a basis. However, as highlighted in the prior content analysis for smoking cessation applications [20], there is a disproportion in the numbers of applications available commercially, as compared to that in the published literature. There is thus a likelihood that there are currently more commercial applications for attention bias modification on the commercial stores, with their basis on various gaming approaches. An understanding of the common gamification approaches that have been adopted in commercial applications, which are potentially widely used by the public, is pertinent, especially if researchers seek to co-create a new gamified cognitive bias modification intervention. Researchers need to be cognizant of gaming techniques that could potentially make the app more appealing for individuals in the public.

The main objective of this review is to identify the gamification approaches adopted in commercial cognitive bias gaming applications. Such an analysis would also help us in the determination if commercial applications are evidence-based and have based their gamification approaches on what has been previously evaluated in the literature. Our current review will help inform future work involving gamification for cognitive bias modification applications.

2. Methods

To identify commercial applications, a manual cross-sectional search was conducted between 1 and 11 November 2017 on the Google Play store. Only the Google Play store has been evaluated in the current review, as previous content analysis has also looked at just this store, given that the Android operating system currently holds the largest market share globally [21]. Moreover, the prior content analysis has also reported that for addiction related applications, similar applications are found in both the Google Play and Apple stores [21]. The following search terminologies were used, namely that of “Attention bias” and “Cognitive bias”. We have selected these two terminologies to look for cognitive bias relevant applications on the store, as these two terminologies were also used in the previous meta-analysis by Cristea et al. [3], that examined the effectiveness of cognitive bias modification for substance use disorders. As it is expected that there will be a diversity of attention or cognitive bias applications identified using the above search terminologies, the application description of each application was examined, along with the screenshots of the applications. Basically, we followed the approach of Ubhi et al. [22] in their comparative analysis of smoking cessation applications, whereby in their initial screening, the

Table 1
Gamification techniques

Studies	Gamification techniques
Boendermaker et al. [17]	a. Addition of gaming elements to the evidence-based training task: Inclusion of rewards systems in the training task, such as motivating feedback, sounds or animations. b. Intrinsic integration with the evidence-based training task as a basis: Involves the transformation of an evidence-based training task into a game. c. Intrinsic integration leaving the evidence-based training paradigm intact: Instead of using the evidence-based training paradigm as a basis, this involves the consideration of the theory behind the paradigm and using the theory as a basis to design the game. d. Adding a game shell around the original evidence-based training task: Involves the addition of a full game shell, incorporating the evidence base task. e. Combining intrinsic integration with game-shell. f. Bias modification using OTS (Over the Shelf) entertainment games.
Hoffman et al. [18]	Economic gamification techniques a. Marketplace and economies b. Digital rewards c. Real world prizes Social gamification techniques d. Avatar e. Agent f. Competition g. Teams h. Parallel communication systems i. Social pressure Performance-orientated j. Feedback k. Levels l. Secondary game objectives m. Ranks of achievement n. Leaderboards o. Time pressure Embedding-focused p. Narrative context q. 3-D environment

decision to retain applications were made based on description and images of the screenshots. Applications were included for the current review only if it was stated explicitly in the application description that the application was a gaming application. If both a free and paid version of the same application were available, only the paid version would be examined, as it is believed that the paid version of the application would offer the full range of functionalities. All the identified applications were downloaded and further evaluated by two reviewers on an Android Device (Xiaomi Note 4) running Android 7.0 operating system.

The classification of the gamification technique for both the published applications and commercial applications were based on the six approaches described by Boendermaker et al. [17] and the 17 gamification techniques described by Hoffman et al. [18]. Table 1 provides an overview of the gamification techniques described in the prior literature.

Following the identification of the applications, the following information was extracted from each application, that of a) application name; b) description of the application; c) Total number of downloads, d) Total ratings of application, e) developer or author details and organisation affiliation and f) gamifica-

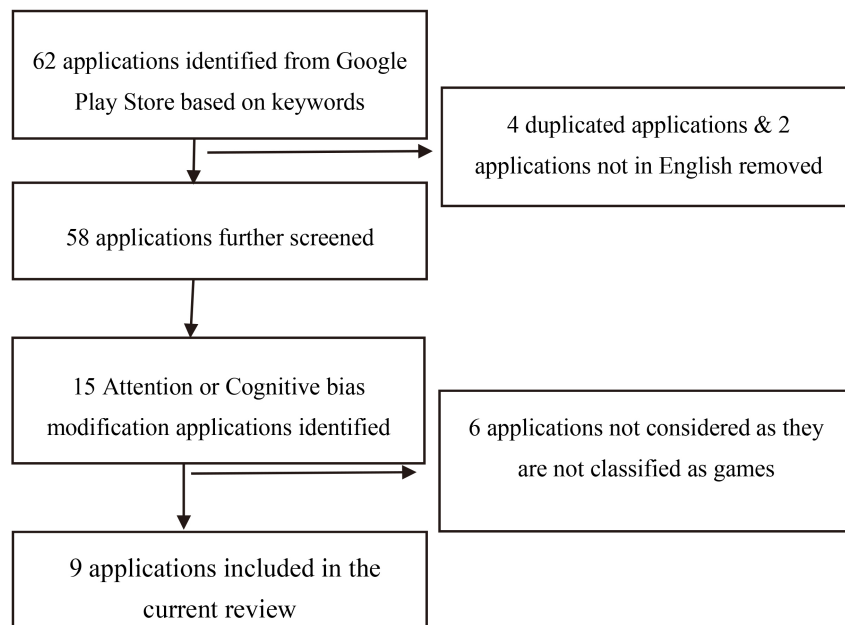


Fig. 1. Flowchart of the selection of applications from the Google Play store.

tion approach. The first author MWBZ and co-author YJB were involved in the extraction of the above information and the coding of the applications based on the above taxonomy of gamification techniques. If there were any disagreements among the authors, it was resolved with discussion. Inter-rater reliability was assessed by the Kappa statistic, whereby < 0.00 represents poor reliability, 0.00 – 0.20 slight, 0.21 – 0.40 fair, 0.41 – 0.60 moderate and 0.61 – 0.80 substantial and 0.81 – 1.00 perfect agreement.

3. Results

The search based on the keywords identified a total of 62 applications from the Google Play store. After the exclusion of duplicates, 58 applications were further screened, and 15 applications were downloaded for further evaluation. Out of the 15 applications, six were excluded as they were not classified as games, based on their application description. Eventually, a total of nine applications were included in the current review.

Among the nine applications that have been identified, most of the applications did not indicate that they were meant to target specific conditions, except for two applications targeting alcohol, two applications targeting smoking and lastly, one application targeting grief respectively. Some of these applications were highly downloaded, in particular, that of Happy Face, which has a total download of 10000–50000. Most of the applications based their bias modification on the attentional visual search task. However, there were exceptions for four applications, in which the specific paradigm that has been used is different from the conventional tasks being described, and hence, we are unable to classify them based the classification of conventional tasks. Four out of the nine applications were paid applications.

The inter-rater reliability (Kappa) for the rating of the application was 0.74, thus there was substantial inter-rater reliability for the gaming applications that were rated based on Boendermaker et al. [17]’s

Table 2
Characteristics of Commercial Games application

Application	Application description (as extracted from store)	Condition targeted and cognitive bias task integrated within game	Downloads	Application ratings	Developer	Gamification approach
Spot Smile, brighten your day (Free application)	The application is based on principles of cognitive bias medication. Marketed as a game and recommended to play the game at least once per day. The application helps to alter harmful thought patterns.	Stress Attentional visual search	5000–10000	4.6	Make Good Apps	Addition of gaming elements to the evidence-based training task Time pressure (countdown timer)
Happytap (Paid application)	The application is based on the principles of cognitive bias medication. Marketed as a game, in which the individual user is supposed to find a smile in the array of faces with varying emotional expressions.	Stress Attentional visual search	100–500	Nil	SuperEgo AS	Addition of gaming elements to the evidence-based training task Time pressure (countdown timer) Feedback Leaderboard (best score) Digital rewards (points)
Bias Modification (Free application)	The application is based on cognitive bias modification, which helps individuals to overcome the tendency to focus on negative stimuli. Marketed a game with match-three gameplay.	Specific condition not mentioned Cognitive bias modification for interpretations	100–500	4.3	Tyrske	Addition of gaming elements to the evidence-based training task Time pressure Feedback Digital rewards (points)
HappyFace (Free app)	Marketed as a game that has a basis on cognitive bias modification, and helps to reduce social anxiety, thus improving personal well-being. Users are encouraged to practice two to three minutes per day over a six weeks period.	Social anxiety Attentional visual search	10000–50000	4.1	NA	Addition of gaming elements to the evidence-based training task Feedback Leaderboard (best score) Digital rewards (points)
Quitty (Paid app)	Marketed as a game that helps individuals to quit smoking, that is based on cognitive bias modification and hypnotic techniques.	Smoking Not based on any conventional cognitive bias modification paradigms	100–500	4.3	Playing for Health	No evidence of integration of any of the four approaches Digital rewards Feedback Levels Time pressure

Table 2, continued

Application	Application description (as extracted from store)	Condition targeted and cognitive bias task integrated within game	Downloads	Application ratings	Developer	Gamification approach
Stop Smoking-Quit smoking (Free app)	Marketed as a mobile runner game that helps individuals to quit smoking. Game is based on cognitive bias modification to help alter attentional biases.	Smoking Not based on any conventional cognitive bias modification paradigms, but the game play scenario involves the participant controlling an avatar and avoiding smoking cues.	1000–5000	4.4	Optimum Design	Intrinsic integration leaving evidence-based training paradigm intact Digital rewards Feedback 3-D environment
Grief Relief App (Paid app)	Marketed as a game that helps to provide more positive thoughts and feelings, which is based on cognitive bias modification.	Grief Attentional visual search	50–100	2.6	Grief Relief	Addition of gaming elements to the evidence-based training task Time pressure Digital Rewards Levels
Stay Sober, Stop Drinking (Free app)	Marketed as a mobile runner game that helps individuals to quit drinking. Game is based on cognitive bias modification to help alter attentional biases.	Alcohol Not based on any conventional cognitive bias modification paradigms but the game play scenario involves the participant controlling an avatar and avoiding alcohol cues.	100–500	NA	Optimum Design	Intrinsic integration leaving evidence-based training paradigm intact Digital rewards Feedback 3-D environment
ChimpShop (Paid app)	A game, which is based on psychological principles, can be helpful for individuals who are attempting to cut back on drinking.	Alcohol Not based on any conventional cognitive bias modification paradigms, but the game play scenario involves the participant controlling an avatar and avoiding alcohol cues.	10–50	NA	Attention Retraining technologies	Intrinsic integration leaving evidence-based training paradigm intact Digital rewards Competition Feedback Leaderboards 3-D environment

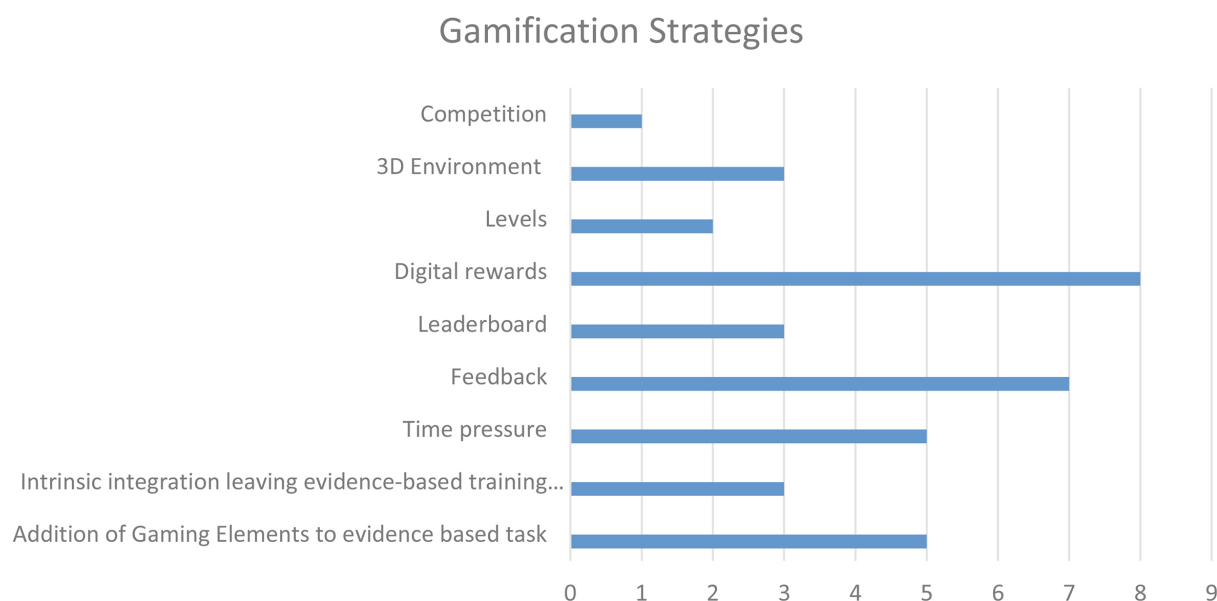


Fig. 2. Summary of gamification methods.

classification, five out of the nine applications involved the addition of gaming elements to an evidence-based task, and three involved the usage of intrinsic integration while leaving the evidence-based task intact. One application did not appear to make use of any of Boendermaker et al. [17]’s proposed methods. Across the applications, a variety of different gamification techniques have been utilised.

Figure 2 summarises the most common gamification techniques commercial applications, based on both Boendermaker et al. [17]’s and Hoffman et al. [18]’s classification. Based on Hoffman et al. [18] taxonomy, the most common gamification strategies are that of the inclusion of digital rewards ($n = 8$) and the provision of feedback ($n = 7$). Considering only gamification techniques based on Hoffman et al. [18]’s classification, all the applications have included at least one gamification technique. The average number of gamification techniques across all the nine applications is 3.2. The range of gamification techniques in a single application ranges from a minimum of 1 through to a maximum of 5.

Table 3 provides an overview of the mean number of gamification techniques integrated within the application by the total download rates of the applications. While the computation of the mean number of gamification techniques per category of the download was limited by the absolute number of applications per category; we found that most of the commercial applications have included a mean of 3.5 gamification techniques and have a download of between 100–500. Feedback and time pressure were common gamification techniques in the 4 apps that have a download range of 100–500. There are outliers, with a single application incorporating 3 gamification techniques and having a total download range of 10000–50000. The analysis also demonstrate that the inclusion of more gamification elements does not lead to an app being more widely download, as there is a single application with 5 gamification techniques incorporated, but only having a total download range of 10 to 50.

4. Discussion

Based on our knowledge, this is the first study that has examined the commercial gamified application for the delivery of cognitive bias modification interventions. As aforementioned, Boendermaker et

Table 3
Mean number of gamification techniques integrated by download rates of applications

Download rates	Mean number of gamification techniques (Hoffman et al., 2017's taxonomy)	Number of apps taken into consideration
10000–50000	3	1
5000–10000	1	1
1000–5000	3	1
100–500	3.5	4
50–100	3	1
10–50	5	1

al. [23] have previously reviewed gamified attention bias interventions evaluated in prior published literature. Our current review has identified nine attention bias applications that are classified as games based on their application descriptions. 5 of the identified applications targeted alcohol use, tobacco use and grief respectively, with the remainder of the applications not specifying the condition they seek to intervene. Application of Boendermaker et al. [23]'s classification system for gamification strategies in attention bias interventions revealed that most applications utilized addition of gaming elements to an evidence-based task ($n = 5$). Only one application did not appear to integrate any of Wouter et al. (2015)'s methods. Application of Hoffman et al. [18]'s classification revealed that the most common gamification strategies applied to the nine applications were that of digital rewards and the provision of feedback. On average, the mean number of gamification techniques (based on Hoffman et al. [18]'s classification system) applied across the nine-identified application was that of 3.2. When applications were classified based on their download rates, we found that most of the commercial applications have included a mean of 3.5 gamification techniques and have a download of between 100–500. The inclusion of more gamification techniques did not necessarily lead to an application having more downloads.

The main objective of the current review was to identify the common gamification techniques that have been adopted by commercial applications. This helps to bridge the existing gaps in the literature. The prior review by Boendermaker et al. [23] have identified conventional methods, and referenced evaluated applications for each strategy. However, as aforementioned, there have been more commercial applications to date, and a number of these applications are widely used. An understanding of the gaming approaches utilized and correlation with downloads rates will enable us to have an understanding which technique are widely used and perhaps more well received by the public. In our current review, we found that the most common gamification method adopted by our cognitive bias intervention tasks was that the addition of gaming elements to an evidence-based task and the use of intrinsic integration while leaving the evidence-based task intact. The addition of gaming elements to an evidence-based training task is the most common, and this is expected, given that this is the most common initial step in gamification [23]. Routinely, this would involve the addition of game-like elements that seek to motivate participants extrinsically, such as the provision of motivating feedback and points [23]. The addition of features that seek to motivate extrinsically has been criticised by prior research, as it has been suggested that extrinsic motivation might eventually undermine intrinsic motivation for a task; and it might also hinder participants' performance on a task. In our current review, we have not managed to identify any commercial applications that have adopted the method of intrinsic integration using evidence-based task as a fundamental basis. This strategy preserves the theoretical basis of the task and helps to motivate participants intrinsically to continue with the intervention. Our review demonstrated that several applications appeared to have applied intrinsic integration leaving the underlying evidence-based training paradigm intact. Several applications appeared to have their basis on an existing popular game, that of a mobile runner game and this game was modified for cognitive bias modification. Boendermaker et al. [23] have

identified an cognitive bias modification game that has its basis on a popular card game and reported that there were disagreements in the biases targeted. Similarly, in our analysis, we believe that the adaptation of a mobile runner game for bias modification does confound the nature of the biases targeted. In each game, participants are asked to avoid either the tobacco or alcoholic substance while running in the gaming environment. It does appear that both biases, that of attention bias and approach/avoidance biases are simultaneously being targeted in such an intervention. As aforementioned, one application (Quitty) does not appear to have utilized any of the approaches that Ubhi et al. [22] have previously described, thus raising doubts about the validity of the bias training that the application provides.

Further analysis of gamification techniques integrated into commercial applications was performed using Hoffman et al. [18]'s taxonomy of gamification strategies. Our current review showed on average 3.2 gamification techniques across the nine-identified applications. Our average number of gamification techniques included appears to be much higher than that of Hoffman et al. [18]'s analysis of gamification techniques in stress-management applications, in which only 0.5 gamification techniques were found across 62 applications. One of the reasons for the discrepancy is because we have specifically looked at applications classified as games. Our analysis, based on Hoffman et al. [18]'s taxonomy also revealed that the most common gamification techniques applied were that of digital rewards and the provision of feedback. Digital rewards, while not commonly utilised among stress management applications [18], are commonly utilized in other gamification applications and offer individuals an extrinsic incentive to continue with the intervention. Feedback is not just a gamification technique, given that the provision of feedback could also encourage behavioural change.

There are several research implications arising from our current review. The adaptation of a typical game for bias modification might confound the nature of the biases being targeted, whether that of attention or approach/avoidance biases. Hence, there needs to be further research investigating how such a strategy could be adopted to gamify a cognitive bias intervention, yet not confound the nature of the biases being targeted. Given that such a strategy has already been implemented in existing commercial applications, there needs to be further evaluation of these commercial applications for the nature of the biases they seek to target. Further research needs to be undertaken to determine the efficacy of including other gamification techniques. Research should determine if the inclusion of these strategies does indeed increase the motivation to train and which strategies are more efficacious. The identified applications in our current review will be helpful in further co-design processes, seeking to implement and evaluate new gamified attention bias modification applications. In terms of clinical implications, while these applications might have included evidence-based gamification strategies, there remains a need for there to be further research evaluating the effectiveness of these application on a community or treatment-seeking cohort.

One of the major strengths of the current study is that we have managed to identify commercially available gamified attention bias modification applications, and we have also managed to apply two gamification taxonomies to classify the gamification strategies that are integrated into these applications. Our findings are of importance for future research seeking to implement and evaluate gamified attention bias modification interventions. Despite the strengths, there remain several limitations of the current study. The identification of the applications was confined to that of the Android store. The Android store was selected as it provides a clear overview of the characteristics of the applications, such as the download rates. Applications from the Apple Store routinely do not provide such comprehensive information, which could be used for further analysis in our current review. In our current review, we have limited our search only to English applications. Also, our search was confined to a fixed duration, and it is possible that new applications are left out given how rapidly new applications are added to the Android store.

5. Conclusions

The findings from the current review pertaining to the gamification techniques of commercial applications add on to the findings of previous review. Even though most commercial applications appear to have their basis on a validated gamification approach for the delivery of attention bias modification, there remains a need for further research in evaluating these applications clinically. Such an understanding of gamification approaches adopted in commercial application is crucial in future conceptualization and co-design of gamification attention bias modification interventions.

Conflict of interest

None to report.

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Discussion

Variations in the Visual Probe Paradigms for Attention Bias Modification for Substance Use Disorders

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Abstract: Advances in experimental psychology have provided evidence for the presence of attentional and approach biases in individuals with substance use disorders. Traditionally, reaction time tasks, such as the Stroop or the Visual Probe Task, are commonly used in the assessment of attention biases. The Visual Probe Task has been criticized for its poor reliability, and other research has highlighted that variations remain in the paradigms adopted. However, a gap remains in the published literature, as there have not been any prior studies that have reviewed stimulus timings for different substance use disorders. Such a review is pertinent, as the nature of the task might affect its effectiveness. The aim of this paper was in comparing the different methods used in the Visual Probe Task, by focusing on tasks that have been used for the most highly prevalent substance disorders—that of opiate use, cannabis use and stimulant use disorders. A total of eight published articles were identified for opioid use disorders, three for cannabis use disorders and four for stimulant use disorders. As evident from the synthesis, there is great variability in the paradigm adopted, with most articles including only information about the nature of the stimulus, the number of trials, the timings for the fixation cross and the timings for the stimulus set. Future research examining attentional biases among individuals with substance use disorders should take into consideration the paradigms that are commonly used and evaluate the optimal stimulus and stimulus-onset asynchrony timings.

Keywords: Visual Probe Task; attention bias; cognitive bias; psychiatry

1. Overview of Attention Bias Assessment and Modification

Advances in experimental psychology have provided evidence for the presence of attentional and approach biases in individuals with substance use disorders. Attentional biases result in individuals having a preferential allocation of their attentional processes to substance-related stimuli [1], while approach biases result in individuals having automatic action tendencies in reaching out for substance-related cues [2]. Various theories have provided explanations for the presence of these biases, including that of the incentive-sensitization theory, the classical conditioning theory and that of the dual-process theory [3]. The dual-process theory is most commonly used in the justification of the presence of attentional biases. It postulates that the repeated use of a substance would result in increased automatic processing and increased automatic tendencies to approach substance-specific cues, with the inhibition of normal cognitive control processes [3]. The discovery and the understanding of these unconscious, automatic biases are of importance clinically, as they help to account for the lapses and relapses among individuals with substance use disorders [4]. Recent neuroimaging studies have highlighted that attentional biases are associated with increased activation in several

neuroanatomical regions, including that of the anterior cingulate cortex, dorsolateral prefrontal cortex, insula, nucleus accumbens and amygdala [5,6].

Traditionally, reaction time tasks, such as the Stroop or the Visual Probe Task, are commonly used in the assessment of attention biases [1]. In the Stroop task, individuals are required to name the colours of both the neutral and the drug-related words. In the Visual Probe Task, participants are required to respond readily to a probe that would replace either the neutral or the drug image. Attentional biases are deemed to be present if individuals respond more readily to a probe or words that replace substance-related images, as compared to the neutral word or images [1]. Ataya et al. (2012) [7] previously reported that both these tasks (the Stroop and Visual Probe Task) are associated with poor internal reliability. Field et al. (2012) [8] have postulated that one of the factors that could account for the poor reliability of the Visual Probe Task pertains to the type of stimulus used. Thus, the authors proposed the use of a personalised stimulus and images that participants could readily identify with. In turn, this could then result in a more demonstrable change in biases [8]. In a review by Lopes et al. (2015) [9], they reported that the Visual Probe Task was effective—in 88% of the studies involving individuals with substance use disorders, there was successful retraining of attentional biases. Jones et al. (2018) [10], in their recent study, have explored methods to improve the internal reliability of the Visual Probe Task. The authors examined the nature of the stimulus included, adopting the previous suggestion of having a personalised stimulus and reported that the inclusion of a personalised stimulus did help to improve the internal consistency of the Visual Probe Task.

Nevertheless, the authors still report the Visual Probe Task to be unreliable and that reliabilities were acceptable if the stimulus cues were presented for short intervals. Jones et al. (2018) [10], in their review, highlighted that there is great variation in the timings of the stimulus intervals used in published studies involving addiction. However, a gap remains in the published literature, as there have not been any prior studies that have reviewed the stimulus timings for the different substance use disorders. Such a review is pertinent, as the nature of the task might affect its effectiveness. Given this, our aim was to compare the different task paradigms and methods for the Visual Probe Tasks used for the most highly prevalent substance disorders—that of opiate use, cannabis use and stimulant use disorders.

2. Visual Probe Task Paradigms in Published Studies

Two recent reviews have synthesised the evidence for attentional biases among substance users. Maclean et al. (2018) [11] identified 21 studies that have previously examined attentional biases in opioid using individuals. Zhang et al. (2018) [4] identified 11 articles involving participants with opioid use disorder, 16 articles with participants with stimulant use disorders and nine articles involving participants with cannabis use disorders. In order to fulfil our aim, we will describe the Visual Probe Task paradigms (the methods of the Visual Probe Tasks) that have been used in each of the published studies.

Table 1 provides an overview of the characteristics of the Visual Probe Task that were utilized in previous studies involving individuals with opioid use disorders. From both Maclean et al. (2018)'s [11] and Zhang et al. (2018)'s [4] review, we managed to identify a total of eight articles that specified the use of the Visual Probe Task for attention bias assessment or modification. We were unable to access the full text of one of the journals as it was published in a Chinese Journal. In the identified articles, there was great variability in the number of stimulus included, ranging from 12 to 44 picture pairs. Some studies included as few as 64 trials [12,13], while others included as many as 512 trials [14]. Across the studies, there was great variation in the Visual Probe Task. Most of the studies presented the fixation cross for 500 ms, except Frankland et al. (2016) [15] and Zhao et al. (2017) [16], who presented the fixation cross for 1000 ms. Several studies have presented the stimulus and neutral image set for both a short and long duration [12–15,17,18]. The short stimulus timing was commonly that of 200 ms, and the long stimulus timing was that of 2000 ms, though, in Frankland et al. (2016)'s [15] study, they presented the images for 500 and 1500 ms as well.

Table 1. Characteristics of the Visual Probe Task used in previous studies involving individuals with opioid dependence ($n = 8$).

Study	Participants	Intervention Details	Nature of Stimulus Included	Details of Assessment Task	Outcomes
Charles et al. (2015) [14]	In total, 23 opiate users and 21 healthy controls	Dot Probe Task for attention retraining in the lab. Participants maintained on Buprenorphine and Methadone Maintenance Therapy (MMT)	In total, 44 picture pairs In total, 40 pairs matched for visual complexity and composition, contained opiate-related items (spoons, needles, lighters, heroin-like substance) The other four pairs were neutral images only	Fixation Cross Timing: 500 ms Stimulus Pair Timing: Short (200 ms) or Long (500 ms) Probe: Arrow pointing upwards or downwards, remained on screen until participant responded Probe Timing: Not mentioned Inter-trial interval: 250–500 ms Stimulus Onset Asynchrony (SOA): Not mentioned Response Timing: Not mentioned Total number of critical trials: 64 (assessment), 512 (Intervention) Total number of neutral trials: 16 Total number of practice trials: Not mentioned	No baseline difference in attention bias between patients and controls No significant effect of Attention Bias Modification (ABM) on Attention Bias (AB) or substance cravings
Constantinou et al. (2010) [17]	In total, 16 opiate users in treatment, 16 ex-users, and 16 healthy controls	Dot Probe Task for attention retraining in the lab. Participants maintained on methadone maintenance therapy	In total, 40 picture pairs Of which, 20 pairs matched for visual complexity and composition, and contained one opiate related picture and one non opiate related picture The other 20 pairs were neutral pairs	Fixation Cross Timing: Not mentioned Stimulus Pair Timing: Short (200 ms) or Long (2000 ms) Probe: Probe appeared on the side of the screen where one of the pictures have been previously Probe Timing: Not mentioned Inter-trial interval: Not mentioned SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 160 Total number of neutral trials: Not mentioned Total number of practice trials: Not mentioned	Greater attentional biases towards drug-related stimuli for current users, as compared to ex-users. Ex-users showed a bias away from drug-related stimuli in the stress condition and this correlated positively with their length of abstinence
Frankland et al. (2016) [15]	In total, 19 were opioid dependent and 20 healthy controls	Dot Probe Task for attention retraining in the lab. Participants maintained on partial MMT	In total, 14 drug-related images (images of drug paraphernalia and an unidentified addict appearing to cook up and inject heroin), Another 14 pairs matched for control pictures (items from a children's building game, and a person building a model railway)	Fixation Cross Timing: 1000 ms Stimulus Pair Timing: 200, 500 and 1000 ms Probe: Probe replaced the images. Participants to press one of the buttons as quickly as quickly as possible, without making mistakes, to indicate whether the probe appeared on the left- or right-hand side. Probe Timing: Not mentioned Inter-trial interval: Not mentioned SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 164 Total number of neutral trials: 84 Total number of practice trials: 10	Opioid dependent group had a significant attentional bias for opioid related information presented at 200 ms and 500 ms. No attentional biases at 150 0ms.
Garland et al. (2013) [13]	In total, 32 were opioid dependent and 33 non opioid-dependent	Dot Probe Task for attentional retraining in the lab. Participants maintained on partial buprenorphine and MMT	In total, 12 opioid images, including photos of pill (Oxycontin, Vicodin), pill bottles, crushed and powdered opioids for insufflation, and a syringe next to a vial of injectable morphine Neutral images included 12 photos from the International Affective Picture System, depicting household items	Fixation Cross Timing: 500 ms Stimulus Pair Timing: 200 or 2000 ms Probe: Target probe will replace the images after 50 ms inter-stimulus interval Probe Timing: 100 ms Inter-trial interval: Not mentioned SOA: 50 ms Response Timing: Not mentioned Total number of critical trials: 64 Total number of neutral trials: 12 Total number of practice trials: Not mentioned	Opioid-dependent individuals had significant attention bias towards opioids cues presented for 200 ms but not for cues presented for 2000 ms

Table 1. Cont.

Study	Participants	Intervention Details	Nature of Stimulus Included	Details of Assessment Task	Outcomes
Garland and Howard et al. (2014) [12]	In total, 28 with a high risk for misuse and 19 with a low risk for misuse	Dot Probe Task for attentional retraining in the lab	In total, 12 opioid images, including photos of pill (Oxycontin, Vicodin), pill bottles, crushed and powdered opioids for insufflation Neutral images included 12 photos from the International Affective Picture System (IAPS), depicting household items	Fixation Cross Timing: 500 ms Stimulus Pair Timing: 200 or 2000 ms Probe: Target probe will replace the images after 50ms inter-stimulus interval Probe Timing: 100 ms Inter-trial interval: Not mentioned SOA: 50 ms Response Timing: Not mentioned Total number of critical trials: 64 Total number of neutral trials: 12 Total number of practice trials: Not mentioned	Biased initial attentional orienting to prescription opioid cues
Garland et al. (2015) [18]	In total, 72 opioid misusers and 26 opioids non misusers	Dot Probe Task for attentional retraining in the lab	Pair of photos containing one emotionally salient image and one neutral image Three blocks of cues (opioid-related, pain-related, and pleasure-related cues) Opioid-related cues included images of pills and bottles Pain-related cues included images of severe injuries, painful medical procedures, and human faces grimacing in pain Natural reward cues included images of romantic couples and food In total, 36 neutral images selected from International Affective Picture System (IAPS)	Fixation Cross Timing: 500 ms Stimulus Pair Timing: 200 or 2000 ms Half of the trials presented at 200ms, half 2000 ms. Probe: Target probe will replace the images after 50 ms inter-stimulus interval Probe Timing: 100 ms Inter-trial interval: Not mentioned SOA: 50 ms Response Timing: Not mentioned Total number of critical trials: 64 Total number of neutral trials: 12 Total number of practice trials: Not mentioned	Opioid misusers exhibit attentional deficits during reward processing
Lubman et al. (2000) [19]	In total, 16 methadone-maintained addicts and 16 age-matched controls	Pictorial Probe Detection task	Drug-related photographs (drug paraphernalia, for example, needles, spoons and heroin wraps) Scenes of unidentified addict cooking up and injecting heroin. Control photographs included items from children building a game and scenes showing an unidentified person building a model railway using various components from the set	Fixation Cross Timing: 1000 ms Stimulus Pair Timing: 500 ms Probe: After each pair of images, a dot probe will appear in the position of one of the pictures Participants are to press as quickly as possible, one of the two response buttons. Probe Timing: Not mentioned Inter-trial interval: Not mentioned SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 160 Total number of neutral trials: Not mentioned Total number of practice trials: 12	Attentional biases in opiate addicts to probe that replaced the drug pictures, rather than neutral images
Wei et al. (2016) [20]	In total, 22 heroin addicts and 22 healthy controls	Visual Probe Task	In total, 10 heroin images The other 10 were natural scenery pictures	Fixation Cross Timing: 1000 ms Stimulus Pair Timing: 500 ms Probe: Appear in the location where one of the images disappear Probe Timing: 200 ms Inter-trial interval: 1350 ms SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 80 and 240 Total number of neutral trials: Not mentioned Total number of practice trials: 20	Heroin addicts have more rapid response when the dot located on the heroin-related picture as compared to the neutral picture

Table 1. Cont.

Study	Participants	Intervention Details	Nature of Stimulus Included	Details of Assessment Task	Outcomes
Zhao et al. (2017) [16]	In total, 30 methadone-maintained outpatients and 38 healthy controls	Visual Probe Task	Drug neutral picture pairs and neutral–neutral picture pairs. In total, 20 pictures of substance-related scenes and 20 similar pictures matched with same layout but lacking substance-related cues Another 20 pairs of pictures matched with similar neutral scenes of daily life	Fixation Cross Timing: 1000 ms Stimulus Pair Timing: 2000 ms Probe: Probe then displayed in one of the positions of the pictures Probe remained until the participant responded by clicking the left or right button of mouse Probe Timing: Not mentioned Inter-trial interval: 200 ms SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 120 Total number of neutral trials: Not mentioned Total number of practice trials: 16	Heroin group reacted faster to probes associated with substance-related pictures than neutral pictures More initial fixations Maintained longer initial fixation durations towards substance-related pictures

While all the studies explicitly stated that they were based on the Visual Probe Task, there were variations in the nature of the task. Some studies [12,13,18] have included an interstimulus interval, before the presentation of the probe. Also, in some studies, the probe remained on the screen until the participant made a response [14,16,17], while in other studies, the probe only appeared for 100 ms, before disappearing [12,13,18]. Some studies also included an inter-trial interval, but there was variation in the timing of this interval (from 250 to 2000 ms). Some of the studies [15,16,19] have included practice trials. Figure 1 provides a graphical representation of the details of the Visual Probe Task that were reported in each of the identified studies for opioid use disorder.

Study	Fixation Cross Timing	Stimulus Timing	Probe Timing	Inter-trial Interval	Stimulus-Onset Asynchrony	Response timing
Charles et al. (2015)						
Constantinou et al. (2010)						
Frankland et al. (2016)						
Garland et al. (2013)						
Garland and Howard et al. (2014)						
Garland et al. (2015)						
Lubman et al. (2000)						
Zhao et al. (2017)						
Wei et al. (2016)						

Figure 1. A graphical representation of the details of the Visual Probe Task that were reported in each of the identified studies for opioid use disorder (n = 8). Green highlights: reported in study; red highlights: not reported in study.

Table 2 provides an overview of the characteristics of the Visual Probe Task that was utilized in previous studies involving individuals with cannabis use disorders. A total of three articles from Zhang et al. (2018)'s [4] prior review were included, as they have reported the use of the Visual Probe Task. For the stimulus, Field et al. (2004) [21] included words instead of pictorial stimuli. In terms of the Visual Probe Task, two studies [21,22] presented the fixation cross for 500 ms, whereas Field et al. (2006) [23] presented it for 1000 ms. There was again variation in the timings for the stimuli cues, with two studies [21,22] presenting the stimulus cue for 500 ms, whereas that of Field et al. (2006) [23] presented it for 2000 ms. In terms of probe presentation, two studies presented the probe [21,22] until a response was made. Vujanovic et al. (2016) [22], presented the probe for 125 or 250 ms. Across all the studies, they have included an inter-trial interval, which ranged from 1000 to 1500 ms. In terms of the number of trials, it ranged between 72 and 96. All the studies included practice trials for participants. Figure 2 provides a graphical representation of the details of the Visual Probe Task that were reported in each of the identified studies for cannabis use disorder.

Table 2. Characteristics of the Visual Probe Task used in previous studies involving individuals with cannabis dependence.

Study	Participants	Intervention Details	Nature of Stimulus Included	Details of Assessment Task	Outcomes
Field et al. (2004) [21]	In total, 17 regular cannabis users and 16 non-users	Visual Probe Task	Cannabis-related words, environment-related words, pleasant words, and unpleasant words	Fixation Cross Timing: 500 ms Stimulus Pair Timing: 500 ms Probe: Immediately after the offset of the words, a small dot probe was presented in the position of one of the words, until the participant gave a manual response. Probe Timing: Not mentioned Inter-trial interval: 1000 ms Stimulus Onset Asynchrony (SOA): Not mentioned Response Timing: Not mentioned Total number of critical trials: 64 Total number of neutral trials: 32 Total number of practice trials: 12	High levels of craving associated with significant attention bias for cannabis-related words
Field et al. (2006) [23]	In total, 23 regular cannabis users and 23 non-user controls	Visual Probe Task with concurrent eye movement monitoring	In total, 18 cannabis-related photographs Depicting a scene relating to cannabis use Control photograph (did not contain cannabis related content)	Fixation Cross Timing: 1000 ms Stimulus Pair Timing: 2000 ms Probe: After picture offset, small visual probe (an arrow which is pointed up or down) was presented on the left or right of the screen Respond to the probe as quickly as possible Probe Timing: Not mentioned Inter-trial interval: 500 ms SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 72 Total number of neutral trials: Not mentioned Total number of practice trials: 10	Regular users had biases to maintain gaze on cannabis cues and faster approach responses to cannabis cues
Vujanovic et al. (2016) [22]	In total, 12 adults with cannabis use disorder and 13 controls	Visual Probe Task	In total, six cannabis pictures—cannabis-related stimuli—and six neutral pictures matched in size, colour and context	Fixation Cross Timing: 500 ms Stimulus Pair Timing: 500 ms Probe: Probe stimulus removed, picture (cue) remained on screen 1500 ms Probe Timing: 125 or 250 ms Inter-trial interval: 1500 ms SOA: Not mentioned Response Timing: 1500 ms Total number of critical trials: 96 Total number of neutral trials: Not mentioned Total number of practice trials: 12	Cannabis use group showed greater attentional biases to cannabis cues at the 125 ms probe time

Study	Fixation Cross Timing	Stimulus Timing	Probe Timing	Inter-trial Interval	Stimulus-Onset Asynchrony	Response timing
Field et al. (2004)						
Field et al. (2006)						
Vujanovic et al. (2016)						

Figure 2. A graphical representation of the details of the Visual Probe Task that were reported in each of the identified studies for cannabis use disorder (n = 3). Green highlights: reported in study; red highlights: not reported in study.

Table 3 provides an overview of the characteristics of the Visual Probe Task that were utilized in the previous studies involving individuals with stimulant use disorders—that of cocaine use disorders. A total of four articles from Zhang et al. (2018)’s [4] prior review was included. While all the studies have their basis in the Visual Probe Task, there was variability in the paradigms. Some studies included 10 sets of images [24], while others [25,26] included up to 20 sets of images. There was variation in the number of trials individuals had to undertake, ranging from 80 to 240 trials. Two studies [25,26] reported the inclusion of practice trials. Three out of the four studies reported that they presented a fixation cross for 500 ms. In terms of stimulus timings, they were presented for 500 ms in three studies [24–26] and for a short (200 ms) and long (500 ms) interval in Mayer et al. (2016)’s study [27]. In all of the studies, the probe appeared up until a response was made. Only two of the four identified studies allowed for an inter-trial interval [24,27]. There was variation in the inter-trial interval, as it ranged from 500 to 1500 ms. Figure 3 provides a graphical representation of the details of the Visual Probe Task that were reported in each of the identified studies for stimulant use disorder.

Table 3. Characteristics of the Visual Probe Task used in previous studies involving individuals with stimulant dependence.

Study	Participants	Intervention Details	Nature of Stimulus Included	Details of Assessment Task	Outcomes
Montgomery et al. (2010) [24]	In total, 32 regular cocaine users and 40 nonusers	Visual Probe Task and Modified Stroop Task	In total, 10 pairs of images, with one cocaine-related image depicting cocaine, cocaine paraphernalia, or close up of an individual using cocaine. Matched with a neutral image, perceptually similar to cocaine image as possible, but did not have cocaine content	Fixation Cross Timing: 500 ms Stimulus Pair Timing: 500 ms Probe: Visual probe (an arrow pointing up or down) presented in the location previously occupied by one of the pictures Required to rapidly identify the orientation of the arrow probe by pressing the appropriate arrow on the keyboard Probe Timing: Not mentioned Inter-trial interval: 500 ms Stimulus Onset Asynchrony (SOA): Not mentioned Response Timing: Not mentioned Total number of critical trials: 80 Total number of neutral trials: Not mentioned Total number of practice trials: 10	Cocaine participants who consumed alcohol had increased attentional biases for cocaine pictures
Tull et al. (2011) [26]	In total, 30 cocaine-dependent patients with Post-traumatic Stress Disorder (PTSD) and 30 cocaine-dependent patients without PTSD	Visual Probe Task	In total, 20 cocaine-related images (crack rocks, powder cocaine, crack pipes, etc.) and 40 images of furniture	Fixation Cross Timing: 500 ms Stimulus Pair Timing: 500 ms Probe: Dot probe appeared in the left or right position, remaining until the participant responded Indicate where the dot appeared by pressing one of the two response keys. Probe Timing: Not mentioned Inter-trial interval: 250 ms SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 240 Total number of neutral trials: Not mentioned Total number of practice trials: 5	PTSD participants have had greater attentional biases towards the location of cocaine imagery than non-PTSD participants
Bardeen et al. (2013) [25]	In total, 22 cocaine-dependent patients with borderline personality disorder and 36 cocaine-dependent patients without borderline personality disorder	Visual Probe Task	In total, 20 cocaine-related pictures (crack pipes, crack rocks, etc.) and 40 pictures of furniture	Fixation Cross Timing: 500 ms Stimulus Pair Timing: 500 ms Probe: Dot appeared on the screen replacing one of the two pictures. Press a button on the computer keyboard that corresponded to the relative position of the dot on the screen Probe Timing: Not mentioned Inter-trial interval: Not mentioned SOA: Not mentioned Response Timing: Not mentioned Total number of critical trials: 240 Total number of neutral trials: Not mentioned Total number of practice trials: 5	Greater bias for attending to cocaine stimuli among male cocaine-dependent patients with or without borderline personality disorder, when presented with a trauma script intervention

Table 3. Cont.

Study	Participants	Intervention Details	Nature of Stimulus Included	Details of Assessment Task	Outcomes
Mayer et al. (2016) [27]	In total, 37 participants randomly assigned to Attention Bias Modification Therap (ABMT) or control therapy	Visual Probe Task	Cocaine and neutral stimuli were equivalent in size and visual angle, generally matched for colour and content	Fixation Cross Timing: Not mentioned Stimulus Pair Timing: Stimulus pairs presented for 200 ms (speed detection trials) or 500 (difficulty to disengage trials). Probe: Stimulus replaced by a probe (arrow) Probe Timing: Not mentioned Inter-trial interval: 1000 or 1500 ms SOA: Not mentioned Response Timing: 1500 ms Total number of critical trials: 240 Total number of neutral trials: Not mentioned Total number of practice trials: 5	Attention bias modification was not more effective than control at reducing attentional biases

Study	Fixation Cross Timing	Stimulus Timing	Probe Timing	Inter-trial Interval	Stimulus-Onset Asynchrony	Response timing
Montgomery et al. (2010)						
Tull et al. (2011)						
Bardeen et al. (2013)						
Mayer et al. (2016)						

Figure 3. A graphical representation of the details of the Visual Probe Task that were reported in each of the identified studies for stimulant use disorder (n = 4). Green highlights: reported in study; red highlights: not reported in study.

3. Implications for Future Research

It is apparent that there is great variability in the paradigm of the Visual Probe Task. In addition, there is also a varied amount of information shared about the nature of the paradigm. Most of the articles included information about the nature of the stimulus, the number of trials, the timings for the fixation cross and the timings for the stimulus set. However, information is missing in some studies, with regards to the inter-stimulus interval, the time that the probe appears for, the inter-trial interval and the time allocated for the individual to respond. The absence of this information limits the reproducibility of the Visual Probe Task by others. For future research, it is essential that the intervention is described in full, carefully specifying the full methodology of the Visual Probe Task used, in order to allow for the replication of studies.

While there were clear variations in the paradigms, there were some common elements across all the studies. For studies involving participants with opioid use disorders, most of the studies presented the fixation cross for 500 ms and presented the set of stimulus images for both a short and long stimulus duration. A shorter stimulus duration would allow for the evaluation of the initial, automatic detection attentional processes, while a longer stimulus duration would allow for the evaluation of the engagement stages of attention [9]. In contrast, for studies involving participants with cannabis use or stimulant use disorders, the stimulus pair was most commonly presented for 500 ms. Most of the studies utilizing these timings have provided positive findings for attentional biases, except for Charles et al. (2015) [14] and Mayer et al. (2016) [27].

This evidence synthesis has direct implications for future research. We propose that future studies assessing and modifying attentional biases among individuals with opioid use disorders should consider the use of both a short and long stimulus timing, whereas studies evaluating attentional processes among people using cannabis or with stimulant disorders could use a single stimulus interval. To date, there is only a single study (Mayer et al., 2016) [27] that has examined a varying timing stimulus for individuals with stimulant use disorder. Future research should also examine whether the presence of a varying stimulus timing interval will enhance the detection and modification of attentional biases among individuals with cannabis and stimulant use disorders.

From the studies that we have included, there were a limited number of studies that have reported the stimulus-onset asynchrony timings. Lopes et al. (2015) [9], in their prior review exploring the Visual Probe Task for various disorders, have reported that there was variation in the timings for the different psychiatric disorders. For substance use disorders, it ranged from 50 to 500 ms; for depressive disorders, it ranged from 500 to 2000 ms; and for anxiety disorders, it ranged from 200 to 1500 ms. Lopes et al. (2015) [9] have previously highlighted that a relatively longer stimulus duration is advantageous as it allows for participants to fully process the nature of the stimuli. However, as evident from this evidence synthesis, there are few studies that report on this timing, and this is indeed an area that future research should evaluate to determine the optimal interval for the different substance use disorders.

Our article is perhaps the first article that has reviewed the task paradigms that have been adopted in previously published studies, involving individuals with substance use disorders. We managed to systematically extract information, primarily from the methods section of each manuscript, to ascertain the details of the visual probe paradigms that were utilized. However, there were limitations in our current study. We were unable to access the full text of one of the published articles, as it was published in a Chinese Journal. We have also attempted to contact each of the authors for further details about the Visual Probe Task they have previously used but, to date, we have only managed to receive replies from a single author, who stated that all the details have already been cited in the methods section of the published manuscript.

4. Conclusions

Our article has reviewed all the visual probe paradigms that have been applied previously for addiction and substance research. While there are variations in the underlying paradigms, there are some commonalities as well. Future research examining attentional biases among individuals with substance use disorders should take into consideration the paradigms that are commonly used and evaluate the optimal stimulus and stimulus-onset asynchrony timings.

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Protocol

Mobile Phone Cognitive Bias Modification Research Platform for Substance Use Disorders: Protocol for a Feasibility Study

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Abstract

Background: Cognitive biases refer to automatic attentional and interpretational tendencies, which could be retained by cognitive bias modification interventions. Cristea et al and Jones et al have published reviews (in 2016 and 2017 respectively) on the effectiveness of such interventions. The advancement of technologies such as electronic health (eHealth) and mobile health (mHealth) has led to them being harnessed for the delivery of cognitive bias modification. To date, at least eight studies have demonstrated the feasibility of mobile technologies for the delivery of cognitive bias modification. Most of the studies are limited to a description of the conventional cognitive bias modification methodology that has been adopted. None of the studies shared the developmental process for the methodology involved, such that future studies could adopt it in the cost-effective replication of such interventions.

Objective: It is important to have a common platform that could facilitate the design and customization of cognitive bias modification interventions for a variety of psychiatric and addictive disorders. It is the aim of the current research protocol to describe the design of a research platform that allows for customization of cognitive bias modification interventions for addictive disorders.

Methods: A multidisciplinary team of 2 addiction psychiatrists, a psychologist with expertise in cognitive bias modification, and a computer engineer, were involved in the development of the intervention. The proposed platform would comprise of a mobile phone version of the cognitive bias task which is controlled by a server that could customize the algorithm for the tasks and collate the reaction-time data in realtime. The server would also allow the researcher to program the specific set of images that will be present in the task. The mobile phone app would synchronize with the backend server in real-time. An open-sourced cross-platform gaming software from React Native was used in the current development.

Results: Multimedia Appendix 1 contains a video demonstrating the operation of the app, as well as a sample dataset of the reaction times (used for the computation of attentional biases) captured by the app.

Conclusions: The current design can be utilized for cognitive bias modification across a spectrum of disorders and is not limited to one disorder. It will be of value for future research to utilize the above platform and compare the efficacy of mHealth approaches, such as the one described in this study, with conventional Web-based approaches in the delivery of attentional bias modification interventions.

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KEYWORDS

attention bias modification; eHealth; mHealth; development

Introduction

Cognitive biases include automatic attentional and interpretational tendencies [1]. Attentional biases, which refer to the preferential tendency for attention to be allocated towards or away from stimuli that are emotionally salient for the individual, have been found to be present in a variety of disorders, ranging from depression and anxiety disorders to addictive disorders [2]. These automatic processes would result in individuals with an anxiety disorder to attend to threat related cues, individuals with depression to attend to negative information, and individuals with addictive disorders to attend to substance-related cues. As such, cognitive biases are highly prevalent and have been implicated in the psychopathologies of various disorders [3-5].

Various theoretical approaches have helped to account for the role of these automatic processes in the different psychopathologies, but, perhaps the best developed theoretical model to date, is the dual-process model for addictive disorders [6]. The dual-process theoretical model proposes that with the recurrent use of a substance, this facilitates increased automatic processing of substance-related cues, with a resultant inhibition of the normal cognitive control processes [6]. Along with the increased recognition of cognitive biases, there has been further research examining how these biases could be modified. Several different cognitive bias modification approaches are routinely used, namely that of the attention bias modification, cognitive bias modification for interpretations, spatial cueing tasks, and attentional visual search [7]. To date, there have been a number of studies reported that have investigated the effectiveness of bias modification. In 2016, Cristea et al conducted a meta-analysis of participants with either a tobacco or alcohol addiction and considered the effect size of cognitive bias modification on cognitive biases and on addiction-related outcomes, such as cravings [8]. This study reported that bias modification had a significant effect on cognitive bias, with an effect size of 0.60 (calculated using Hedge *g*). Despite its effect on cognitive biases, there were no effects reported on other addiction outcomes. In a commentary published online, responding to the study by Cristea et al [8], a key limitation of the meta-analysis was identified, namely that Cristea et al considered clinical and nonclinical trials jointly in their synthesis of the results. When considering only clinical trials, there was a significant effect of bias modification. This finding from the meta-analysis demonstrates the importance of targeting automatic processes and the potential efficacy of bias modification in substance using individuals. A review of meta-analyses published by Jones et al in 2017 [1], conducted for a diverse group of participants, reported that the current evidence supports the effectiveness of bias modification, mainly for anxiety disorders.

Conventional cognitive bias interventions have typically been delivered using a computer in the confines of a laboratory, but there is potential to change this. In the past decade, there have been an increasing number of remote online therapies available

and this has been attributed to the advances in eHealth, or electronic health. eHealth technologies facilitate the delivery of online psychotherapy at a low cost and allows therapy to be highly accessible and anonymous [9]. There have been an increasing number of studies examining the effectiveness of Web-based cognitive bias modification interventions. In 2015, Wittekind et al evaluated an online avoidance retraining intervention for 257 individuals with a tobacco use disorder; and demonstrated that avoidance bias retraining was associated with a significant reduction in the number of cigarettes smoked and the cravings to smoke [10]. In 2017, Cougle et al conducted a trial which evaluated an online interpretation bias modification program for hostility with 58 individuals [11]. They found that the online intervention led to a greater reduction in interpretative bias compared to the control group. These trials have demonstrated the feasibility and effectiveness of Web-based bias modifications. Further advancement in technology, coupled with increased ownership of mobile devices, has led to there being increasingly more interventions that use mobile technologies (mHealth). Based on the published literature to date, there are several studies that have evaluated the potential and effectiveness of mHealth bias modification. Of the studies, seven reported that mHealth bias modification was effective for participants with a variety of disorders, namely insomnia, alcohol, tobacco use, or social anxiety disorders [12-18]. mHealth technologies are increasingly being harnessed for the delivery of bias modification, as mobile technologies allow for the training to be conducted in diverse locations, thus helping in the generalization of clinical benefits [19]. In addition, such technologies help to increase accessibility to the intervention and aid in the reduction of costs associated with treatment. The use of mobile technologies in the delivery of bias modification interventions could help to improve outcomes, in that it helps to increase the frequency of training [19]. mHealth technologies have an advantage over existing Web-based versions, given that web interventions would require individuals to be consistently connected to the internet to undertake the bias modification task. There is also the potential to couple the bias modification with other sensors in the mobile phone, such that users will be prompted to engage in training tasks to help them with their symptoms if they are deemed to be in a high-risk locality [20].

While the existing mHealth studies have demonstrated the feasibility of such technologies, most of these studies are limited to a description of the conventional bias modification methodology that has been adopted. None of the previous studies have shared the platform that they have used in the development of their cognitive bias task, thus limiting the replicability of the intervention. Most studies are limited to a description of the conventional task paradigm that have been adopted, for example, in the study reported by Clarke et al in 2016, it was reported that their intervention task was based on the conventional attentional probe training paradigm [12]. In the supplementary material, details of the words that were utilized for their task were provided. Whilst this allows for replicability to a certain extent, a number of resources are needed to develop a mobile

version of the platform to deliver cognitive bias modification. Hence, it is thus of great import to have a common platform that could easily facilitate the design and customization of such interventions for a variety of psychiatric disorders. As a start, we will describe the design of a research platform that allows the customization of bias modification interventions for a range of substance use disorders.

Methods

Overview of Research Platform

A multidisciplinary team, comprising of 2 psychiatrists specializing in addiction psychiatry, a psychologist with prior expertise on attentional bias modification, and a computer engineer were involved in the development of the research platform. It was decided that the platform would comprise of a mobile phone version of the cognitive bias task (as an example, the visual probe task), which is controlled both by a server that could customize the algorithm for the tasks and collate the reaction time data in realtime (Figure 1). The server would also allow the researcher to program the specific set of images that will be present in the task. The mobile phone app would synchronize with the backend server in realtime.

The mobile phone app that will be created needs to be modelled against the conventional visual probe task approach [21]. Based on the conventional approach, in the assessment phase, individuals would be presented with a fixation cross upon commencement. After that, both a neutral and non-neutral stimulus would be presented simultaneously. Both of these stimuli would disappear and a probe (usually in the form of an asterisk) would replace either stimulus. Individuals are required to indicate the position of the asterisk by indicating a response within a predetermined time. In the bias assessment phase, the asterisk would replace either stimulus equally (50% of the time). However, in the bias modification phase, the asterisk would replace the neutral stimulus all the time (100% of the time).

Individuals with biases would spend more time engaging with the stimuli and have difficulties with disengaging after. This will be reflected in their increased reaction time towards identifying the exact locality of the probe (asterisk).

The graphic user interface will be similar across the different substance disorders. The server will allow for the collation of reaction time data, as well as other variables that are essential when using reaction time to compute the presence of attentional biases. These variables include the positions of the probes, the positions of the substance-related stimuli, and whether the participant has indicated a correct response. Figure 2 provides an overview of the sample dataset that is collated by the server. In addition, the server has been programed with a specific algorithm, such that it enables the control of the frequencies of the probe replacing the substance stimuli (whether 50% or 100%). The research platform would also allow the researchers to vary the number of repeats of a particular set of images. Figure 3 provides an overview of how the server is able to control these parameters.

Development of Research Platform

The cognitive bias modification app was developed using an open-source cross-platform gaming software, React Native. The development team decided to utilize this approach for several reasons. The integration of an open-source approach would ensure that the intervention is compatible and could be utilized across a variety of platforms, without any differences between platforms. Thus, participants are able to undertake the task on their mobile phone devices, as well as on a normal computer. The gaming platform that has been used also allows for the future incorporation of gamification elements, as gamification has been shown to help increase motivation for bias modification [22]. In addition, the current platform is verstaile and allows for scaling or modification of the entire program to be used for a different disorder. This would drastically reduce the time and cost associated with development, while ensuring that the timings of the conventional paradigms are retained.

Figure 1. Overview of the research platform for the cognitive bias intervention for substance use disorders.

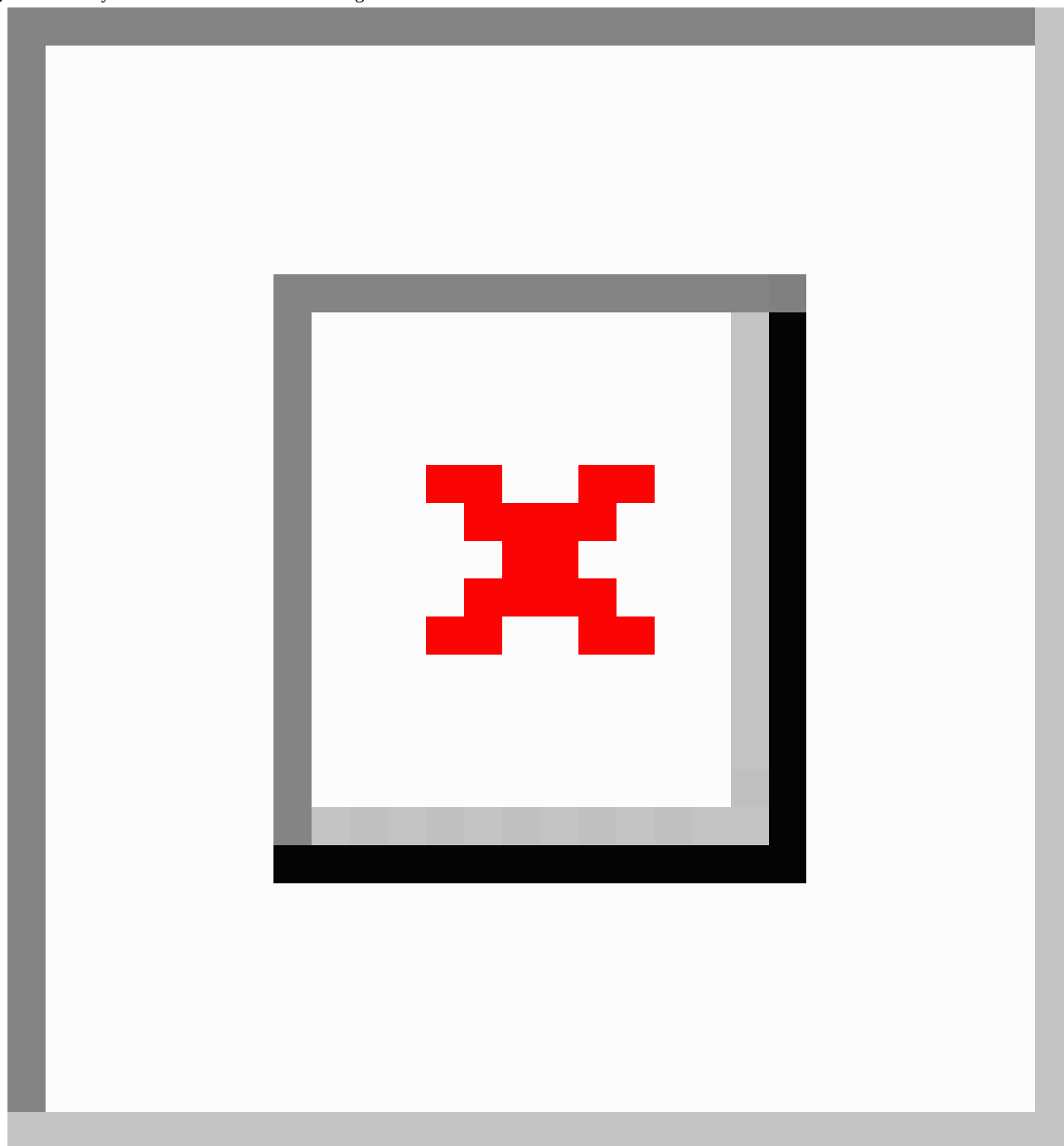


Figure 2. Sample dataset of reaction time data collated by the server.

Results Sobriety Admin 

Filter EXPORT 

Created Date	Name	Type	Category	Image	Asterisk	Test Result	Time (ms)
Dec 12, 2017 11:08:06	 Melvyn	Assessment	Alcohol	Left	Right	incorrect	2,000
Dec 12, 2017 11:08:03	 Melvyn	Assessment	Alcohol	Left	Left	incorrect	2,000
Dec 12, 2017 11:08:00	 Melvyn	Assessment	Alcohol	Right	Right	incorrect	2,000
Dec 12, 2017 11:07:57	 Melvyn	Assessment	Alcohol	Left	Left	incorrect	2,000
Dec 12, 2017 11:07:54	 Melvyn	Assessment	Alcohol	Right	Right	incorrect	2,000
Dec 12, 2017 11:07:50	 Melvyn	Assessment	Alcohol	Right	Left	incorrect	2,000
Dec 12, 2017 11:07:47	 Melvyn	Assessment	Alcohol	Right	Right	incorrect	2,000
Dec 12, 2017 11:07:44	 Melvyn	Assessment	Alcohol	Left	Left	incorrect	2,000
Dec 12, 2017 11:07:41	 Melvyn	Assessment	Alcohol	Left	Right	incorrect	2,000
Dec 12, 2017 11:07:38	 Melvyn	Assessment	Alcohol	Left	Left	correct	1,929

Figure 3. Ability of the server to customize the algorithm for the Visual Probe task.

Results

[Multimedia Appendix 1](#) contains a video demonstrating the operation of the app, as well as a sample dataset of the reaction times captured by the app ([Multimedia Appendix 2](#)).

Discussion

Principal Findings

The current design could be utilized for cognitive bias modification across a spectrum of disorders and is not limited to just one disorder. This research platform could be adopted by various cognitive bias modification interventions and the usage of this platform would potentially drive down the costs

associated with the development of such mHealth interventions. This is congruent with the recommendation made in the study published by Zhang et al for the usage of low-cost methodologies in app development [23]. The framework we have developed could be easily distributed and fellow researchers could make use of the created platform for their own interventions. While we have presented and discussed evidence mainly for substance use disorder, cognitive bias modification is also efficacious for other disorders, such as social anxiety disorders [24]. As compared to the conventional method, or even Web-based interventions, the mobile phone bias modification intervention would imply that individual users are no longer confined to a laboratory environment to receive the intervention. Individuals can make use of the interventions

in their naturalistic environments, and the app could also be coupled with geolocation services intrinsic to the mobile phone. By doing so, this would facilitate the delivery of timely interventions when individuals are in their high-risk locality, when they are most prone to a relapse.

Furthermore, there has been growing interest in consideration of incorporating of serious game elements to conventional cognitive bias tasks [7], and subsequently a study has been published which highlighted several possible gamification strategies [22]. A variety of serious games strategies have been proposed, which include the addition of game elements, the intrinsic integration with the evidence-based task as a basis, intrinsic integration leaving the evidence base task intact, or the addition of a game shell around the original evidence base task [22]. These four different mechanisms could easily be achievable in the current design, given that the design of the current mobile phone based attentional bias modification paradigm has been based on a gaming engine. Whilst most gamification techniques

seek to increase an individual's motivation to continue with a task, it is important to recognize that the consequences of the game do have an impact on gaming behaviors [19]. In our case, the pairing of an aversive consequences in the game play might help to enhance our aim of decreasing individuals' typical behavior towards rewarding stimuli.

Conclusions

In conclusion, we have shared a research platform for the design of a mobile phone version of a bias modification task, which could be easily modified to be applied to a spectrum of disorders. It will be of value for future research to utilize the above platform and compare the efficacy of mHealth approaches, such as the one described in this study, with conventional Web-based approaches in the delivery of cognitive bias modification interventions. Additionally, the use of a gaming platform in the current design opens future opportunities to consider the addition of serious gaming elements to enhance the appeal of these tasks.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Demonstration of the research platform app.

[[MP4 File \(MP4 Video\)](#), 15MB-Multimedia Appendix 1]

Multimedia Appendix 2

Sample dataset of reaction times.

[[XLSX File \(Microsoft Excel File\)](#), 16KB-Multimedia Appendix 2]

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Abbreviations

eHealth: electronic health

mHealth: mobile health

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Protocol

A Smartphone Attention Bias Intervention for Individuals With Addictive Disorders: Protocol for a Feasibility Study

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Abstract

Background: Substance use disorders are highly prevalent globally. Relapse rates following conventional psychological interventions for substance use disorders remain high. Recent reviews have highlighted attentional and approach or avoidance biases to be responsible for multiple relapses. Other studies have reported the efficacy of interventions to modify biases. With advances in technologies, there are now mobile versions of conventional bias modification interventions. However, to date, no study has evaluated bias modification in a substance-using, non-Western sample. Existing evaluations of mobile technologies for the delivery of bias interventions are also limited to alcohol or tobacco use disorders.

Objective: This study aims to examine the feasibility of mobile-based attention bias modification intervention among treatment-seeking individuals with substance use and alcohol use disorders.

Methods: This is a feasibility study, in which inpatients who are in their rehabilitation phase of clinical management will be recruited. On each day that they are in the study, they will be required to complete a craving visual analogue scale and undertake both a visual probe-based assessment and a modification task in a smartphone app. Reaction time data will be collated for the computation of baseline attentional biases and to determine whether there is a reduction of attentional bias across the interventions. Feasibility will be determined by the number of participants recruited and participants' adherence to the planned interventions up until the completion of their rehabilitation program and by the ability of the app in detecting baseline biases and changes in biases. Acceptability of the intervention will be assessed by a short questionnaire of users' perceptions of the intervention. Statistical analyses will be performed using SPSS version 22.0, while qualitative analysis of the perspectives will be performed using NVivo version 10.0.

Results: This study was approved by the National Healthcare Group Domain Specific Research Board, with approval number (2018/00316). Results will be disseminated by means of conferences and publications. Currently, we are in the process of recruitment for this study.

Conclusions: To the best of our knowledge, this is the first study to evaluate the feasibility and acceptability of a mobile attention bias modification intervention for individuals with substance use disorders. The data pertaining to the feasibility and acceptability are undoubtedly crucial because they imply the potential use of mobile technologies in retraining attentional biases among inpatients admitted for medical-assisted detoxification and rehabilitation. Participants' feedback pertaining to the ease of use, interactivity, and motivation to continue using the app is crucial because it will determine whether a codesign approach might be warranted to design an app that is acceptable for participants and that participants themselves would be motivated to use.

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KEYWORDS

addiction; approach bias; attention bias; bias modification; feasibility; pilot; psychiatry; mobile phone; mHealth; eHealth

Introduction

Background

Illicit drug and alcohol use are highly prevalent globally. The United Nations Office on Drugs and Crime reported that in 2015, a quarter of a billion individuals experimented with substances, and 29.5 million individuals were diagnosed with substance disorders [1]. Cannabis, opioids, and stimulants such as amphetamines are most commonly abused [1]. Substance use is associated with other comorbidities like retroviral diseases and hepatitis C infection. In addition, substance use is associated with significant mortality, and in 2015, an estimated 190,000 deaths were attributed to drug use [1]. Globally, alcohol use is a major problem too [2]. Reportedly, alcohol disorders tend to be more prevalent in developed countries and higher-income status countries [2]. In the most recent report released by the World Health Organization, it was reported that the harmful use of alcohol resulted in an overall mortality of 3 million individuals in 2016 [3]. In Singapore, in a prior study conducted by the World Health Organization in 2004, the prevalence of alcohol use disorders among females and males was estimated to be 0.19% and 1.40%, respectively, and the prevalence of drug use disorders among females and males to be 0.07% and 0.28%, respectively [4]. While there are no large-scale prevalence studies in Singapore, the Central Narcotics Bureau has reported that in 2017, 40% of those apprehended were new abusers, and >64% of these new abusers were under the age of 30 years [5]. Of 3091 abusers arrested in 2017, 1991 were abusing methamphetamine, and the remaining 848 and 204 were abusing heroin and cannabis, respectively. Of importance, 2570 abusers were polysubstance abusers. Thus, substance use disorders are of growing concern as indicated by the increasing numbers of offenders and their changing demographics. Taking into consideration the prevalence, there is a growing need for efficacious interventions.

The treatment options for substance use are both pharmacological and nonpharmacological. Pharmacological options are varied; for opioid use disorders, opiate substitution therapy such as that with methadone or buprenorphine could be considered. In Singapore, opiate substitution therapy is only prescribed for elderly individuals and pregnant women [6] as legislation restricts its administration for other patient groups. The prescription of opiate substitution medications such as buprenorphine is limited due to the risk of diversion [7] and medical comorbidities like infective endocarditis and other cutaneous complications [8,9]. For cannabis and amphetamine disorders, pharmacological options are limited, and symptomatic medications such as hypnotics or antipsychotics are considered in the acute treatment phase. Given the limited pharmacological therapeutic options, especially with the absence of medications to help with abstinence, psychological options are integral. Therapies like cognitive behavioral therapy are effective, with an effect size of 0.45 (Cohen *d*) [10]. Nonetheless, despite this

effectiveness, 40%-50% of individuals relapse within a year of successful treatment and another 70% relapse within 3 years [11]. Such high relapse rates following a moderately effective intervention demonstrate that conventional psychological therapies may not be adequately addressing the factors leading individuals to a lapse or relapse.

Recent advances in experimental psychology have reported how automatic attentional biases could predispose individuals toward a relapse. Field et al [12] and Cox et al [13] have highlighted the presence of these automatic attentional processes in individuals with substance use disorders and recommended the use of interventions to modify these automatic processes. Attentional biases refer to the preferential allocation of attention toward substance-related stimuli [14,15], while approach biases refer to automatic tendencies to reach out and approach substance-related cues [16]. The underlying theoretical basis is that of the dual-process model, which suggests that the repeated use of a substance would lead to increased automatic processing of the substance-related cue and, hence, increased automatic tendencies to approach substance-specific cues and corresponding inhibition of normal cognitive control processes. Tasks such as the visual probe task have been used for bias assessment and modification. In the conventional visual probe task, a pair of images is presented, in which one is substance related and the other is a neutral image. Following the presentation of the images, a small probe (or stimulus such as an arrow) would replace one of these images. Participants are required to indicate the position of the stimulus or the direction of the arrow as quickly as they could. When the visual probe task is used for bias modification, the task is as described, but the frequencies at which the probe or stimulus replace the drug or neutral image is altered [14].

There has been an extensive evaluation of bias modification for substance use disorders, and a recent meta-analysis study synthesized the overall effectiveness of bias modification [14]. Cristea et al [14] were only able to identify trials relating to alcohol or tobacco use disorders (25 trials). They reported that bias modification for both attentional and approach biases was moderately effective with an effect size of 0.60 (Hedge 0.60) [14]. However, a prior review found no association between the reduction in biases and other outcomes such as cravings, and the authors posited that this might be because more time is needed for a change in biases to be reflected regarding a change in symptomatology [14]. Nevertheless, a prior review demonstrated that bias modification could potentially reduce biases. Since the publication of Cristea et al's [14] meta-analyses, there have been other publications [17] highlighting the problems with the evidence synthesized, given that the evidence synthesis included both experimental laboratory studies and clinical studies. Wiers et al [17] reviewed the evidence by the nature of studies and reported small and robust effects of bias modification on treatment outcome when biases were retrained in a clinical setting for individuals with

alcohol use disorders. Since Cristea et al's meta-analysis [14], Zhang et al [18] conducted a systematic review and reported that attentional biases were present in opioid use and stimulant use disorders. Other studies have evaluated attention bias modification among substance-using individuals. Ziaee et al [19] recruited a sample of opioid users who were on methadone maintenance and found that attentional bias modification led to a reduction in attentional biases, as well as cravings to use, dosing of medications, and relapses. Wolf et al [20] recruited a sample of moderate and heavy cannabis-using students and found an attentional bias only for heavy users of cannabis and not moderate users; the authors did not find bias retraining to be effective. Mayer et al [21] undertook the first study evaluating the efficacy of bias modification for treatment-seeking individuals with cocaine use disorders. Like Wolf et al [20], Mayer et al [21] also reported that bias modification was not effective. Not all studies have examined treatment-seeking individuals in a clinical setting. Schoenmakers et al [22] administered attentional bias modification to 43 individuals with alcohol dependence and reported that bias modification was effective in increasing individuals' ability to disengage from alcohol cues. Manning et al [23] stressed the importance of evaluating a clinical sample that was in a detoxification and rehabilitation program because intervening during this period could capitalize on neural recovery. To date, Wiers et al [24], Eberl et al [25], and Manning et al [23] have examined bias modification among individuals admitted for medical-assisted detoxification and rehabilitation. While these studies have provided evidence for the effectiveness of bias modification during this critical period, the biases targeted were approach or avoidance biases and the evaluation was limited to individuals with alcohol disorders. To date, no study has evaluated attention bias modification in a non-Western sample among a group of substance-using individuals who are in treatment (medical-assisted detoxification or rehabilitation).

Advances in technologies in the last decade have transformed how bias modification interventions are delivered. An increase in the number of remote Web-based therapies has been attributed to the advances in electronic health (eHealth). eHealth technologies facilitate the delivery of low-cost psychotherapy, which is highly accessible and enables anonymity of use [26]. This has led to increasing research examining the effectiveness of Web-based interventions. Further advances in technologies coupled with increased ownership of mobile devices have resulted in a growing number of interventions that tap on mobile technologies. Mobile health (mHealth) technologies are increasingly being harnessed for the delivery of bias modification as mobile technologies allow for training to be conducted in diverse locations, thus, helping in the generalization of clinical benefits [27]. The use of mobile technologies enables the frequency of training to be increased, which may improve outcomes [27]. mHealth technologies have an advantage over existing Web-based version as they do not require individuals to be consistently connected to the internet to undertake the bias modification task. Zhang et al [28] in their review managed to identify 8 studies that have evaluated the potential and effectiveness of mHealth bias modification. Seven studies [29-35] reported that mHealth bias modification was effective; these studies were conducted among participants with

insomnia, alcohol, tobacco use, or social anxiety disorders. Only a single study reported mobile bias modification to be ineffective. Despite the evidence for effectiveness being inconclusive, Zhang et al's [28] prior review reported bias modification to be effective for addictive disorders such as alcohol and tobacco use disorders.

Rationale for This Study

To date, no study has evaluated bias modification in a substance-using, non-Western, treatment-seeking sample. In addition, while technologies like eHealth and mHealth have been widely utilized for the delivery of bias modification interventions, our prior review [28] of the published literature demonstrated that mobile technologies have only been evaluated among individuals with alcohol or tobacco use disorders. Hence, this proposed study aims to examine the feasibility of a mobile-based attention bias modification intervention among treatment-seeking individuals with alcohol or substance use disorders. If deemed feasible, this will guide further evaluative research investigating the efficacy of such a complex intervention.

Objectives

The primary aim of this study is to determine the feasibility of an attention bias modification mobile app for the reduction of attention biases to substance-related cues among individuals with addictive disorders. Feasibility is determined by the number of participants recruited, participants' adherence to the planned interventions up until the day of discharge, and the ability of the app to detect baseline biases and changes in biases. The secondary aim is to determine the acceptability of the intervention, which will be assessed through a questionnaire of users' perceptions.

Research Questions

1. Will the mobile attention bias modification intervention be feasible and acceptable among individuals with addictive disorders?
2. Is the developed mHealth app capable of detecting the changes in biases?

Methods

Study Setting and Study Design

This study will be conducted among individuals who are admitted for inpatient medication-assisted detoxification and rehabilitation at the National Addictions Management Service (NAMS), Institute of Mental Health Singapore. Notably, at NAMS, all patients are admitted voluntarily for treatment, which implies that patients are free to discharge should they be not willing to complete the detoxification or rehabilitation phase of the program. At any one time, a maximum of 30 patients could be accommodated in the ward environment. Patients are managed by an attending psychiatrist with a multidisciplinary team comprising addiction-trained counselors, nurses, and social workers. In the first week of the treatment program, patients would undergo medication-assisted detoxification. In the second week of their treatment program, patients would attend community meetings and group-based counseling. Individual

counseling will also be provided to patients. Only participants who have completed their detoxification phase (first week of their stay) will be recruited for this study as participants would be free from withdrawal symptoms. This is a feasibility study, where participants' attention biases will be assessed following the bias modification intervention. The study protocol has been approved by the National Healthcare Group's Domain Specific Research Board (May 2, 2018; Ethics Approval Reference Number: 2018/00316).

Recruitment

All participants will be recruited from the inpatient unit at the NAMS, Institute of Mental Health, Singapore. Participants will be informed of the study by their attending health care professionals on admission and will be approached by the study team on the first day of their rehabilitation phase. The study team will provide participants with further information about the study, and if participants agree to participate, they will complete the informed consent form.

Sample Size

Power computation has not been undertaken for this study as study design is that of a feasibility study. Considering the diversity of the addictive disorders included, the proposed sample size is 30 participants.

Eligibility Criteria

Inclusion and Exclusion Criteria

Participants will be eligible for the feasibility study if they meet the inclusion criteria presented in [Textbox 1](#).

Participants will not be eligible if they meet any of the exclusion criteria presented in [Textbox 2](#).

Participants with moderate to severe symptoms of comorbid psychiatric disorders are excluded from this feasibility study as there is a high likelihood that their comorbid psychiatric disorder will affect their attentional bias scores. Moreover, patients with other psychiatric disorders will usually be on other psychotropic medications. Zhang et al have highlighted that several pharmacological agents, such as those targeting dopaminergic, noradrenaline, glutaminergic, and serotonergic neurotransmissions, have an acute effect on attentional biases [36].

Intervention

Patients will be invited to participate in this study only upon the completion of their medical detoxification treatment. If they consent to participate, they will complete a set of baseline questionnaires including a demographic and clinical information questionnaire, the Addiction Severity Index (ASI)-Lite questionnaire, the Severity of Substance Dependence (SDS) questionnaire, and the Short-Form 12 (SF-12) questionnaire. In addition, participants are required to complete a visual analogue scale for craving before and after the completion of each session. [Table 1](#) provides an overview of the outcome measures that participants need to complete for each session. Participants will receive a 15-minute briefing on the use of the mobile app (by members of the study team who are familiar with the app) before the commencement of the assessment and intervention. Participants will be provided with tablets by the study team to use the mobile attention bias modification intervention.

Textbox 1. Inclusion criteria.

- Participants aged 21-65 years
- Participants diagnosed with a primary psychiatric disorder of alcohol dependence, opioid dependence, cannabis dependence, stimulant dependence, or polysubstance use disorder
- For participants diagnosed with polysubstance use disorder, the main substance of use must be alcohol, opioid, cannabis, or a stimulant
- Participants need to be able to read and write in English
- Participants need to be able to use a smartphone or a tablet device

Textbox 2.

Exclusion criteria

- Having a known history of cognitive impairment or dementia
- Having a history of seizures (apart from febrile seizures) or a prior history of withdrawal seizures
- Having a medical history of migraines (triggered by flashing lights)
- Having moderate to severe symptoms of comorbid psychiatric disorders (affective disorders, anxiety disorders, and psychotic disorders) based on clinical assessment

Table 1. An overview of the outcome measures that participants need to complete for each session.

Instrument	Aim	Day of rehabilitation				
		1	2	3	4	5 ^a
Baseline demographic and clinical information questionnaire	Baseline characteristic of participants	✓				
Addiction Severity Index questionnaire	Details about substance use	✓				
Severity of Substance Dependence questionnaire	Assessment of severity of psychological dependence	✓				
Short-Form 12	Baseline health status	✓				
Attention bias modification assessment task	Measurement of attentional biases	✓ ^b	✓	✓	✓	✓
Attention bias modification intervention task	Retraining of attentional biases	✓	✓	✓	✓	✓
Visual analogue scale for craving	Assessment of cravings	✓ ^c	✓ ^c	✓ ^c	✓ ^c	✓ ^c
Perspective questionnaire	Acceptability of intervention			✓		

^aParticipants will undertake a maximum of 5 sessions considering that the study will not be conducted on weekends.

^bThe attention bias modification assessment task will be completed twice on the first day: first assessment will provide information pertaining to the baseline attentional biases; second assessment will assess for the change in attentional biases following the first intervention.

^cStart and end of each session.

On the first day of their rehabilitation, participants will be required to complete a baseline attention bias assessment task and an attention bias modification task. They will be allowed to rest for 15 minutes before they complete a reassessment of their attention bias. Participants can rest for slightly longer on the first day, given that they are required to complete two tasks—an assessment and a modification task. On the subsequent days of their rehabilitation, they will complete the attention bias modification task and will be allowed 10 minutes of rest before retaking an attention bias assessment task. Participants will be required to complete the visual analogue scale for craving before and after the completion of each of the bias modification task. Participants who have completed 3 sessions will be asked to complete the app perception questionnaire. Participants are expected to undertake the intervention throughout their rehabilitation stay on the ward, except for weekends and public holidays. The intervention is not administered on these days due to the possibility of image-triggered cravings and the absence of a counselor to address the heightened cravings.

The mobile version of the visual probe task that participants will use adheres to the protocol of the original visual probe task [37]. In the attention bias assessment task, participants will be required to complete a total of 200 trials (with 10 set of images

being repeated 20 times). In each trial, participants will be presented with a fixation cross in the center of the screen for 500 ms. Subsequently, they will be presented with a set of two images for another 500 ms. In each set of images, one of the images will be a neutral image, which is closely related to that of the alcohol or drug image (eg, an image of a man drinking from a can of beer, which will be paired with an image of a man drinking from a soft drink can). Following the disappearance of the images, an asterisk will replace the position of one of the images (either on the right or on the left). Participants will be required to indicate a response by selecting the physical onscreen buttons as fast as they could. The next set of images will be presented once participants have indicated a response (by pressing the left or right button depending on where the probe is) or if the time of 2000 ms has lapsed (Figure 1). In the assessment phase, 50% of the time, the asterisk will replace the neutral image, and the rest 50% of the time, it will replace the alcohol or substance image. For the intervention or bias modification task, participants will be required to take the same task as that described. However, the asterisk will replace the position of the neutral image 100% of the time for the attentional bias to be retrained. Figure 1 provides an overview of the task that participants undertake on the smartphone or tablet device.

Figure 1. Overview of the task that participants undertake on the smartphone or tablet device.

Outcomes

The primary outcome feasibility is defined by the number of participants recruited and participants' adherence to the intervention. In our protocol, we have proposed a total recruitment sample size of 30 participants, and the study is considered feasible if we manage to recruit 25% of the invited number of participants (8 participants). We have proposed a 25% recruitment target for feasibility as we anticipate that there will be challenges to recruitment as the inpatient treatment program is a voluntary program (ie, patients could be discharged voluntarily from the program at any time) and that some patients would leave following the completion of their medical-assisted detoxification. In addition, 25% has been proposed as the target, due also, in part, to our strict inclusion and exclusion criteria. We have specifically mentioned that we will exclude participants with medical comorbidities such as seizures and migraines. To a large extent, most individuals with alcohol disorders often have a history of withdrawal seizures and, hence, they are not eligible for the study, thus, potentially affecting the overall recruitment. Furthermore, we have specifically mentioned that individuals with moderate to severe psychiatric comorbidities are not included. As other psychiatric conditions like depression or anxiety disorders are often comorbidities of substance use disorder, a large group of individuals cannot be recruited. The other criterion for feasibility is patients' adherence to the planned interventions, and we will consider the study to be feasible if all participants complete at least 60% of the planned interventions.

Attention bias will be computed using the mean reaction time that participants take to react to asterisks or probes that replace the neutral and alcohol or substance images in the assessment task. Attention bias is present if the mean reaction time taken by participants to react to probes that replace the neutral image is longer in comparison to that of alcohol or substance images. The underlying rationale is that an alcohol or substance image would preferentially draw one's attention, and the reaction time taken to react to asterisk or probes replacing the image is

naturally much faster. Attention bias, as measured by the assessment tasks, will be compared to determine if the interventions result in a reduction in overall biases (by comparing the final attention bias score with the baseline score). Cravings will be assessed using the single-item measure, the visual analogue scale [38], with scores ranging from 0 (no cravings) to 100 (extreme levels of cravings). The visual analogue scale is often used for the assessment of current cravings and urges mainly in terms of craving frequency and intensity [30]. There are inherent advantages to the use of the single-item visual analogue scale given that it is easy to administer [30], and in our case, it would also help reduce respondents' burden and risk of refusal, given the need for repeated measures. The scores on the visual analogue scales will be compared before and after the sessions and between sessions. If participants report increased cravings, they will be referred for counseling.

The secondary outcome acceptability will be assessed through a perception questionnaire, which consists of the following questions:

1. Prior to using the app, how confident are you in managing your addiction problems? (rated on a 5-point Likert scale)
2. How easy was it to use the app? (rated on a 5-point Likert scale and participants are asked to provide verbatim comments)
3. How interactive was the app? (rated on a 5-point Likert scale and participants are asked to provide verbatim comments)
4. Do you feel motivated to continue using the app? (rated on a 5-point Likert scale and participants are asked to provide verbatim comments)
5. Do the images in the app remind you of your substance use? (rated on a 5-point Likert scale)
6. After using the app, how confident are you in managing your addiction problem? (rated on a 5-point Likert scale).

The study is deemed acceptable if participants are willing to use the app daily; if at least 30% of participants rate ease of use,

interactivity, motivation, and reality (questions 2-5) positively (either very or extremely on the 5-point Likert scale); and if at least 30% of participants perceive a change in their confidence level after having received 3 sessions of the intervention task (questions 1 and 6). The app is also deemed acceptable by the absence of any severe adverse events (such as intense cravings leading to a premature discharge from the inpatient program).

Baseline demographic and clinical information will be collected from participants. This includes information about nationality, gender, marital status, race, religion, highest level of employment, housing conditions, current substance use, method of consumption of substance, quantity of substance consumed each time, frequency of use, previous treatment history, chronic diseases, (psychiatric or physical disorders), and current psychiatric medications. Furthermore, participants are required to complete a modified ASI-Lite, SDS, and SF-12 questionnaires.

The ASI-Lite collates information for the following domains: drug and alcohol use, medical, employment or school, legal, family, and social and psychiatric [39]. In our modified version, we have retained the drug and alcohol use questions. Participants will be asked about their alcohol and substance use in the last 30 days, last month, and their lifetime use. The SDS comprises 5 items, all of which are explicitly concerned with the psychological components of dependence [40]. The scale has been used to measure the degree of dependence among individuals using different types of substances [40]. The SF-12 has been widely used in the assessment of self-reported quality of life. It covers the 8 health domains as the original SF-36 [41].

Data Management and Monitoring

All participants will be allocated a subject number upon recruitment. No participant-related identifiers will be captured on the hard copy forms. The completed hard copy forms and questionnaires will be stored in secure, locked cabinets in a restricted area. The electronic data from the smartphone app will be automatically synchronized onto a secured, password-protected cloud database. The main investigator will back-up a copy of the electronic data records onto a local secured computer. The principal investigator and the research assistants will take the responsibility for coding the data from the hard copy forms. An independent coinvestigator will routinely check the data entry for reliability and quality. All records will be kept securely for at least 6 years after the completion of the study.

Planned Statistical Analyses

Data collated will be analyzed using SPSS version 22 (SPSS Inc, IL, USA). Baseline demographic information of subjects will be summarized using descriptive statistics, including means and SDs. Chi-square tests or Fisher's test will be considered to examine any differences in the baseline demographic characteristics among the different substance disorders. The presence of attentional biases will be determined based on the

mean reaction times taken to respond to the position of the probes that replace drug or neutral stimuli. In addition, statistical tests (analysis of variance) will be performed to determine whether there are statistically significant differences in the attentional bias scores across the sessions for participants. $P < .05$ will be considered statistically significant. Participants' perspectives and feedback will be analyzed qualitatively using a thematic analysis approach using NVivo version 10.0.

Adverse Events

Any adverse events that occur during the conduct of the feasibility study will be reported to the Domain Specific Research Board in accordance with the local institutional policy.

Dissemination Policies

We will publish our research in peer-reviewed journals and will also present the findings at regional and international conferences.

Patient and Public Involvement

Patients and public were not involved in planning for this protocol.

Results

This study was approved by the National Healthcare Group Domain Specific Research Board, with approval number (2018/00316). Results will be disseminated by means of conferences and publications. Currently, we are in the process of recruitment for this study.

Discussion

To the best of our knowledge, this is the first study to evaluate the feasibility and acceptability of a mobile attention bias modification intervention for individuals with substance use disorders such as cannabis opioid, stimulant, and alcohol disorders. The data pertaining to the feasibility and acceptability are undoubtedly crucial because they imply the potential use of mobile technologies in retraining attentional biases among inpatients who are admitted for medical-assisted detoxification and rehabilitation. Participants' feedback pertaining to the ease of use, interactivity, and motivation to continue using the app is crucial because it will determine whether a codesign approach might be warranted to design an app that is acceptable for participants and that participants themselves would be motivated to use. Apart from substance use disorders, increasing research has demonstrated the presence of attentional biases in behavioral disorders such as gambling and internet gaming disorders [42,43]. If deemed feasible, attention bias modification could potentially be applicable to behavioral disorders, and the use of mobile technologies would be most appropriate for low-resource settings [44]. Moreover, prior meta-analysis research has demonstrated that behavioral forms of addiction, such as internet addiction, are positively associated with alcohol abuse [45]. Hence, attentional biases appear to be a common therapeutic target in both these conditions.

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Authors' Contributions

MZ, JY, GS, DSSF, and HS conceived the study and were involved in study design and protocol development. MZ wrote the initial draft of the manuscript, which was revised by JY, GS, DSSF and HS.

Conflicts of Interest

None declared.

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Abbreviations

ASI: Addiction Severity Index

eHealth: electronic health

mHealth: mobile health

NAMS: National Addictions Management Service

SDS: Severity of Substance Dependence

SF-12: Short Form-12

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Original Paper

A Smartphone Attention Bias App for Individuals With Addictive Disorders: Feasibility and Acceptability Study

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Abstract

Background: Conventional psychology therapies are unable to address automatic biases that result in individuals relapsing into their substance use disorder. Advances in experimental psychology have led to a better understanding of attention and approach biases and methods to modify these biases. Several studies have demonstrated the effectiveness of bias modification among clinical cohorts. The advances in mobile health technologies have allowed remote delivery of these interventions. To date, there is a lack of studies examining bias modification in a substance-using non-Western sample.

Objective: This study was designed to determine the feasibility of an attention bias modification intervention and an attention bias modification smartphone app for the reduction of attention biases among treatment-seeking individuals. The secondary aim is to determine the acceptability of the intervention.

Methods: A feasibility study was conducted among inpatients who were in their rehabilitation phase at the National Addictions Management Service. Participants were to complete a set of baseline questionnaires, and on each day that they are in the study, undertake an attention bias assessment and modification task while completing a visual analogue scale to assess their craving. Feasibility was determined by the acceptance rate of participation and participants' adherence to the interventions. Acceptability was assessed by a perception questionnaire. Descriptive statistical analyses were performed using SPSS version 22. A thematic analysis approach was used in the qualitative synthesis of users' perceptions.

Results: Of the 40 participants invited to participate in the feasibility study, 10 declined, yielding an acceptance rate of 75%. Of the recruited participants, 6 participants were diagnosed with alcohol dependence; 17, with opioid dependence; 2, with cannabis dependence; and 5, with stimulant dependence. In addition, of the final 30 participants, 11 (37%) failed to complete all the planned interventions and 22 (73%) completed the perspective questionnaires; of these 22 participants, 100% rated the app as extremely and very easy, 77% rated it as extremely or very interactive, 54% rated it as extremely or very motivating, and 33% reported a change in their confidence levels.

Conclusions: Our results highlight the feasibility of recruiting participants to undertake attention bias modification interventions. Participants generally accept use of a mobile version of such an intervention. Nevertheless, our acceptability data indicate that there could be improvements in the existing app, and a participatory design approach might be helpful in its future conceptualization.

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KEYWORDS

attention bias; cognitive bias; psychiatry; substance abuse; alcohol abuse; opioid abuse; cannabis abuse; addiction; digital health; mhealth

Introduction

According to the United Nations Office on Drugs and Crime, substances like cannabis, opioids, and stimulants are commonly abused [1]. Substance abuse and substance dependence are associated with significant morbidity and mortality. An estimated 190,000 deaths were attributed to substance use in 2015 [1]. The recent statistics from the World Health Organization also highlighted the high prevalence of alcohol use [2], particularly in higher-income countries. In Singapore, the most recent study found that the prevalence of alcohol use disorders was 0.19% and 1.40% among women and men, respectively, and the prevalence of drug use disorders was 0.07% and 0.28% among women and men [3]. Given the prevalence of these disorders, there is clearly a need for effective interventions. Conventionally, treatment and interventions of addictive disorders involve a combination of medications and psychological therapies. For psychological therapies to help individuals achieve abstinence, frequently used therapies include cognitive behavioral therapy, cue-exposure therapy, contingency management, and mindfulness-based relapse prevention. Cognitive behavioral therapy has had an immediate effect size of 0.45 [4]; 40%-50% of the individuals relapsed within a year and 70% relapsed within 3 years [4]. This may be because such therapies mainly address the cognitive control processes, but fail to address the underlying unconscious automatic processes that contribute to an individual's lapse and relapse.

Among individuals with addictive disorders, there are two common biases: attentional bias and approach bias. Attentional biases are automatic, unconscious processes that result in the preferential allocation of attention toward substance-related stimuli [5,6], and approach biases are the automated tendencies for individuals to reach out and approach substance stimuli [7]. These biases have been well-studied with a theoretical underpinning based on the dual-process model, which posits that the chronic administration of the substance leads to enhanced automatic processing of the substance-related cue, with a corresponding inhibition in the normal cognitive control processes [8]. Interventions to modify bias have been extensively evaluated. Ziaee et al [9] reported that the introduction of bias modification reduced attentional biases among individuals maintained on methadone as well as their cravings to use, the dose of methadone, and the number of relapses. Several other studies that have involved participants undergoing detoxification on an addiction treatment unit [10-12] also found that bias modification was effective in reducing attentional biases. More recently, Cristea et al [13] highlighted that bias modification interventions were effective in modifying both attentional and approach biases in individuals with alcohol and tobacco use issues [13].

Although conventional bias modification interventions are confined to a laboratory setting, advances in technologies now enable remote delivery of such interventions. A recent review [14] showed that seven of eight studies reported the effectiveness

of a mobile-based cognitive bias modification intervention. These studies were targeting conditions such as insomnia, social anxiety, tobacco use, and alcohol use disorders [14]. Another recent review [15] explored the utilization of technology for retraining of attentional biases in individuals with tobacco use disorder and reported that mobile delivery of bias retraining was effective. Subsequently, the effectiveness of a mobile health approach for methamphetamine use disorder [16] was evaluated, and improvements in cognitive impairments and impulsive control, but not attentional biases, were reported [16].

To date, no study has evaluated bias modification in a substance-using, treatment-seeking, non-Western cohort. Although technologies have been used for the delivery of remote bias modification intervention, the evaluation was limited to alcohol and tobacco disorders and stimulant disorders. Although a previous study reported negative findings in this regard [16], future research should seek to evaluate the effectiveness of mobile apps for modification of attentional biases, given that the training task used in that study was a newly developed task and differs significantly from conventional bias assessment and modification paradigms. In addition, according to the recommendations of the National Institute of Health Research [17], a feasibility study is crucial, as such a study seeks to determine primarily whether a study could be conducted. This is pertinent in our case, as there are no prior studies that examined bias assessment and retraining in a treatment-seeking, non-Western cohort. In addition, feasibility studies are typically limited to the evaluation of important parameters that will be crucial in the design of the main study and do not routinely evaluate the main outcome of interest [17]. Typically, a feasibility study is conducted first, before a pilot, as a pilot study. It is essentially a version of the main study that is run on a small scale to test whether the components of the main study can all work together [17].

Our study aimed to examine the feasibility of a mobile-based attention bias modification intervention among treatment-seeking individuals with alcohol or substance use disorders. If deemed feasible, this will guide further pilot and definitive randomized trials investigating the effectiveness of the mobile intervention. The objectives of the study were to determine (1) the feasibility of participants undertaking a mobile attention bias modification intervention, (2) the feasibility of the mobile intervention for reducing attention biases, and (3) the acceptability of the intervention. The specific research questions were as follows: (1) Will the mobile attention bias modification intervention be feasible and acceptable among individuals with addictive disorders? (2) Is the developed mobile intervention capable of assessing for and reducing attention biases?

Methods

Study Setting and Design

The target population comprised individuals admitted for inpatient medication-assisted detoxification and rehabilitation (total duration of 14 days, with 7 days in detoxification and 7 days in rehabilitation) at the National Addictions Management Service (NAMS), Institute of Mental Health, Singapore. At NAMS, the treatment is entirely voluntarily, which implies that patients and participants could self-discharge at any time. The NAMS inpatient unit has approximately 22 beds, and most of these beds are occupied by patients who are undergoing detoxification. Patients who had completed their detoxification treatment and were in the rehabilitation phase of the program were recruited. The study design is that of a feasibility study, where participants are recruited by means of convenience sampling.

Ethics Approval

This study was approved by the National Healthcare Group's Domain Specific Research Board (reference number: 2018/00316) on May 2, 2018.

Recruitment and Sample Size

Patients were recruited on completion of their inpatient detoxification treatment (7 days) and at the start of day 1 of their rehabilitation treatment. Potential participants were identified by their primary psychiatrist, provided with further information by the study team, and given time to consider participation. Participants who agreed to participate completed an informed consent form, which was signed in the presence of an impartial witness, in accordance with the Human and Biomedical Act regulations. As the study was designed to assess feasibility and acceptability, power computation was not performed. Given the diversity of the disorders, the minimum recruitment target was 30 participants and the maximum was 34 participants.

Inclusion and Exclusion Criteria

Patients were included in the study if they were aged between 21 and 65 years; diagnosed with a primary psychiatric disorder of alcohol, opioid, cannabis, stimulants, or polysubstance dependence; diagnosed with polysubstance dependence, with alcohol, opioid, cannabis, or stimulants as the main substance of use; able to read and write in English; and capable of using a smartphone or tablet device.

Patients were excluded from the study if they had a known history of cognitive impairment or dementia, a history of seizures or a prior history of withdrawal seizures, a history of migraines triggered by flashing lights, and moderate to severe comorbid psychiatric disorders based on clinical assessment.

Measures

Baseline demographic and clinical information was collected from the participants. This included information about nationality, gender, marital status, race, religion, highest level of education, housing conditions, current substance use, method of consumption of substance, quantity of substance consumed

each time, frequency of use, previous treatment history, chronic diseases (psychiatric or physical disorders), and current psychiatric medications. Participants also completed a modified Addiction Severity Index (ASI)-Lite, Severity of Drug Dependence Scale (SDS), and the Short Form (SF-12) questionnaires.

The ASI-Lite collated information for the following domains: drug and alcohol use, medical, employment/school, legal, family, and social and psychiatric aspects [18]. In our modified version, we retained only the drug and alcohol use questions. Participants were asked about their alcohol and substance use in the last 30 days, last month, and lifetime. Participants were asked whether they had used alcohol, nicotine, heroin, amphetamine-type stimulants, cannabis, other opioids, benzodiazepines and other sedatives, barbiturates, ketamine, cocaine, inhalants, hallucinogens, and new psychoactive substances. The SDS comprised five items, all of which are explicitly concerned with the psychological components of dependence [19]. A previous study [20] reported that the total severity score is highly positively correlated with the severity of dependence, as measured by the Diagnostic and Statistical Manual of Mental Disorders-IV. The SF-12 has been widely used in the assessment of the self-reported quality of life. It only covers the eight health domains from the original SF-36 [21] and has demonstrated good content and criterion validity without any evidence of any systematic biases [22].

Intervention

Following completion of enrollment, participants were required to complete a visual-analogue scale for craving before and after the completion of each session. Members of the study team familiar with the app gave participants a 15-minute briefing on the use of the mobile app before the commencement of the assessment and intervention. The study team provided participants tablets to use the mobile attention bias modification intervention.

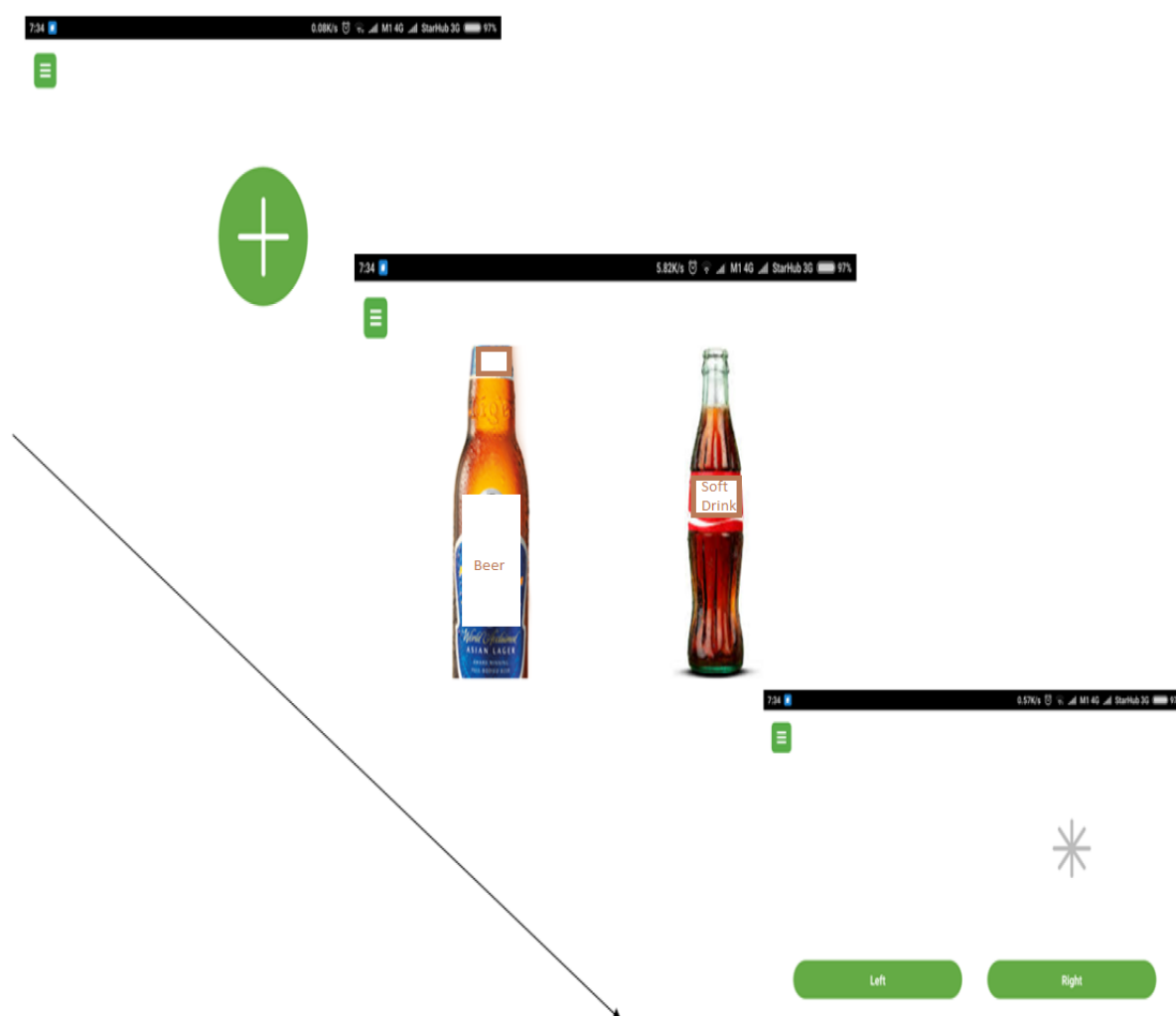
On day 1 of the intervention, participants were required to complete both a baseline attention bias assessment task and an attention bias modification task. They could rest for 15 minutes before they completed a reassessment of their attention bias. On the subsequent days (days 2-7) of their rehabilitation, they completed the attention bias modification task and were allowed 10 minutes of rest before retaking an attention bias assessment task. Participants were required to complete the visual-analogue scale for craving before and after completion of each bias modification task. Participants who completed three sessions were asked to complete the app perception questionnaire. Participants were expected to undertake the intervention on each day of their rehabilitation stay, except for weekends and public holidays. Participants were allowed to undertake the intervention a maximum of five times in total.

The mobile version of the visual probe task was the same as the original visual probe task. In the attention bias assessment task, participants were required to complete a total of 200 trials (with 10 sets of images repeated 20 times). In each trial, participants were presented with a fixation cross in the center of the screen for 500 milliseconds. Subsequently, they were presented with a set of two images for another 500 milliseconds. In each set of

images, one of the images was neutral but closely related to the image of the alcohol or drug (for example, an image of a man drinking from a can of beer, which was paired with an image of a man drinking from a soft drink can). Following the disappearance of the images, an asterisk replaced the position of one of the images (either on the right or left). The participants were required to indicate where the position of the asterisk was by selecting the physical on-screen buttons as fast as they could. The next set of images was presented once the participant has indicated a response (by pressing the left or right button, depending on where the asterisk was) or if the time of 2000

milliseconds had lapsed (Figure 1). In the assessment phase, 50% of the time, the asterisk replaced the neutral image and 50% of the time, the asterisk replaced the alcohol or substance image. For the intervention or bias modification task, the participant was required to take the same task as that described, but the asterisk replaced the position of the neutral image 100% of the time, enabling retraining of attentional bias. The substance images presented to participants are either a picture of the drugs, pictures of individuals using substances, or paraphernalia used for the administration of the drugs.

Figure 1. An overview of the task that participants undertake on the smartphone/tablet device.



Outcomes

Feasibility was the primary outcome and defined by the number of participants recruited and participants' adherence to the intervention. The study was considered feasible if 25% of the recruitment target (of 30 participants) was met and 60% of the patients managed to adhere to the planned interventions (ie,

completed all the planned interventions up until day 5 of their program).

The secondary outcome of acceptability was assessed through a perception questionnaire, which included the following questions:

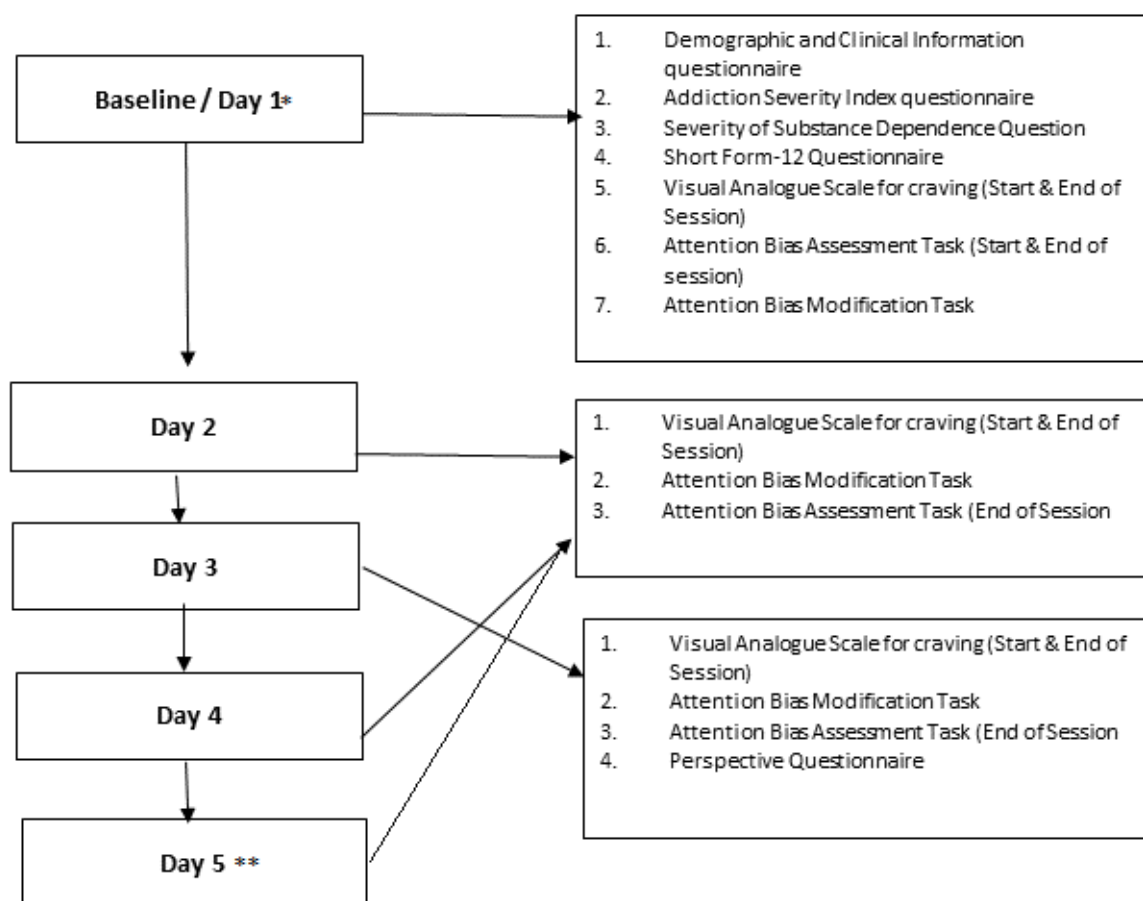
1. Prior to using the app, how confident are you in managing your addiction problems? (5-point Likert scale, ranging from not at all to extremely)
2. How easy was it to use the app? (5-point Likert scale, ranging from not at all to extremely)
3. How interactive was the app? (5-point Likert scale, ranging from not at all to extremely)
4. Do you feel motivated to continue using the app? (5-point Likert scale, ranging from not at all to extremely)
5. Do the images in the app remind you of your substance use? (5-point Likert scale ranging from not at all to extremely)
6. After using the app, how confident are you in managing your addiction problem? (5-point Likert scale, ranging from not at all to extremely)

For questions 2, 3, and 4, respondents were also asked to provide free-text comments.

Acceptability was predefined as a willingness to use the app daily, and if at least 30% of the participants rated ease of use, interactivity, motivation, and reality (questions 2, 3, 4, and 5) positively (either very or extremely on the 5-point Likert scale), and if at least 30% of the participants perceived there to be a change in their confidence level after receiving three sessions of the intervention task (questions 1 and 6). The app was also deemed acceptable by the absence of any severe adverse events (such as intense cravings leading to premature discharge from the inpatient program).

Figure 2 provides an overview of the task that participants undertake each day they are in the study.

Figure 2. Overview of the outcomes measures that participants need to complete for each session. *Attention bias modification assessment task will be completed twice on the first day. The first assessment will provide information pertaining to the baseline attentional biases. The second assessment will assess for the change in attentional biases following the first intervention. **Participants will undertake a maximum of 5 sessions, taking into consideration that the study will not be conducted on weekends.



Data Management and Monitoring

All participants were allocated a subject number upon recruitment, and no participant-related identifiers were captured on the hard-copy forms. These forms, together with the questionnaires, were stored in secured, locked cabinets in a restricted area. The electronic data from the smartphone app was automatically synchronized onto a secured,

password-protected cloud database. The main investigator backed-up a copy of the electronic data records onto a local secured computer daily. The principal investigator and the research assistants took the responsibility of coding the data from the hard-copy forms. An independent coinvestigator routinely checked the data entry for accuracy, ensuring that the translation of scores from the hard-copy forms to the electronic

form was free of errors. All records will be kept securely for at least 6 years after completion of the study.

Statistical Analyses

Data collated was analyzed using SPSS (version 22. IBM Corp, Armonk, NY). Baseline demographic information of the subjects was summarized using descriptive statistics, including means and SD. The presence of attentional biases was determined based on the mean reaction times taken to respond to the position of the probes that replace drug or neutral stimuli. The formula used for the computation of attentional biases was $(\sum T_1/n_1) - (\sum T_0/n_0)$, where T_1 refers to the time for probes that replaced the neutral stimulus, n_1 refers to the number of trials for probes that replaced the neutral stimulus, T_0 refers to the time for probes that replaced the substance stimulus, and N_0 refers to the number of trials for probes that replaced the substance stimulus.

Qualitative Analysis of Acceptability Data

Patients' perspective and feedback were collated by means of the perspective questions. Two separate independent researchers coded their verbatim, handwritten comments using NVivo, version 12.0 (QSR International, London, United Kingdom). Similar codes were grouped together and further analyzed, giving rise to higher-order themes.

Results

Feasibility of Recruitment and Adherence

Of the 40 participants invited to participate in the feasibility study, 10 declined, yielding an acceptance rate of 75%. Of the recruited participants, 6 participants were diagnosed with alcohol dependence; 17, with opioid dependence; 2, with cannabis dependence; and 5, with stimulant dependence. In addition, 11 participants of the 30 participants failed to complete all the planned interventions. The adherence rate was thus 63%. For 10 participants, discontinuation was linked with them electing for premature discharge from the ward, and another participant withdrew from the study after the initial intervention. [Table 1](#)

provides an overview of the baseline demographic characteristics of the 30 participants recruited.

The mean age of the participants with alcohol and opioid dependence was 43.7 (SD 11.6) years and 47.9 (SD 11.8) years, respectively, and that for participants with stimulant dependence and cannabis dependence was 37.6 (SD 7.0) and 58.0 (SD 1.4), respectively. Most of the participants were Singaporean (90%), and most were of male gender (86%). In addition, 53% had a secondary school education, 76% were unemployed, and 20% of the participants reported being homeless. Furthermore, 50% of the participants with alcohol dependence and 50% of the participants with cannabis dependence had comorbid medical conditions. Moreover, 60% of the participants with stimulant dependence reported having an underlying psychiatric disorder. Participants with alcohol dependence had a mean score of 11.2 (SD 1.9) on the severity of substance dependence questionnaire; those with opioid dependence, stimulant dependence, and cannabis dependence had mean scores of 11.7 (SD 2.2), 9.0 (SD 5.7), and 8.8 (SD 4.5), respectively. These scores demonstrated that participants sampled had a psychological dependence on the substances they were using. The physical health and mental health composite scores were lower for individuals with alcohol use disorders as compared to those with the other disorders.

[Table 2](#) provides the mean attention bias scores for each participant across the trials. Based on the protocol, participants were expected to complete a total of five training sessions. However, not all participants have completed a total of five sessions, as some participants had a public holiday during their stay. Of the 30 participants, 14 participants had positive attentional biases at baseline, whereas the other 16 participants did not have any underlying baseline attentional biases. For those with baseline attentional biases, there was a general decrease in the attention bias scores from baseline to the end of the planned intervention trials. The changes in the scores ranged from 12.0 to 409.5 milliseconds, comparing the final attention bias scores (upon the completion of the intervention) with the baseline scores (at the start of the intervention).

Table 1. Baseline demographic characteristics of participants (n=30).

Demographic characteristics	Alcohol dependence (n=6)	Opioid dependence (n=17)	Cannabis dependence (n=2)	Stimulant dependence (n=5)
Age (years), mean (SD)	43.7 (11.64)	47.9 (11.8)	58.0 (1.4)	37.6 (7.0)
Nationality, n (%)				
Singaporean	4 (66.7)	16 (94.1)	2 (100)	5 (100)
Others	2 (33.3)	1 (5.9)	0 (0)	0 (0)
Gender, n (%)				
Male	4 (66.7)	15 (88.2)	2 (100)	5 (100)
Female	2 (33.3)	2 (11.8)	0 (0)	0 (0)
Race, n (%)				
Chinese	2 (33.3)	2 (13.3)	0 (0)	3 (60.0)
Malay	1 (16.7)	11 (64.7)	0 (0)	0 (0)
Indian	3 (50.0)	3 (17.6)	1 (50.0)	2 (40.0)
Others	0 (0)	1 (5.9)	1 (50.0)	0 (0)
Religion, n (%)				
Christianity	2 (33.3)	4 (23.5)	0 (0)	2 (40)
Hinduism	1 (16.7)	0 (0)	0 (0)	2 (40)
Muslim	2 (33.3)	12 (70.6)	2 (100)	0 (0)
Others	1 (16.7)	1 (5.9)	0 (0)	1 (20)
Education, n (%)				
Primary education	2 (33.3)	3 (17.6)	1 (50.0)	1 (20.0)
Secondary education	2 (33.3)	11 (64.7)	1 (50.0)	2 (40.0)
Junior college/polytechnic/technical studies	1 (16.7)	3 (17.6)	0 (0)	1 (20.0)
Undergraduate studies	1 (16.7)	0 (0)	0 (0)	1 (20.0)
Employment, n (%)				
Unemployed	6 (100)	12 (70.6)	1 (50.00)	4 (80.0)
Part-time employment	0 (0)	1 (5.9)	1 (50.0)	1 (20.0)
Full-time employment	0 (0)	4 (23.5)	0 (0)	0 (0)
Housing, n (%)				
Homeless	1 (16.7)	3 (17.6)	0 (0)	2 (40.0)
1 room	3 (50.0)	5 (29.4)	0 (0)	0 (0)
2 rooms	0 (0)	2 (11.8)	0 (0)	0 (0)
3 rooms	1 (16.7)	1 (5.9)	0 (0)	1 (20)
4 rooms	1 (16.7)	3 (17.6)	1 (50.0)	2 (40.0)
5 rooms	0 (0)	2 (11.8)	0 (0)	0 (0)
Others	0 (0)	1 (5.9)	1 (50.0)	0 (0)
Presence of other chronic diseases, n (%)	3 (50.0)	7 (41.2)	1 (50.0)	1 (20.0)
Presence of psychiatric disorder, n (%)	1 (16.7)	0 (0)	0 (0)	2 (40)
Severity of Substance Dependence scores, mean (SD)	11.2 (1.9)	11.7 (2.2)	9.0 (5.7)	8.8 (4.5)
Short Form-12 questionnaire scores, mean (SD)				
Physical health composite scores	40.5 (24.5)	54.7 (21.6)	82.0 (15.6)	70.2 (21.2)
Mental health composite scores	29.3 (11.1)	41.0 (17.3)	52.0 (0)	39.2 (24.3)
Total scores	33.7 (9.2)	46.5 (16.3)	64.5 (6.4)	51.4 (15.2)

Table 2. Change in attentional bias scores.

Parti- pant	Drug	Baseline		Session 1		Session 2		Session 3		Session 4		Session 5		Overall change in atten- tional bias
		Atten- tional bias	Task ra- tio (neu- tral: drug)	Atten- tional bias	Task ra- tio (neu- tral: drug)	Atten- tional bias	Task ra- tio (neu- tral: drug)	Atten- tional bias	Task ra- tio (neu- tral: drug)	Atten- tional bias	Task ra- tio (neu- tral: drug)	Atten- tional bias	Task ra- tio (neu- tral: drug)	
1	Stimulants	30.3	96:100	70.6	99:101	36.3	98:102	9.3	98:102	-23.6	96:98	13.3	99:99	17
2 ^a	Stimulants	-22.4	103:97	-23.4	97:103	-11.7	95:105	N/A ^b	N/A	N/A	N/A	N/A	N/A	10.7 (in- creased)
3	Stimulants	6.7	100:100	-3.6	98:101	-28.9	99:99	-11.3	100:99	4.1	100:99	-7.3	100:99	14
4 ^c	Opioid	32.1	96:93	28.7	99:100	12.2	99:100	31.2	100:99	20.1	100:99	N/A	N/A	12
5 ^c	Alcohol	91.2	97:98	-23.3	100:99	-37.4	100:99	-5.3	99:100	-33.2	99:100	N/A	N/A	124.4
6 ^c	Opioid	98.9	28:116	33.4	60:46:00	14.5	71:66	-9.7	88:86	-31.5	86:84	N/A	N/A	130.4
7	Stimulants	-30.5	100:100	-13.5	100:99	-23.4	98:99	-27.7	100:99	-28.2	98:99	-7.6	96:99	22.9 (in- creased)
8 ^a	Opioids	58.7	36:56:00	85.1	40:57:00	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	26.4 (in- creased)
9 ^a	Opioids	25.8	97:97	13.5	96:98	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	12.3
10	Cannabis	-9.9	97:99	-20.7	60:40:00	-54.6	93:90	-14.1	96:95	-22.9	99:100	-48.4	100:99	38.5
11	Opioids	-30.9	33:66	2.4	97:97	-15.4	99:99	-7.4	97:99	14.2	99:99	7.3	98:99	38.2 (in- creased)
12 ^a	Opioids	0.7	99:97	34.8	100:99	-15.3	98:99	-52.4	100:98	N/A	N/A	N/A	N/A	53.1
13	Alcohol ^d	-20.9	99:98	-12.3	100:98	N/A	N/A	N/A	N/A	-75.8	90:92	-48.6	99:100	27.7
14 ^a	Alcohol	397.7	26:94	44.2	97:98	45.3	99:99	-32.0	98:100	-11.7	99:100			409.4
15	Cannabis	-7.7	100:96	-40.5	100:99	8.6	99:100	-33.6	99:99	-31.8	99:100	-50.3	100:99	42.6
16 ^a	Opioids	-27.4	93:96	N/A ^d	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
17	Opioids	-42.5	49:49:00	-64.8	75:71	63.4	63:61	8.9	73:78	-15.5	78:82	26.7	96:92	69.2 (in- creased)
18	Opioids	27.9	92:92	-17.8	99:96	3.2	100:99	-22.6	97:97	-104.6	99:99	-9.2	97:95	37.1
19 ^a	Opioids	3.8	99:96	35.1	99:98	13.7	99:98	32.4	100:98	N/A	N/A	N/A	N/A	28.6 (in- creased)
20	Opioids	10.1	99:98	9.4	100:98	105.2	99:98	54.1	100:99	-1.7	100:99	20.3	99:100	10.2 (in- creased)
21	Alcohol	224.5	79:54:00	61.5	98:97	73.3	99:100	176.7	94:97	130.3	98:100	107	99:97	117.4
22	Opioids	-52.9	100:99	10.9	99:100	5.6	98:98	39.1	99:99	36.5	98:100	76.6	99:100	129.6 (in- creased)
23	Opioids	-36.4	96:97	18	95:96	45	98:97	74.8	97:97	35.9	94:96	41.3	100:97	77.7 (in- creased)
24	Opioids	-16.9	97:97	45.2	99:98	1.49	100:99	3.8	99:100	33.9	99:100	N/A	N/A	50.8 (in- creased)
26 ^a	Opioids	-77.1	84:79	-82.5	92:91	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	5.4
27	Stimulants	-15.2	100:100	-11.6	98:100	10.1	98:100	-27.0	99:97	-25.7	100:98	-1.6	98:100	13.6 (in- creased)
28	Alcohol	-33.3	99:100	-29.4	99:98	-48.3	99:100	-10.9	99:100	-15.6	99:100	-11.6	100:99	21.8 (in- creased)

Participant	Drug	Baseline		Session 1		Session 2		Session 3		Session 4		Session 5		Overall change in attentional bias
		Attentional bias	Task ratio (neutral: drug)	Attentional bias	Task ratio (neutral: drug)	Attentional bias	Task ratio (neutral: drug)	Attentional bias	Task ratio (neutral: drug)	Attentional bias	Task ratio (neutral: drug)	Attentional bias	Task ratio (neutral: drug)	
29 ^a	Alcohol	-41.4	98:100	-18.0	99:99	20.6	99:99	28.2	99:100	N/A	N/A	N/A	N/A	69.6 (increased)
30	Opioids	1.3	96:94	38.6	98:93	7.9	98:95	11.5	98:91	13	98:98	-8.9	99:98	10.2
31	Opioids	-38.4	88:62	-282.7	96:33:00	-166.4	96:03:00	-190.1	97:03:00	N/A	N/A	N/A	N/A	151.6

^aParticipants did not complete the study, as they left the voluntary program.

^bN/A: Not available.

^cThere was a holiday during the participant's stay, and hence, the maximum number of sessions completed was four.

^dDue to a technical issue, participant 13 was not administered an assessment task following the second intervention, and the participant took another intervention task instead. Attentional bias assessment was performed only after the fourth session.

Acceptability of the Intervention

Of the 30 participants, 22 (73%) completed the perspective questionnaires. All the participants sampled rated the app as at least very easy (10/22 participants) or extremely easy (11/22 participants) to use, with one participant describing it as “like a primary school application” [Participant 1]. Participants also commented on the adequacy of the provided instructions:

Easy to follow instructions and exercise. [Participant 3]

First of all you give me instructions how to press. [Participant 22]

Other participants felt that the app was easy to use due to the simplicity of the task:

No need to take time to think, just look at the photos and press either one of them. [Participant 6]

*Just to follow the asterisk * star.* [Participant 15]

Just need to follow the stars. [Participant 24]

Participants commented on the ease of responding to the task:

Only 2 options – left or right that's why it is easy. [Participant 4]

Just press only. [Participant 10]

Participants also felt that the task could be undertaken by a diverse group of participants

But both young and old adults would be able to. [Participant 7]

Very simple and easy to be administered to subjects at almost any level of intelligence and age. [Participant 3]

With regard to interactivity, eight participants rated the app as extremely interactive, nine rated it as very interactive, and five rated it as moderately interactive. Participants commented that the application was “like playing the game” [Participant 4] and that the app “becomes more engaging” [Participant 3] over time.

With respect to motivation, there was a range of views: Eight participants reported being extremely motivated, four participants reported being very motivated, five participants reported being moderately motivated, four participants reported

being slightly motivated, and one participant reported not being at all motivated. Participants who were motivated shared that the app helped them “pass time” [Participant 1] and that it was “just like playing game” [Participant 4]. Other participants were motivated, as they felt that the app “makes me feel better” [Participant 21] and could “help me with my treatment” [Participant 29]. Some participants who indicated that they were motivated in using the app highlighted possible reasons:

Continually using on a daily basis will become repetitive and boring. [Participant 3]

It is a repetitive task and some may find it boring to continue using it, unlike a game which really interacts with the user. [Participant 5]

If I concentrate, if I do this all the way, boring. [Participant 10]

The participant who was not at all motivated commented that he/she finds that the app “doesn't help with my addiction problem” (Participant 22).

There was a range of responses to the question concerning whether the images reminded the participants of their drug use: 5 participants responded very, 4 responded moderately, 3 responded slightly, and 10 responded not at all. With regard to participants' confidence in managing their underlying addiction problem, 54% (12 participants) reported no change in their confidence level before and after using the app, and 10 participants reported a change in their confidence level, with 8 participants reporting a positive change.

All participants were invited to provide any additional feedback they had, and these were mainly related to the need to concentrate on the task:

Put your mind on it, follow the star, it would not go wrong. [Participant 14]

Must be alert. [Participant 23]

It requires your full attention because the switch between the image and the asterisk is very fast so I have to be really focused. [Participant 5]

Discussion

Principal Findings

The results from our study answered our intended research questions. In the published protocol [23], the study was proposed to be feasible if 25% invited agreed to participate and 60% of the recruited patients adhered to the planned intervention. Our results demonstrated the feasibility of the study in terms of participation and adherence. A 25% recruitment rate was necessary because of the strict inclusion and exclusion criteria. Participation rates are expected to be lower, as individuals with a prior history of withdrawal seizures or any prior history of diagnosed seizures and individuals with moderate to severe psychiatric conditions (as assessed clinically) are excluded. The acceptance rates in our study are higher potentially due to the diversity of substance disorders considered and because most of the participants who sought help were patients with opioid dependence who did not have a prior history of withdrawal seizures, as withdrawal seizures are not common in opioid withdrawal. It is also important to recognize that our inpatient detoxification and rehabilitation program are entirely voluntary, and therefore, individuals are free to request discharge should they not be motivated to stay on. Despite the nature of our program, the adherence rate for this study was not affected. One of the other objectives of the feasibility study was to determine if the mobile attention bias modification intervention could assess and modify attentional biases. We found that the mobile intervention was capable of reducing attentional biases in most of the participants, although there were individuals who did not present with baseline biases.

In the protocol, acceptability is defined as the willingness to use the app daily, if at least 30% of the participants rate the ease of use, interactivity, and motivation positively and if at least 30% of the participants perceived a change in their confidence in managing their addictive disorders after receiving three intervention tasks. Except for one participant who withdrew from the study, the remaining participants were amenable to using the app daily (except for those who decided to leave the ward prematurely and hence did not complete the planned interventions). All these individuals decided to leave prematurely for reasons not related to the study, and there were no adverse outcomes reported during the course of the study. In addition, 100% of the participants rated the app to be either very easy or extremely easy to use, which exceeded our projection of 30%. Moreover, 77% of the participants rated the app as very or extremely interactive and 54% reported being very or extremely motivated to use the app, which exceeded our projection of 30%. Finally, 36% of the participants reported a change in their confidence in managing their addictive disorders, which is congruent with our projection.

In the qualitative feedback, 10 participants reported that the images included did not remind them of their substance use. The images used in the existing app might be different from the images of the substances that they have previously used and thus did not manage to capture their attention. This is in line with a previous commentary [24], which reported that one of the key factors leading to the poor reliability of the visual probe

task is that of the nature of the stimulus used. That study [24] highlighted the importance of personalization of the stimulus presented to the participants, as it is postulated that stimulus that is relevant and identifiable to the participant would increase the baseline attentional bias score and provide evidence of greater change in the magnitude of attentional biases. Most of the images included in the existing mobile app were extracted from the internet through the United States Drug Enforcement Agency media library. Some of the images were extracted from Singapore's Central Narcotics Bureau's website. It might be possible that the images included do not approximate and are not realistic enough for participants. In our image set for opioids, we showed images of oxycodone and morphine pills, but in Singapore, these are not commonly abused. In addition, in our image set for cannabis, we showed images of spice, which is also not commonly abused in Singapore.

There are clearly several research implications arising from this study. The qualitative feedback from the acceptability part of the study suggests that it is important for us to consider involving patients in improving the app, to allow for personalization of the images and other functionalities of the app. Participatory research methods could be considered, in particular, for focus groups and codesign workshops. In their review, Zhang et al [25] reported that participatory research design methods have been widely applied in both medicine and psychiatry. For psychiatry, these methods have been applied mainly for perinatal depression, dementia, self-harm, and general and youth mental health issues. Their previous review [14] of attention bias and cognitive bias apps in the published literature and the commercial stores revealed that there is a disconnect between academics and developers. Through participatory design, there is potential to enhance the existing app by involving patients and health care professionals in a joint codesign in order to create an app that is more feasible; acceptable; and capable of detecting and modifying biases in opioid, cannabis, stimulants, and alcohol disorders. Our results might also be affected by the images that we chose to include in the app. In the next iteration of this intervention, we will recommend that participants rate the relevance of the images first, before embarking on the actual intervention. Our study also showed that some participants who are in the rehabilitation phase might not present with baseline attentional biases. Thus, this suggests that future research on such an intervention among individuals who are undergoing rehabilitation ought to consider assessing baseline attentional biases first; otherwise, the intervention would be futile in modifying biases.

Conclusions

To our knowledge, our study is the first study to recruit an Asian cohort of participants with substance use disorders and examine the feasibility and acceptability of the mobile bias intervention. Our results highlight the feasibility to recruit participants to undertake attention bias modification interventions and that participants generally accept a mobile version of such an intervention. Nevertheless, our acceptability data highlight that there could be improvements in the existing app. It is important for future research to take into consideration our findings and adopt a participatory design approach when refining the

conventional visual probe task to cater to the needs of the participants.

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MZ, JY, SA, ZM, GS, DF, and HE jointly conceptualized the study. MZ, SA, and ZM were involved in data collation. MZ and JY coded and analyzed the initial data. MZ, JY, SA, ZM, GS, DF, and HE reviewed the final dataset. MZ wrote up the first draft of the manuscript, with guidance from DF and HE. All authors read and approved of the manuscript prior to submission.

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Conflicts of Interest

None declared.

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Abbreviations

ASI: Addiction Severity Index

NAMS: National Addictions Management Service

SDS: Severity of Drug Dependence Scale

SF: Short Form

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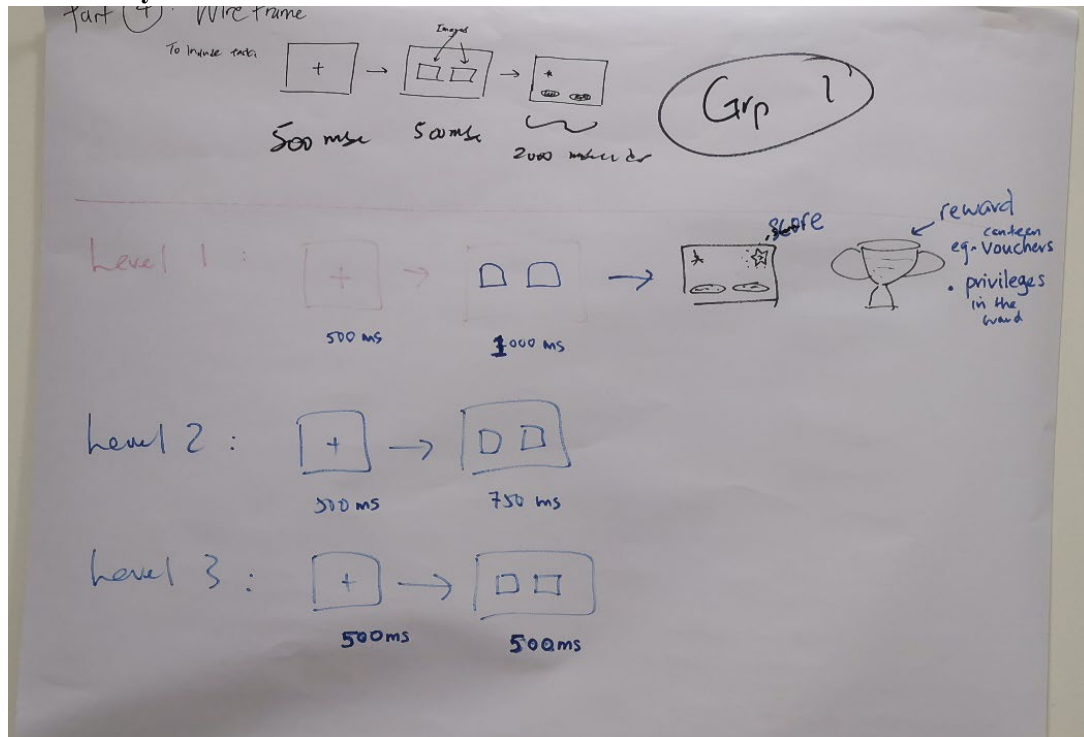
doi: [10.2196/15465](https://doi.org/10.2196/15465)

PMID: [31586359](https://pubmed.ncbi.nlm.nih.gov/31586359/)

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Co-design Workshop Sketched Prototypes

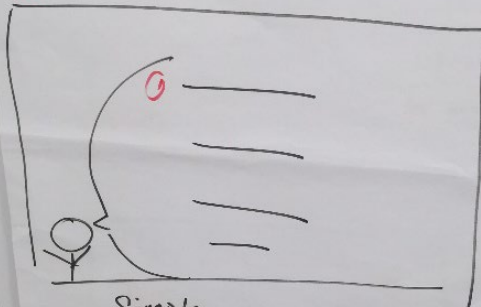
1. Sketches by Healthcare Professionals



(1) Diff Sensory modalities

- Visual, Sound, Vibration,
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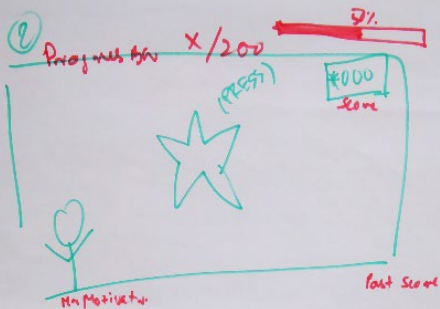
①



Simple
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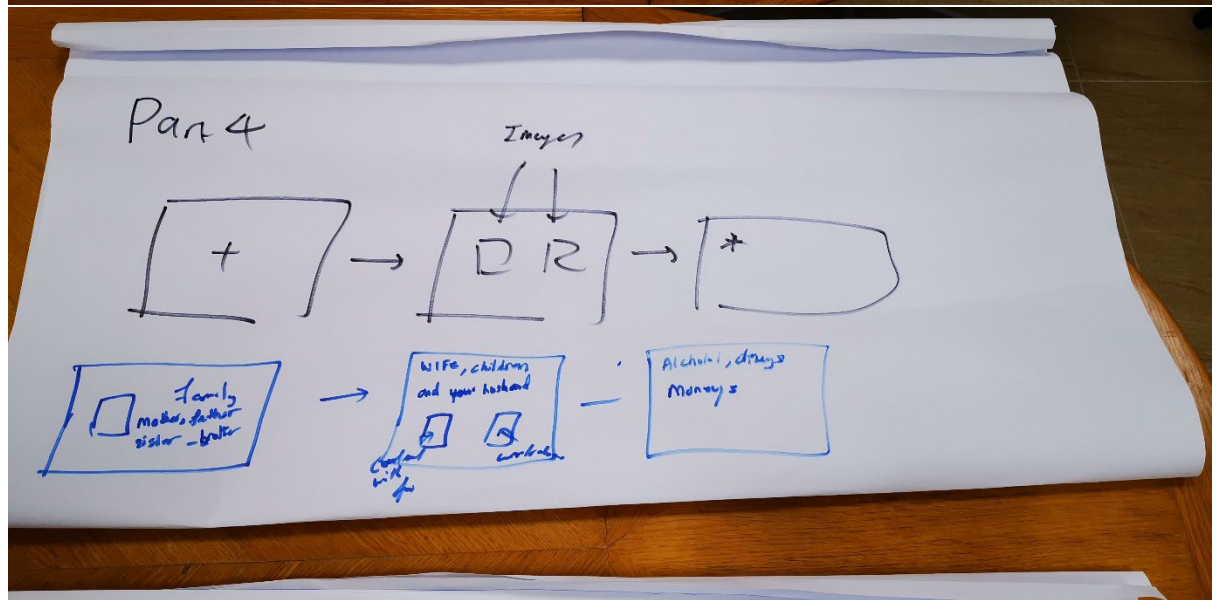
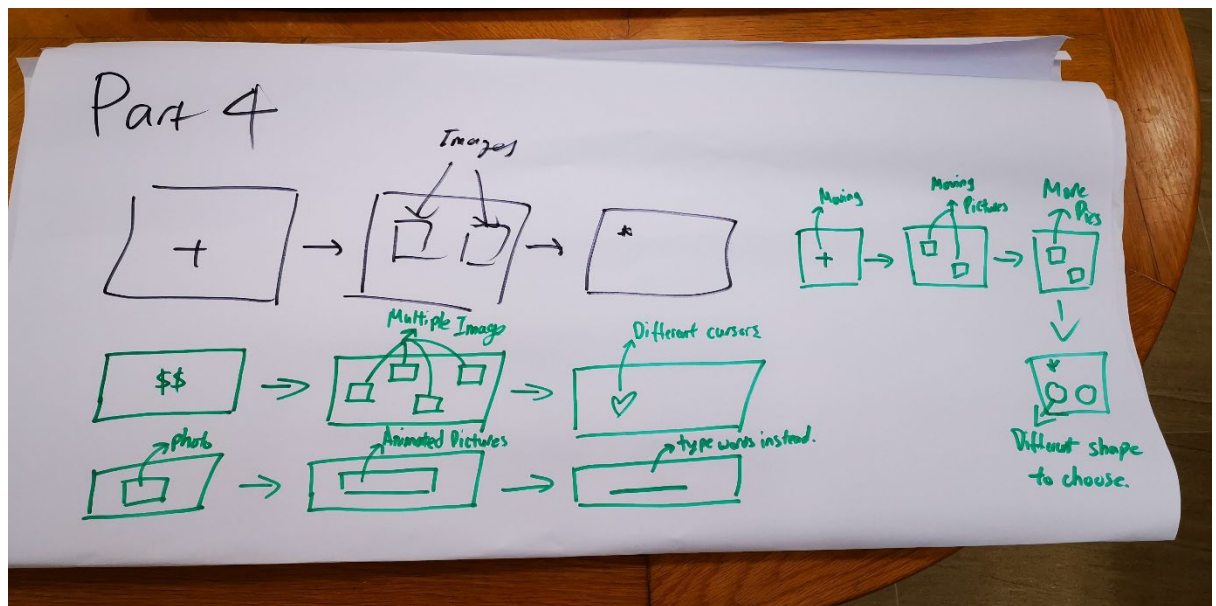


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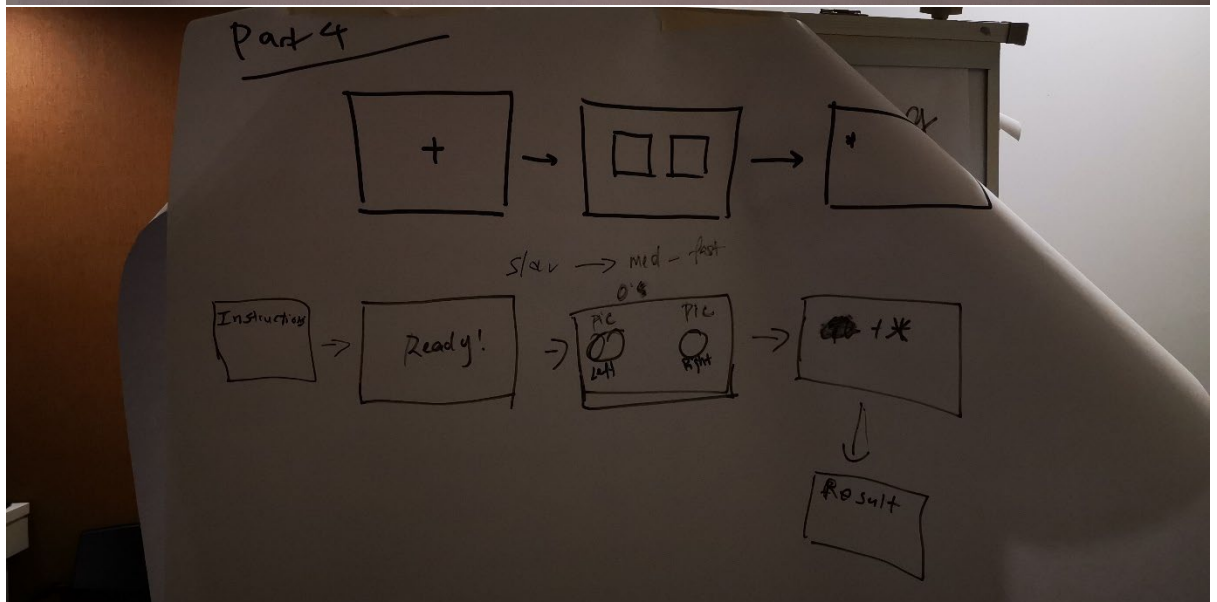
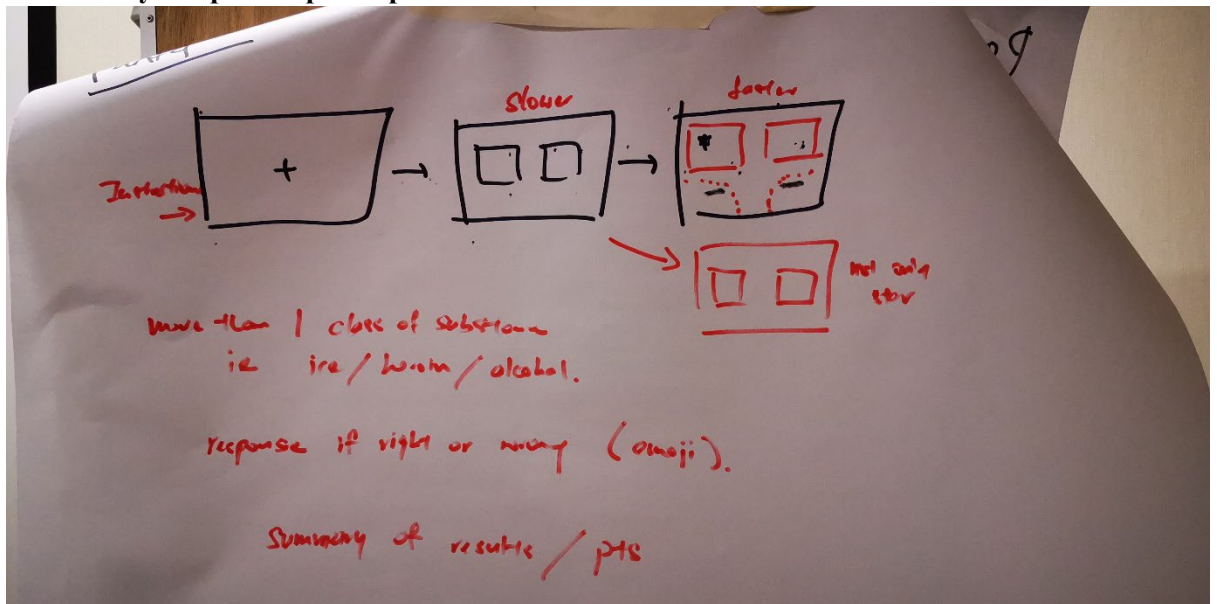


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2. Sketches by Inpatient participants



3. Sketches by Outpatient participants





Protocol

Gamified M-Health Attention Bias Modification Intervention for Individuals with Opioid Use Disorder: Protocol for a Pilot Randomised Study

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Abstract: Introduction: Globally, there is an epidemic of opioid use disorders. Locally, in Singapore, there is an increase in the number of individuals abusing opioids. The advances in experimental psychology have highlighted the need to modify unconscious, automatic biases. These automatic, unconscious biases result in individuals having preferential attention to substance-related cues in their natural environment, thus leading to a slip or relapse back into their underlying addictive disorders. Prior studies have demonstrated not only the presence of robust attentional biases amongst individuals with opioid use disorder, even when maintained on methadone; and the effectiveness of bias modification amongst these individuals. There remains limited evaluation of attention bias modification amongst a treatment-seeking cohort of Asian individuals. The objective of this pilot is to ensure that the methods of the planned definitive randomized trial could be conducted. **Methods and Analysis:** A non-blinded pilot randomized trial will be conducted. A total of 30 participants will be randomized to receive either the conventional application or the newly designed co-designed application. In order to identify these 30 participants, 60 participants will be recruited and screened to determine if they have baseline biases. Participants will be recruited from the inpatient unit at the National Addictions Management Service (NAMS) Singapore. All participants who are enrolled into the trial will complete a baseline assessment task, and a bias modification assessment and modification task daily. They will have to complete a baseline demographic and clinical information questionnaire, as well as a cravings rating scale before and after the intervention daily. Perspectives—that of self-reported experiences—will be sought from the participants following their completion of three intervention tasks. Descriptive statistical analyses will be performed, and chi-square and ANOVA analyses will be performed. Qualitative analyses will be undertaken for the perspectives shared. **Ethics and Dissemination:** Ethical approval has been obtained from the National Healthcare Group's Domain Specific Research Board (DSRB) (approval number that of 2019/00934). The findings arising from this study will be disseminated by means of conferences and publications.

Keywords: attention bias; cognitive bias; addiction; psychiatry

1. Introduction

Substance use disorders are becoming increasingly prevalent. In 2015, the United Nations Office of Drugs and Crime (UNDOC) estimated that at least a quarter of a billion individuals have experimented

with substances, and 0.06% of the global adult population (or 29.5 million individuals) were diagnosed with a substance use disorder [1]. According to the latest report released by the UNDOC, there has been an increase since then, with an estimated 35 million individuals diagnosed with substance use disorder [1]. The UNDOC's latest report also highlights there being a treatment gap, given that only one in every seven individuals have received treatment. In 2015, the most common substances that were abused were that of cannabis, opioids and amphetamines, with annual prevalences of these of 3.8%, 0.7% and 0.77% respectively, each year [1]. In 2019, there has been a large increase in the number of opioid-using individuals; in fact, a 56% increment from previous estimates [1]. It is well-known that substance use disorders are associated with significant morbidities and mortality. With regards to mortality, two thirds of individuals diagnosed with substance use disorders who died in 2017 were opioid users [1]. With regards to morbidities, an estimated 1.4 million substance-using individuals are diagnosed with HIV (human immunodeficiency virus), and another 5.6 million individuals with hepatitis C [1].

Globally, there is an epidemic of opioid use, according to the World Health Organization. In 2016, an estimated 27 million individuals were diagnosed with opioid use disorders. Most of these individuals have abused illicit opioids, but an increasing number are using prescription opioids, such as tramadol and oxycodone [2]. Several factors are responsible for the current epidemic of abuse of prescription opioids, and they include that of the increased accessibility to prescription opioid analgesics, the enhanced purity of heroin and the introduction of more potent illicit fentanyl compounds [3,4]. Several public health approaches have been considered, such as that of prescribing only the right quantities, heightened measures to prevent diversion and changes in drug formulation in order to prevent abuse [3,4]. Whilst these approaches are essential, there needs also to be efficacious treatment for opioid use disorder. Opioid substitution medications like methadone (opioid receptor agonist) and that of buprenorphine (partial opioid receptor agonist) are routinely used. Psychosocial treatment is also routinely coupled with pharmacological treatment, to help in harm minimization and eventual abstinence.

In Singapore, there remains no recent large-scale epidemiological study that has been conducted for substance use disorders. However, in 2004, the World Health Organisation estimated the prevalence of substance use disorders in females to be 0.07% and in males to be 1.40% [5]. Statistics from the Central Narcotics Bureau Singapore (2018) have revealed that heroin was among the top three most commonly abused drugs apart from that of methamphetamine and novel psychoactive substances (NPS) [6]. Traditionally pharmacological medications, that of opioid substitutes, have been recommended in conjunction with psychosocial interventions. However, in Singapore, opioid substitutes are not available, due to Singapore's zero tolerance for drug use policy. Instead, individuals with opioid use disorders undergo detoxification using symptomatic medications, followed by psychological interventions [7].

In the Singapore context, psychosocial interventions are of particular importance, given the limited pharmacological options that are available. Psychological therapies help individuals to achieve and maintain abstinence. Traditionally, therapies like cognitive behavioural therapy for relapse prevention, mindfulness-based relapse prevention and cue-exposure therapies are used. Whilst these therapies, such as cognitive behavioural therapy, have been proven to be effective for disorders including alcohol disorders, in some studies, a proportion of individuals still relapse following intervention [8]. It is likely that these therapies have addressed only the cognitive control processes leading someone to lapse or relapse into an addictive disorder, but not the underlying unconscious processes [9]. The advances in experimental psychology have led to the greater understanding of these unconscious, automatic biases—that of attention and approach biases [9,10]. The dual-process theoretical approach states that attention biases (preferential allocation of attention to substance-related cues) and approach biases (automatic action tendencies to reach out for substance-related cues) develop as the repetitive usage of a substance leads to increased automatic processing and automatic tendencies to acquire the substance, with the inhibition of the normal cognitive control processes [10,11]. Maclean et al.

(2018) [12], in their prior review, highlighted there being robust attentional biases present amongst individuals with opioid use disorders. This was based on the evidence synthesized from 21 studies. Maclean et al. (2018) [12] also reported there being a moderate to large effect size for the presence of attentional biases amongst individuals with opioid use disorders, as compared to healthy controls. With regard to attention bias modification, studies like that of Hietmann, J. et al. (2018) [13] in their systematic review, which included nine studies on alcohol use disorder, six studies on nicotine use and three on opiate use disorders, reported that whilst there have been negative findings, multi-session attention bias modification has had positive effects on attentional change, particularly for alcohol use disorders. Ziaee et al. (2016) [14] reported bias modification to be effective in reducing attention bias for drug-related stimuli and temptations to use, amongst individuals maintained on methadone maintenance therapy. However, the fact that attentional biases are still persistent despite being on methadone maintenance therapy also highlights the need for specific intervention to address these unconscious attentional processes [15]. Most of these studies are limited to the evaluation of attentional biases in western individuals, and to date, from our knowledge, there remains only a single study (Zhang et al., 2019) [15] that has explored attentional bias modification in an Asian cohort of substance-using individuals. In Zhang et al. (2019)'s [15] prior study, they reported the feasibility and acceptability of a mobile attention bias intervention and reported there being individuals without baseline biases. In their sample of 30 participants, 17 participants had a diagnosis of opioid dependence, of which eight had an absence of baseline biases [16]. Zhang et al. (2019)'s [15] prior study did demonstrate that there was a change amongst participants with baseline biases, and this warrants further exploration.

Zhang et al. (2019) [17] subsequently undertook a co-design study and involved both healthcare professionals and patients in the joint conceptualization of a new intervention to address the shortcomings of the conventional application, particularly that of motivation to continue training and the inherent repetitiveness of the task. Both groups of participants suggested for there to be a lengthier stimulus presentation interval at the start of the intervention, before gradual decreasing to a short presentation interval. Gamification strategies, mainly that of feedback, were recommended. To date, Zhang et al. (2019) [17] remains the first study to have involved participants in the design of an attention bias modification intervention, and there needs to be further evaluation of the co-design application against that of the original application to determine if it is more effective.

The objective of the current pilot randomized trial is to determine if the intended processes of the definitive study (i.e., the recruitment of participants with opioid use disorder, the process of randomization into two separate intervention arms, and the administration of the intervention) would work. The current pilot differs from the actual definitive randomized trial, in that the intent is essentially in testing out the process for the definitive trial. This pilot is of importance, as it will help identify and eliminate problems that might affect the eventual success of the definitive trial. Prior research has highlighted how as much as 85% of research investment has been wasted due to the poor design and conduct of trials [18]. Some of the previously identified issues that render a trial to be poor include a lack of systematic literature review and inadequate concealment of treatment allocation [18].

2. Methods

2.1. Study Design and Setting

The study design will be that of a non-blinded randomised controlled trial. Participants will be allocated to receiving either the conventional attention bias modification task, or that of the co-designed task. Simple randomisation will be used. The study will be conducted on the inpatient unit at the National Addictions Management Service, Institute of Mental Health, Singapore. This is a non-blinded randomised trial, as participants who are allocated to both the groups will knowingly be aware of their treatment allocation. It is also not practical for study team members to be blinded, as they are to be responsible for the group allocation, intervention and data collation.

2.2. Inclusion and Exclusion Criteria

Participants are considered eligible for the study if they fulfil the following inclusion criteria, (a) aged between 21 and 65 years old; (b) primary psychiatric diagnosis of opioid use disorder; (c) for patients diagnosed with polysubstance use disorder, their primary substance of abuse needs to be that of opioids; (d) able to read and write in English; and (e) completed their detoxification program. For participation in the trial, participants are required to have baseline attentional biases (i.e., have a positive attentional bias).

2.3. Sampling and Recruitment

Convenience sampling will be used in the recruitment of participants over a period of 12 months, at the inpatient unit of the National Addictions Management Service (NAMS), Institute of Mental Health Singapore. The inpatient unit at NAMS offers a 2-week program, in which the first week of the program is focused on the provision of medication-assisted detoxification and the second week of the program is focused on rehabilitation. The unit can have a total of 22 inpatients at any one time. It is also crucial to note that the program is voluntary in nature, which implies that participants are free to leave the ward if they wish to, at any juncture of their inpatient treatment. All participants who have demonstrated interest in the study will be asked to undertake a baseline attention bias assessment task. Only participants who have baseline biases will be recruited into the trial and will be randomly assigned to any of the two groups by means of simple randomisation. Figure 1 provides an overview of the participant flowchart following screening and recruitment.

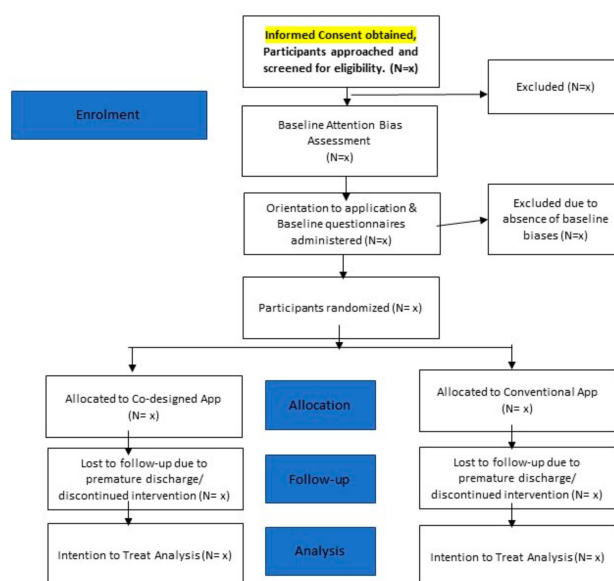


Figure 1. Overview of Participant Flowchart.

2.4. Sample Size

For the purposes of this pilot, we plan to screen 60 participants for baseline biases. Based on our prior feasibility and acceptability study [15], approximately 50% of these participants will have baseline biases. We anticipate that 50% of the participants (or 30 participants) may not have baseline attentional biases and hence would not be eligible for the eventual pilot. Therefore, the sample size for the eventual pilot is that of 30 participants, with 15 participants being randomised to receiving the co-design application and the remaining 15 being randomised to receiving the conventional applications. The sample size of 30 participants in total, with 15 in each group, was selected, taking into consideration previous pilot randomized trials evaluating web-based cognitive bias interventions for individuals with obsessive-compulsive disorder [19,20]. In those previous studies, the sample size per group

ranged from between 6 and 37 participants. Moreover, based on Bell LM et al. (2018)'s [21] guidance for using pilot studies in informing the design of confirmatory studies, the proposed sample size for the pilot study if the effect size is small (i.e., Cohen D is between 0.1 and 0.3), is an estimated 25 participants per arm of the intervention. We have not performed a power computation for the purposes of the pilot, as the pilot study is supposed to inform the definitive sample size for the confirmatory trial [22,23].

2.5. Randomisation

Simple randomisation, by means of a computer program, will be used, and each participants' treatment will be determined independently, without any constraints. In this study, the method proposed by SD Simon (1999) [24] will be used. Making use of Microsoft Excel, a spreadsheet will be created, with a column indicating the participant number of 60 participants. Another column will be created in which the intended treatment will be arranged systematically. Using a column of random numbers, by using the RAND () functionality, the column comprising of the random numbers will be sorted, which will in turn result in the treatment conditions being allocated to participants in a random and unpredictable order [25].

3. Experimental Procedure and Data Collation

a. Screening for Eligibility

Informed consent will be acquired from participants on the last day of their detoxification stay (Day 7), for the purposes of screening, in the presence of an impartial witness. For the screening for the presence of baseline attentional biases, participants are required to undertake an attention bias task on a tablet device. In the assessment task, participants will be shown a fixation cross for 500 milliseconds, followed by a set of images (one related to their substance of use and another neutral image that is similar in complexity). While 50% of these images will be presented for a short stimulus duration of 200 milliseconds, the other 50% of the set of images will be presented for a long stimulus duration of 2000 milliseconds. Following the disappearance of the images, participants are presented with a probe (in the form of an asterisk) for 200 milliseconds. Participants are required to indicate their response, by means of tapping the buttons on the screen, to indicate if the asterisk is presented on the left or right side. If they do not respond, they will be presented with the next trial. In the screening phase, 50% of the trials (100 trials) will involve the presentation of the probe with the substance image, and 50% of the remaining trials will involve the presentation of the probe with the neutral image. The presence of attentional bias will be computed by means of subtracting the reaction time that participants take to respond to probes that replace the neutral image from the reaction time to the probe that replaced the substance image.

b. Experimental Procedure

Participants who are screened positive (i.e., having a positive baseline biases) will be eligible to be recruited into the pilot randomized trial. Informed consent from these participants will have already been obtained in the screening stage. Participants who are ineligible (those without baseline biases) will be dismissed from the study, given due compensation and allowed to go on with their rehabilitation program. Members of the study team will orientate the participants on the use of the mobile application. Participants will be provided with a tablet device to use the mobile application daily. Participants will be also provided with a unique username and password to allow them to have access to the application daily. Participants will be required to complete the following baseline questionnaires, the baseline demographic and clinical information questionnaire, on Day 8 of their stay in the ward, or the first day of their intervention. The following baseline demographic and clinical information will be collected from the participants—that of nationality, gender, marital status, race, religion, highest level of education, housing conditions, current substance use, method of consumption of substance, quantity of substance consumed each time, frequency of use, previous treatment history,

chronic diseases (psychiatric and physical disorders) and current psychiatric medications. Participants will also be required to complete a visual analogue scale for the assessment of cravings before and after undertaking the intervention. The experimental procedure will not differ for participants who are randomized to receiving the co-designed application versus that of the conventional application. Participants will be asked to spend 10 min to complete 200 repeats of the intervention task. Upon completion of the first intervention task, participants can rest for 10 min, before spending another 10 min to complete 200 repeats of the assessment task. Participants will continue to retake the intervention daily, each day they are an inpatient, except for weekends and public holidays. On the subsequent days, participants are to take the intervention task, rest for 10 min, before completing an assessment task. Participants will be asked to retake the craving questionnaire prior to and after the tasks on each of the days that they are involved in the study. Participants will be also asked to complete a questionnaire to acquire their feedback pertaining to the intervention (after they have completed three interventions). If participants request premature discharge from the ward, they are not required to return to the ward to complete the intervention.

Participants will also be asked to complete a perspective/self-reported questionnaire on Day 3 of the intervention (i.e., when they have completed a total of three intervention tasks). This questionnaire has previously been used in our feasibility and acceptability study [15]. Participants will be asked the following questions:

1. Prior to using the application, how confident were you in managing your addiction problem? (5-point Likert Scale)
2. How easy was it to use the application? (5-point Likert Scale, ranging from Not at all to extremely, and written comments)
3. How engaging was the application? (5-point Likert Scale, ranging from Not at all to extremely, and written comments)
4. Do you feel motivated to continue to use the app? (5-point Likert Scale, ranging from Not at all to extremely, and written comments)
5. Do the images in the app remind them of their substance use? (5-point Likert Scale)
6. After using the app, how confident are you in managing your addiction problem? (5-point Likert Scale)

Figure 2 provides an overview of the study schedule/data collection time points and tasks participants are required to undertake.

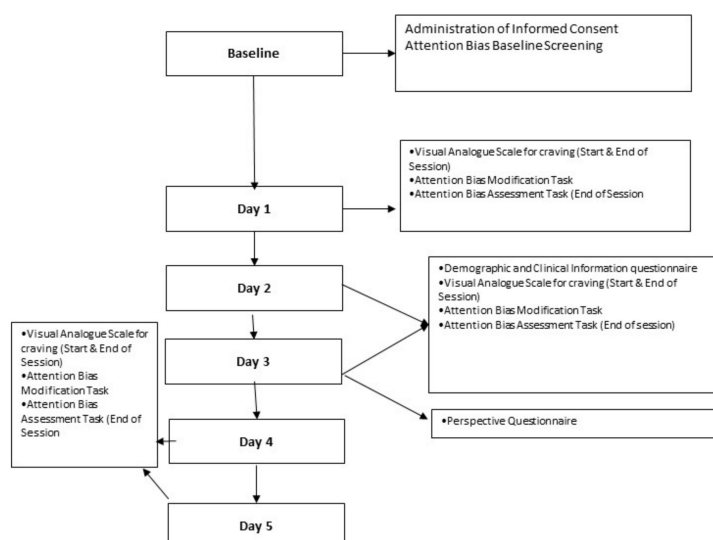


Figure 2. Overview of the data collection time points and tasks to be undertaken.

c. Details of Intervention Tools

For the conventional mobile attention bias modification application, there are two tasks that participants are to undertake daily—that of the assessment task and that of the intervention task. In the assessment task, participants are presented with a fixation cross at the centre of the screen for 500 milliseconds. The fixation cross will then disappear, and a set of images will be presented. 50% of the set of images (i.e., 100 sets of images) will be presented for 200 milliseconds, and 50% of the set of the images (i.e., 100 sets of images) will be presented for 2000 milliseconds. The set of images will comprise a substance image and a neutral image, that is similar in colour, size and complexity. The images that will be used will be obtained from the Central Narcotics Bureau's database. Following the disappearance of the images, a probe (asterisk) will appear, either replacing the substance image or the neutral image, for 200 milliseconds, before disappearing. Participants are supposed to indicate the position of the probe by selecting the buttons on the screen (i.e., left button if the probe is on the left side, right button if the probe is on the right side). In the assessment task, 50% of the time, the probe will replace the substance image, and in the remaining 50% of the time, it will replace the neutral image. Participants are to complete 200 repeats in the assessment task. There are 10 sets of images, which will be repeated 20 times over the 200 repeats. The time interval between each repeat is 250 milliseconds. In the intervention task, the procedure is like that of the assessment task, with the exception that the probe will always replace the neutral image (100% of the time). This allows for the retraining of biases away from the substance image, and towards that of the neutral image. Participants are to also complete 200 repeats during the intervention task.

For the co-designed intervention, there are also two tasks that participants are to undertake daily, that of the assessment and that of the intervention task. The application contains an instructional video to help participants better understand what they would need to do in these tasks. Participants are to complete 5 sample trials before they undertake the assessment or intervention task. In the assessment task, participants are presented with a fixation cross at the centre of the screen for 500 milliseconds. The fixation cross will then disappear, and a set of images will be presented. The duration for which the images stay on the screen will vary across the days of the intervention. Table 1 provides an overview of the timings of the images by days of the intervention.

Table 1. Overview of timings of the images by the days of intervention.

Day of Intervention	Total Number of Trials	Percentage of Image Sets Presenting for 200 Milliseconds	Percentage of Image Sets Presenting for 2000 Milliseconds
Day 1	200	10%	90%
Day 2	200	20%	80%
Day 3	200	30%	70%
Day 4	200	40%	60%
Day 5	200	50%	50%

The set of images will comprise of a substance image and a neutral image which is similar in colour, size and complexity. The images that are used will be obtained from the Central Narcotics Bureau's database. Following the disappearance of the images, a probe (asterisk) will appear, either replacing the substance image or the neutral image for 200 milliseconds, before disappearing. Participants are supposed to indicate the position of the probe by selecting the buttons on the screen (i.e., left button if the probe is on the left side, right button if the probe is on the right side). If participants responded correctly, they will be presented with a smiley emoji. If they have not responded correctly, they will be presented with a frowning emoji. The scores that they have accumulated across the trials will be presented on the top right-hand corner of the application. Participants are to complete 200 repeats in the assessment task. There are 10 sets of images, which will be repeated 20 times over the 200 repeats.

Participants will be presented with their final scores upon the completion of the task. The time interval between each repeat is 250 milliseconds.

In the intervention task, the procedure is like that of the assessment task, but with the exception that the probe will now always replace the neutral image, to allow for retraining of biases away from the substance stimulus.

4. Outcomes

The main outcome that is being evaluated in this pilot study is whether the intended number of participants could be recruited, within the duration of one year. This pilot study also seeks to determine if the intended processes of randomization and the administration of the intended interventions would be successful. In this current pilot study, we acknowledge that selection biases are present, in that we are selecting a cohort of participants that voluntarily seek admission to the inpatient unit. Moreover, the administration of the screening test would also imply that we are selecting specifically for individuals with positive baseline biases only. We are of the opinion that such biases could not be reduced and removed, and we will acknowledge them in our final published study. We will also acknowledge that such biases might affect the overall generalizability of our results.

4.1. Statistical Analyses

For data analysis, an intention to treat analytical approach will be used, to include all participants, including those who withdrew and those who are prematurely discharged from the inpatient unit. Microsoft Excel will be used for the computation of the attention bias scores for each participant for each of the assessment task, in accordance to this formula:

$$(\sum T_1/n_1) - (\sum T_0/n_0),$$

where

T_1 refers to the time for probes that replaced the neutral stimulus

n_1 refers to number of trials for probes that replaced the neutral stimulus

T_0 refers to the time for probes that replaced the substance stimulus

N_0 refers to number of trials for probes that replaced the substance stimulus

SPSS Version 24.0 (SPSS Inc., Chicago, IL, USA) will be used for the analysis of the quantitative data. Demographic and clinical information data of the subjects in both groups will be summarized using descriptive statistics, including that of means and standard deviations. Chi-square tests will be used to determine if there are differences in the two groups for each of the demographic or clinical information variables. We plan to run ANOVA (analysis of variance) analysis to examine the differences in the outcome measure (attention bias scores/reaction time) across the time points in the actual definitive trial. P-values less than 5% will be considered statistically significant.

For the qualitative data obtained by means of the perception questionnaire, the data will be coded using NVivo 12, and a thematic analysis approach will be used in the analysis.

4.2. Data Management and Monitoring

In order to protect the confidentiality of the participants and for the data to be de-identified, all the participants will be allocated a unique subject number upon recruitment. All the hard copy questionnaires will contain the unique subject number and no other participant-related identifiers. All the informed consent forms and the completed hard copy questionnaires will be stored in secured, locked cabinets in restricted areas. The electronic data (which comprise mainly reaction times of the participants) will be automatically synchronized to a cloud database in Singapore (Digital Ocean, Singapore). A copy of the electronic data will be downloaded daily onto a local secured computer and stored onto a research network drive. The password of the local computer will be changed frequently.

The study team members will code the data and an independent co-investigator will routinely check the data coding for reliability and quality. All the hard copy forms and electronic data will be kept for at least six years following the completion of the study.

Adverse Events: Any adverse events that occur during the conduct of the pilot study will be reported to the Domain Specific Research Board in accordance with the local institutional policy.

Ethics: The protocol for this study has been approved by the National Healthcare Group Domain Specific Research Board (DSRB Reference Number: 2019/00934).

Expected Results and Conclusions: This pilot study will provide valuable information about whether the intended processes for the definitive trial would work. This study is of importance, as it will help guide the actual definitive randomised trial. Recruitment and data-analysis is expected to be completed in a duration of 12 months. The results obtained from this study will be disseminated by means of local and international conferences, and by means of peer-reviewed publications.

Author Contributions: M.W.B.Z. conceptualized and designed the methods for this pilot study. D.S.S.F. and H.E.S. provided further inputs to refine the methods for this pilot study. M.W.B.Z. wrote the draft of the protocol, and all the authors commented and revised the final draft. All authors read and approved of the protocol prior to submission. All authors have read and agreed to the published version of the manuscript.

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