Investigating the verbal working memory network in children with Dyslexia : an effective connectivity study

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**INVESTIGATING THE VERBAL WORKING
MEMORY NETWORK IN CHILDREN WITH
DYSLEXIA: AN EFFECTIVE CONNECTIVITY STUDY**

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“For of Him, and through Him, and to Him, are all things: to whom be glory forever. Amen.” Romans 11: 36

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ABSTRACT

Most of the existing theories of dyslexia have been based on the behavioural deficits and aberrant neural activity observed in individuals with dyslexia. However, growing evidence has pointed towards a possible deficit in the effective network connectivity, whereby a shift in directional modulatory connectivity from one region to another is documented. Thus, the present dissertation aimed to explicate the impact of dyslexia on the effective connectivity network during verbal working memory using dynamic causal modeling (DCM). Throughout the thesis, three lines of investigation were conducted.

Study 1 set the stage for the dissertation by extending the verbal working memory network established by Chen and Desmond (2005a) to elucidate the effective network connectivity in typical adults during verbal working memory. The results were consistent with previous studies, demonstrating activations at both the cortical and subcortical regions. Notably, results from the Bayesian model selection analysis indicated that the data obtained from the typical adult population showed a better fit for the model where the connectivity pathway from the left inferior frontal gyrus (IFG) to the left inferior parietal lobule (IPL) was modulated in addition to the modulatory effects on both the frontal/superior cerebellar articulatory control system and the parietal/inferior cerebellar phonological storage system.

Subsequently, Study 2a examined the underlying neural network during verbal working memory in typically developing children. Reduced neural activity was observed across all the regions of interest. Additionally, an analysis of hemispheric laterality showed a left-cerebro right-cerebellar lateralisation, which is similar to that documented in the adult population. Moving beyond functional activation, results revealed unique dynamics in effective connectivity, whereby data obtained from the

typically developing children population displayed a better fit for the model with unilateral modulatory effect on three distinct pathways: (1) from the inferior frontal gyrus to the inferior parietal lobule, (2) the frontal/superior cerebellar articulatory pathway and (3) the parietal/inferior cerebellar phonological storage pathway. These findings were similar to that of adults.

Lastly, study 2b examined how dyslexia contributes to the differences in effective connectivity pathway during verbal working memory in the pediatric population. Results indicated that, in comparison to typically developing children, children with dyslexia displayed significantly reduced activation at both the inferior and superior cerebellum. Consistent with the functional activation results, Bayesian model selection showed that the data obtained from the children with dyslexia indicated a slight better fit for the model with only modulatory effects from the left inferior frontal gyrus (IFG) to the left inferior parietal lobule (IPL). Further analysis revealed that the data obtained from the children with dyslexia showed a better fit for models without modulatory connectivity from the cortical to subcortical regions.

Taken together, this dissertation shed light on the effective connectivity between one neuronal region to another within the verbal working memory network in three distinct populations. It has advanced present knowledge of the influence of cross-sectional age-related effects, and the contributions of dyslexia on the effective connectivity network during verbal working memory. More importantly, the results from the study support the case for a new hypothesis that may provide a more holistic explanation of the deficits observed in dyslexia: the cerebro-cerebellar network theory of dyslexia.

In conclusion, the findings from the present dissertation serve as a springboard for future studies which aim to explore the possible differences in network

connectivity pathways used by children with dyslexia using different task paradigms. More importantly, the study provided important implications that may facilitate the development of more targeted interventions for dyslexia.

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CHAPTER I: INTRODUCTION

Dyslexia is a prevalent neurodevelopmental learning disorder whereby impairment in reading hinders learning and knowledge gathering in the important formative years of a child. Internationally, it is estimated that approximately 15-20% of the population has dyslexia (IDA, 2012). In Singapore, the Dyslexia Association of Singapore (DAS) has estimated that 3-10% of the population has dyslexia. Given the prevalence of dyslexia and its detrimental impact on reading development, many studies have attempted to understand both the behavioural deficit and underlying neural mechanism of individuals with dyslexia. However, before delving into the deficits linked to dyslexia, it is first essential to have a working knowledge of the processes involved in reading. This is necessary for understanding dyslexia holistically, as individuals with dyslexia are primarily characterised by their specific impairments in reading.

One of the most influential models of reading is the dual route-reading model (Coltheart, Curtis, Atkins, & Haller, 1993; Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001). This model comprises of two routes—the lexical route and the sub-lexical route. The lexical route is typically used for sight words that have been stored in the internal lexicon (long term memory) of readers. As such, pseudowords such as “liuxe” cannot be read through the lexical route and is dependent on the sub-lexical route. In the sub-lexical route, words are pronounced through the mapping of the grapheme (letters) to the phoneme (speech sound). Studies have shown that individuals with dyslexia have dysfunction with their sub-lexical route making it hard for them to read (by mapping word sounds to the letters) (Jobard, Crivello, & Tzourio-Mazoyer, 2003), as evident by their poorer performance on non-word decoding tasks which rely on the sub-lexical route (Herrmann, Matyas, & Pratt, 2006; Melby-Lervåg, Lyster, & Hulme, 2012; Rack, Snowling, & Olson, 1992). Additionally, in a meta-

analysis examining the dual-route reading model, researchers found converging brain structures involved in the sub-lexical route processing such as the left superior temporal gyrus, left supramarginal gyrus and the left inferior frontal gyrus (Jobard et al., 2003). Activations at both the left supramarginal gyrus and the left inferior frontal gyrus is indicative of an increase load in working memory and the role of working memory in reading.

The deficits observed on the sub-lexical route in individuals with dyslexia are congruent with the behavioural and neurological deficits observed. Behavioural studies have shown that the core cognitive deficits in individuals with dyslexia lie in the areas of phonological awareness, verbal working memory, and lexical retrieval (rapid automatised naming) (Ramus & Szenkovits, 2008) These deficits have been linked to abnormalities in brain regions such as the left inferior parietal lobule, left inferior frontal gyrus, and right inferior and superior cerebellum, all of which subserve the aforementioned cognitive processes. Consensus on the impairment of the phonological loop (verbal working memory)—the part of working memory responsible for the storage and processing of verbal information (Baddeley, 1979)—has been established with converging findings from both behavioural and neuroimaging studies (Baddeley, 2003a; Beneventi, Tønnessen, Ersland, & Hugdahl, 2010; de Jong, 1998). However, few studies have strived to explicate the impairment in verbal working memory in individuals with dyslexia. This may partly be due to the dearth of research examining this network in typically developing individuals. Therefore, it is pertinent to have an in-depth understanding on the effective network connectivity during verbal working memory in typically developing individuals, before elucidating how dyslexia causes a difference in the network.

Prior to examining the effective connectivity network during verbal working memory, it is important to understand how verbal working memory functions. This can be best explained by one of the more established working memory models—the Baddeley’s verbal working memory model (Baddeley, 1986, 1992). The model postulates that a phonological loop is responsible for the temporary storage and manipulation of verbal information. Studies have since established the relationship between reading/language and the phonological loop (Baddeley, 1979, 2003a; Baddeley, Gathercole, & Papagno, 1998; Chein, Ravizza, & Fiez, 2003). In addition, studies have found impaired phonological loop capacity in children with developmental dyslexia (Beneventi et al., 2010; Coltheart et al., 2001; de Jong, 1998; Gathercole & Baddeley, 1990), further highlighting the importance of the phonological loop in reading and language.

Neuroimaging studies examining verbal working memory have documented the involvement of the left inferior frontal gyrus in the phonological output buffer and the left inferior parietal lobule in the phonological store (Vallar & Papagno, 2002). Apart from the cerebral cortex, the role of the cerebellum during language processing using verbal working memory and phonological processing tasks (Ben-Yehudah & Fiez, 2008; Booth, Wood, Lu, Houk, & Bitan, 2007; Chen & Desmond, 2005a, 2005b; Desmond & Fiez, 1998; Fabbro, 2000) has also been examined. The study by Chen and Desmond (2005a) went further by providing evidence for two cerebro-cerebellar networks—a frontal/superior cerebellar articulatory control system and a parietal/inferior cerebellar phonological storage system, which was subsequently verified using transcranial magnetic stimulation (TMS) (Desmond, Chen, & Shieh, 2005). Although the network components have been identified, the directionality of the connectivity and task modulation has yet to be examined. Therefore, it is pertinent

to further understand how these regions are functionally connected and affect each other during verbal working memory within this functional network. This can be investigated through the use of functional connectivity and effective connectivity. More specifically the analyses of functional connectivity investigate the correlation of activation between brain regions and effective connectivity examines the directional (or causal) influence of one neuronal system exerted over another. Thus, our current analysis of network connectivity goes beyond the understanding of co-activation of neuronal regions during verbal working memory as it also addresses causal interactions (directionality) between distinct units of the network. Studies have highlighted the importance of analysing the functional and effective connectivity within a network, showing that task-dependent alteration in the interaction between network components can be independent of the level of brain activation (Bitan et al., 2005; Friston, 2011).

To the best of our knowledge, there is no published research evaluating the effective connectivity of the cerebro-cerebellar network during verbal working memory using the Sternberg verbal working memory task paradigm. Therefore, the dissertation endeavours to first evaluate the cerebro-cerebellar functional network connectivity in typical adults by furthering the findings of Chen and Desmond (2005a, 2005b). After establishing the effective connectivity network in adults, the dissertation then seeks to further explore the cross-sectional differences in effective connectivity network during verbal working memory between children and adults. In keeping with the main objective of the thesis to understand how the functional network of verbal working is disrupted in dyslexia, an emphasis will be placed on the evaluation of this network between children with dyslexia and children with typical development. It is hoped that the findings of this study will provide a stepping-stone for the development

of more targeted intervention methodologies.

The dissertation will approach this by first providing a literature review of the overarching theme of dyslexia and verbal working memory in the following chapter. This will provide readers with an understanding of the subject matter, which builds up to the rationale and objectives of the proposed study. A framework and integrative rationale of the proposed investigations will also be presented in the next chapter. The dissertation will then seek to investigate the effective connectivity network during verbal working memory in typical adults through a secondary analysis of existing neuroimaging data in chapter three. This is followed by an empirical examination of the effects of neurodevelopment on verbal working memory network by doing a cross sectional comparison of the differences in effective network connectivity between typical adults and children. With the effective network in the typically developing population established, chapter five of the dissertation embarks on elucidating the effect of brain development on the effective network connectivity during verbal working memory through comparing the effective network connectivity in the adult and children samples. A flowchart of the research framework can be seen Figure 1.1. The proposal will conclude with a critical discussion that summarises the possible significant findings that may be derived from the studies, as well as possible limitations and future research directions.

Figure 1.1. Research Framework.

CHAPTER II: LITERATURE REVIEW

Dyslexia

Dyslexia is one of the most prevalent neurodevelopmental disorders internationally. The International Dyslexia Association (IDA) estimates that 15-20% of the world population may have symptoms of dyslexia. The Dyslexia Association of Singapore (DAS) has estimated the prevalence of dyslexia in Singapore to be between 3% to 10% of the population. These figures are an approximation based on individuals with developmental dyslexia.

There are two main types of dyslexia: (i) acquired and (ii) developmental. Acquired dyslexia typically occurs later in life. The root causes of acquired dyslexia have been associated with damage to areas of the brain responsible for general visual, phonological or semantic abilities (Woollams, 2014). A review of the research and theoretical models of acquired dyslexia demonstrates increasing convergence on two basic subtypes, namely, “surface” dyslexia and “deep” dyslexia (Manis, Seidenberg, Doi, McBride-Chang, & Petersen, 1996). Surface dyslexia involves impaired whole word reading and an intact ability to sound out words. In contrast, deep (phonological) dyslexia involves intact whole-word reading and impaired ability to sound out words. Surface dyslexia suggests impairment in orthographic skills and encompasses individuals with significant reading deficits caused by possible visual and visual-perceptual anomalies while deep (phonological) dyslexia has been linked with impairment in phonological skills.

In comparison to acquired dyslexia, developmental dyslexia is hereditary in nature. Genetic studies examining the gender ratio have shown a greater proportion of males diagnosed with developmental dyslexia (Miles, Haslum, & Wheeler, 1998). Males with developmental dyslexia have also been found to exhibit more severe impairments than their female counterparts (Berninger, Nielsen, Abbott, Wijsman, &

Raskind, 2008). However, it is important to note that the higher prevalence rate observed in males may possibly be attributed to referral bias whereby boys are more likely to be diagnosed due to their higher tendency of disruptive behaviour (Shaywitz, Shaywitz, Fletcher & Escobar, 1990). The present study will focus on children with developmental dyslexia.

Despite a long history of research and investigation, the study of developmental dyslexia continues to be fraught with divergent diagnostic criteria, putative classification and a myriad of theoretical explanations. Nevertheless, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013) defines dyslexia as a “Specific Learning Disorder (SLD) with impairment in reading”. According to DSM-5 (American Psychiatric Association, 2013), an individual has to meet the following criteria to be diagnosed with a SLD:

- A. Difficulties learning and using academic skills, as indicated by the presence of at least one of the following symptoms that have persisted for at least 6 months, despite the provision of interventions that target those difficulties:*
  - 1. Inaccurate or slow and effortful word reading*
  - 2. Difficulty understanding the meaning of what is read*
  - 3. Difficulties with spelling*
  - 4. Difficulties with written expression,*
  - 5. Difficulty mastering number sense, number facts or calculation*
  - 6. Difficulties with mathematical reasoning*
- B. The affected academic skills are substantially and quantifiably below those expected for the individual’s chronological age, and cause significant interference with academic or occupational performance, or*

with activities of daily living, as confirmed by individually administered standardized achievement measures and comprehensive clinical assessment. For individuals age 17 years and older, a documented history of impairing learning difficulties may be substituted for the standardized assessment.

- C. The learning difficulties begin during school-age years but may not become fully manifest until the demands for those affected academic skills exceed the individual's limited capacities (e.g., as in timed tests, reading or writing lengthy complex reports for a tight deadline, excessively heavy academic loads).*
- D. The learning difficulties are not better accounted for by intellectual disabilities, uncorrected visual or auditory acuity, other mental or neurological disorders, psychosocial adversity, lack of proficiency in the language of academic instruction, or inadequate educational instruction.*

Note: *The four diagnostic criteria (A-D) are to be met based on a clinical synthesis of the individual's history (developmental, medical, family, educational), school reports, and psycho- educational assessment.*

To be diagnosed with the subcategory "with impairment in reading", individuals have to display impairments the following: (1) word reading accuracy, (2) reading rate or fluency and (3) reading comprehension

Clinical assessment of dyslexia

Clinical assessment for dyslexia is typically administered by a qualified psychologist in a controlled setting. The core domains that are evaluated during the

assessments usually include intellectual functioning, literacy, phonological awareness and visual perceptual processing. There are several standardised psychological test batteries that examine these domains. Table 2.1 documents a selection of some of the available test batteries. Choice of test battery administered may differ based on the training background and practices of individual psychologists, as well as the age and cognitive ability of the child.

Table 2.1.

Selection of possible test batteries for the core domains typically tested during the clinical assessment of dyslexia in children

Test Batteries for Clinical Assessment for Dyslexia	
Domain	Selection of Test Batteries
Intelligence	1. Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V) 2. Differential Ability Scales, 2nd Edition (DAS-II) 3. Stanford-Binet Intelligence Scales, 5th Edition (SB-5) 4. British Ability Scales (BAS3)
Literacy	1. Wechsler Individual Achievement Test, 3rd Edition (WIAT-III) 2. Woodcock-Johnson Diagnostic Reading Battery, 3rd Edition (WJ-III DRB)
Phonological Awareness	1. Comprehensive Test of Phonological Processing, 2nd Edition (CTOPP-2) 2. Phonological Assessment Battery (PhAB)
Visual Perception	1. Test of Visual-Perceptual Skill, 3rd Edition (TVPS-3)

Apart from the aforementioned core domains, tests evaluating fine motor, visual motor integration and language skills are also periodically administered. These are conducted to obtain a more comprehensive neurocognitive profile of possible deficits in other areas, in particular, cerebellar functions where impairment has been observed in individuals with dyslexia. Results from the psychological assessment are typically integrated with historical and other information to guide clinicians in forming a diagnosis.

Behavioural deficits and functional impairments in children with dyslexia

In line with the core domains assessed during the clinical assessment of dyslexia, children with dyslexia have been found to display poorer phonological awareness (Bruck, 1992), weaker verbal short-term memory (Baddeley, 2003a; Beneventi et al., 2010) and slower lexical retrieval (Denckla & Rudel, 1976; Wolf & Bowers, 1999) relative to typically developing children. These behavioural deficits observed may be explained by the functional impairments found in children with dyslexia across various studies.

Over the past two decades, extensive research has been conducted to examine the differential neuronal activation observed in children with dyslexia in comparison to typically developing controls. Thus far, four meta-analytic studies examining the functional activation of individuals with dyslexia in the alphabetical languages (Kwok, 2013; Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008; Richlan, Kronbichler, & Wimmer, 2009; Richlan, Kronbichler, & Wimmer, 2011) have been conducted. A convergence of the findings across the meta-analyses revealed several key regions with differential activation. These include but are not limited to the left inferior frontal gyrus (Brambati et al., 2006; Paulesu et al., 2001; Paulesu et al., 1996; Richlan et al., 2010) left inferior parietal lobule (Temple et al., 2001), left fusiform gyrus (Cohen et

al., 2002; Liu et al., 2008) and the right superior and inferior cerebellum (Stoodley & Stein, 2012).

Left inferior frontal gyrus (IFG). Aberrant activation found in the left IFG has been postulated to be a plausible cause of the phonological deficit observed in children with dyslexia. The IFG is found to act as the central executive system for the networks in the language system (Richards et al., 2006). As such, the inferior frontal gyrus connects to numerous brain regions such as the superior temporal gyrus, insula, parietal operculum, inferotemporal lobe, and the cerebellum. These connections enable the neurons within the IFG to map phonological representations for speech output (Eckert, 2004). Therefore, tasks requiring the selection, retrieval and manipulation of phonological representations such as reading pseudowords have been found to activate the IFG (Cao, Bitan, Chou, Burman, & Booth, 2006). In particular, the connection between the IFG and the right superior cerebellum has been found to sub serve as an articulatory control system (Chen & Desmond, 2005a, 2005b).

Studies examining the underlying neural activation across a range of language based tasks (E.g. homophone judgment tasks and phonological processing tasks) have shown decreased activity in the IFG of children with dyslexia in comparison with typical readers (Booth, Bebko, Burman, & Bitan, 2007; Cao et al., 2006; Hoeft et al., 2006; Meyler, Keller, Cherkassky, Gabrieli, & Just, 2008; Shaywitz et al., 2002; Temple et al., 2001). The decrease in activations documented at the left IFG is not isolated to the pediatric population. Similar atypical activations have been found in both the adult and adolescent population with dyslexia (Brambati et al., 2006; Paulesu et al., 2001; Paulesu et al., 1996; Richlan et al., 2010).

Although converging findings have indicated aberrant neuronal activation at the left IFG, the precise location of the activation at the left IFG has been found to be

dependent on the type of phonological task utilised. During phonological tasks involving letter or rhyme judgment—which require the conversion of orthographic information to phonological codes in order to decipher the sound patterns—activations have been found at a region of the left IFG that is anterior and inferior to those observed during sound segmentation tasks (Burton, 2001). Conversely, tasks such as reading of pseudo-words, which necessitate the selection, retrieval or manipulation of phonological representations, have been found to activate the dorsal left inferior frontal gyrus (BA 44) (Cao et al., 2006).

Taken together, the reduced activation observed in the left IFG in individuals with dyslexia is well established and supported by the literature. In particular, the differential neural activation between dyslexic and typically developing individuals is exceptionally salient during tasks involving phonological processing (Richlan, Kronbichler, & Wimmer, 2011; Stanovich & Siegel, 1994). Hence, the decreased activation of the inferior frontal gyrus is a plausible explanation of the phonological deficits characteristic of dyslexia.

Left inferior parietal lobule (IPL). The left IPL plays an important role in the mapping between phonological and orthographic representations (Booth et al., 2002; Chen, Fu, Iversen, Smith, & Matthews, 2002; Xu et al., 2001). Additionally, studies have also found the left IPL to be implicated in the sub-vocal rehearsal (Pugh et al., 1996) and segmentation (Fiez & Petersen, 1998) of phonological information.

Decreased activation at the left IPL has been well documented in children with dyslexia relative to typical developing children (Cao et al., 2006; Hoeft et al., 2006; Meyler et al., 2008; Schulz et al., 2008). Differences in neuronal activation are predominantly observed in tasks involving the reading of conflicting word pairs (e.g., true-through, has-jazz), which pose greater demands in the mapping of orthographic

representations to phonological representations (Bitan et al., 2007; Shaywitz et al., 1998).

Likewise, typical readers were found to display an increase in neuronal activity at the left IPL, which has been linked to the reading of conflicting pairs—conflicting orthography and phonology (e.g., pint-mint, has-jazz)—rather than for non-conflicting pairs—similar orthography and phonology (e.g., gate-hate, iron-tape) (Bitan et al., 2007). This increase in activation has been associated with the greater demand required for the mapping of orthography to phonology during conflicting words (conflicting orthography and phonology) and enhanced phonological segmentation processing (Bitan et al., 2007). Furthermore, it is noteworthy that decreased activation at the left IPL was observed to be more conspicuous in children with dyslexia as compared to adults with dyslexia (Richlan et al., 2011).

Left fusiform gyrus (FG). The left FG, also known to be the visual word form area (Cohen et al., 2002), is typically associated with visual word form analysis in various languages, such as the alphabetical languages, and the Chinese language (Liu et al., 2008). Some researchers have suggested that the left FG also plays a role in semantic processing; increased activation has been noticed in children performing auditory semantic decision tasks (Balsamo, Xu, & Gaillard, 2006).

In summary, reduced activation at the left FG has been documented in individuals with developmental dyslexia (Cohen et al., 2002; Liu et al., 2008). Although studies have suggested a link between reduced activation at the left FG and the difficulties in orthographic and phonological processing in children with dyslexia, it is important to note that the dysfunction of the left FG is not solely responsible for the reading difficulties they encounter. The dysfunction of other regions (i.e. the left IFG, left IPL, left STG, right inferior and superior cerebellum) and the effective

connectivity between the left FG and other neuronal regions may contribute to the deficits observed.

Superior temporal gyrus (STG). The left STG is involved in the mapping of the visual principles of print onto the phonological structure of language (Benson, 1994). Individuals with dyslexia have typically been found to exhibit reduced activity in the left superior temporal gyrus. Nevertheless, the Richlan et al. (2011) study showed that decreased activation seen in this area is more pertinent in adults with dyslexia rather than children with dyslexia.

Right inferior and superior cerebellum. Little was known about the role of the cerebellum in individuals with dyslexia until the early 2000s. The shift in interest to examine the cerebellum was prompted by the studies establishing the role of the cerebellum in higher cognitive processing (Nicolson & Fawcett, 1999). In particular, activation of the right posterolateral cerebellum has been observed for language-related tasks such as phonological processing (Raichle et al., 1994).

In a meta-analysis examining the activation of the human cerebellum, ipsilateral activity was found in right-handed subjects during language tasks (Stoodley & Schmahmann, 2009). Apart from the role of the cerebellum in language; studies have also shown that the cerebellum is part of verbal working memory network (Chen & Desmond, 2005a; Chen & Desmond 2005b), which has been identified as a core deficit in individuals with dyslexia. More recently, a meta-analysis by E, Chen, Ho & Desmond (2012) established the involvement of the cerebellum in higher cognitive functions, such as language, memory, music, emotion and executive functions (Leiner, Leiner, & Dow, 1993; Nicolson & Fawcett, 2006; Stoodley & Schmahmann, 2009). Taken together, findings from recent studies suggest that the cerebellar impairment in

individuals with dyslexia leads to difficulties in verbal working memory and language processing.

Structural impairments in children with dyslexia

Review of the literature yielded only one meta-analysis (Richlan, Kronbichler, & Wimmer, 2013) focusing on structural impairments in dyslexia. Nevertheless, the meta-analysis provided an objective quantification of structural abnormalities based on nine studies investigating the grey matter aberration in individuals with dyslexia using the voxel-based morphometry technique. Findings from the study (Richlan et al., 2013) found a convergence of grey matter reduction at the right superior temporal gyrus and in the left superior temporal sulcus. The structural abnormalities found were congruent with neuronal regions displaying aberrant activation in the aforementioned meta-analyses (Kwok, 2013; Maisog et al., 2008; Richlan et al., 2009, 2011) reviewed earlier.

Superior temporal sulcus. The planum temporal is a triangular area located at the STG and is traditionally found to be larger on the left side of the brain (i.e. planum temporale asymmetry) in non-impaired readers (Shapleske, Rossell, Woodruff, & David, 1999). Studies examining the superior temporal gyrus or superior temporal sulcus in individuals with dyslexia have predominantly shown reversed asymmetry (right greater than left) of the planum temporal (Duara et al., 1991; Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopoulos, 1990; Larsen, Høien, Lundberg, & Ødegaard, 1990). Therefore, it was difficult to reconcile the finding (abnormalities in the right STG) from the meta-analysis conducted by Richlan et al. (2013) with earlier research findings. Nevertheless, Richlan et al. (2013) suggested that the impairment in the right STG could possibly be explained by Carreiras et al. (2009) findings where researchers examined the anatomical signature of literacy through adult guerillas (illiterate

Colombians that have spent decades in irregular warfare with no formal education) that were re-integrating back into society and learning to read for the very first time. Results from the study indicated an increase in grey matter activation at the bilateral angular, dorsal occipital, middle temporal, left supramarginal and superior temporal gyri (Carreiras et al., 2009). These findings led Richlan et al. (2013) to postulate that the right superior temporal gyrus grey matter reduction found in the analysis was correlated with the reduced reading experience in individuals with dyslexia.

Apart from the right superior temporal gyrus Richlan et al (2013) also reported abnormalities observed at the left superior temporal sulcus. Structurally, the superior temporal sulcus is the sulcus separating the superior temporal gyrus and the middle temporal gyrus. Functionally, it is postulated to be associated with auditory spectrotemporal analysis, which has been found to play a pertinent role in the representation and/or processing of phonological information (Hickok & Poeppel, 2007). Additionally, activation of the superior temporal sulcus was found during both perception production and active maintenance of speech (Richlan et al., 2013).

Non-convergent structural impairments. Although the meta-analysis (Richlan et al., 2013) did not identify structural abnormalities at the other key regions involved in language processing, such as the left IFG, left IPL and the cerebellum, other studies (Eckert et al., 2003; Pernet, Poline, Demonet & Rousselet, 2009; Robichon, Levrier, Farnarier, & Habib, 2000) suggest otherwise. Work by Eckert et al. (2003) found that individuals with dyslexia had a smaller anterior cerebellum relative to their typically developing peers, and less grey matter in their posterior cerebellum. Individuals with dyslexia were also found to have larger right than left inferior frontal gyrus and show greater leftward asymmetry of the parietal peri-sylvian region in the study conducted by Robichon et al. (2000).

The aforementioned behavioural, functional and structural studies have provided a fundamental understanding of the impairments observed in children with dyslexia. With that in mind, various theories have been postulated in an attempt to account for the documented deficits.

Theories of dyslexia

Three main theories have attempted to elucidate the reading deficits seen in dyslexia: the (i) phonological theory (Stanovich, 1988), (ii) cerebellar theory (Nicolson & Fawcett, 2001) and (iii) magnocellular theory (Stein & Walsh, 1997). For the purpose of the dissertation, only the phonological theory (including its extension, the double-deficit hypothesis) and the cerebellar theory will be discussed in greater detail in the subsequent paragraphs. However, in short, the magnocellular theory postulates that the magnocellular channel of the visual system is impaired in individuals with dyslexia, which leads to impaired visual, sensory and motor systems (Stein, 2001). As the focus of the dissertation is on the cerebro-cerebellar effective network, the magnocellular theory will not be elaborated further.

Phonological theory of dyslexia. The phonological theory postulates that phonological impairment is the single dominant cause of dyslexia (Stanovich, 1988). Phonology is associated with speech sounds used in languages. Individuals with phonological awareness display proficiency in grapheme-phoneme mapping (the mapping of speech codes to speech sounds). Behaviourally, studies have constantly shown that competent readers have higher levels of phonological awareness than poor readers, thereby highlighting the importance of phonological awareness in the acquisition of reading skills (Fletcher et al., 1994; Shankweiler, Liberman, Mark, Fowler, & Fischer, 1979; Stanovich & Siegel, 1994)

Reduced phonological awareness in individuals with dyslexia has been associated with specific cognitive impairments in the representation, storage and/or retrieval of speech, all of which are governed by the phonological loop. Therefore, the phonological theory of dyslexia was postulated to account for the clear relationship between cognitive deficits and observed behavioural difficulties (Ramus, 2003). According to the theory, phonological impairment of individuals with dyslexia leads to poor reading ability because the acquisition of grapheme-phoneme correspondence is necessary for gaining mastery in reading an alphabetic system (Ramus et al., 2003).

Apart from the aforementioned behavioural deficits, proponents for the phonological theory have also found aberrant neuronal activation through the utilisation of imaging techniques. Differential activations have been predominantly observed in the left IFG, left STG and the left IPL. These regions sub-serve the different cognitive functions involved in phonological processing, as described in detail in the previous section.

In summary, research has provided both behavioural as well as neuroimaging evidence supporting the phonological theory. From a behavioural perspective, children with dyslexia experience problems with tasks requiring phonological awareness such as spelling and reading (Ho & Bryant, 1997; Swan & Goswami, 1997). Findings also indicate that children with dyslexia display a deficit in both rapid automatised naming and verbal working memory, which suggests a more basic phonological deficit (Baddeley, 1986; Ramus, 2003; Snowling, 2000). From a neurological standpoint, children with dyslexia are found to have decreased activation in the left IFG, and brain imaging studies have found that the basis of phonological deficits lies primarily in Brodmann areas 44/45—which includes regions such as Broca’s area and the IFG (Cao et al., 2006; Paulesu et al., 2001; Paulesu et al., 1996; Richlan et al., 2010).

In spite of the wide consensus, critics of the phonological theory point out that the theory is unable to account for the range of deficits observed in children with dyslexia that are unrelated to phonetic decoding difficulties, such as impairments in the short-term memory, visual processing, as well as gross and fine motor coordination (Ramus et al., 2003). In view of the limitations of the phonological theory and the need to more holistically account for the array of deficits associated with dyslexia, an extension of the phonological theory has been proposed—the double-deficit hypothesis (Wolf & Bowers, 1999).

Double-deficit hypothesis. The double-deficit hypothesis (Wolf & Bowers, 1999) posits that both rapid automatised naming (RAN) and phonological awareness (PA) impairments are independent core deficits that can cause reading difficulties seen in many individuals with dyslexia. According to the theory, individuals with both these deficits display more pronounced impairments in reading than their counterparts, who possess only a single deficit (Wolf & Bowers, 1999).

Behaviourally, studies have shown that RAN is associated with the speed of an individual's ability to name consecutively presented visual stimuli, reflective of the automaticity process that is essential for reading (Norton & Wolf, 2012). Children with dyslexia have largely been observed to display difficulties with lexical retrieval (rapid automatised naming), making it one of the core deficits (Ramus & Szenkovits, 2008).

The first neuroimaging study examining the double deficit hypothesis discovered that the networks related to PA and RAN were independent of each other (Norton et al., 2014). Findings from the study also indicated that the left fronto-parietal network were associated with PA, while the right cerebellum Lobule VI was involved in RAN (Norton et al., 2014). Additionally, converging behavioural and

neuroimaging findings from the study indicated that children with PA deficit, RAN deficit and double (PA + RAN) deficit displayed differential performance and neural activation.

In contrast, a meta-analysis conducted by Vukovic & Siegel (2006) reviewed studies examining the double-deficit hypothesis and found converging findings of a significant association between phonological processing and RAN. This suggests that more evidence is required to substantiate the theory's postulation of RAN and phonological impairments as two independent core deficits (Vukovic & Siegel, 2006).

Cerebellar Theory of Dyslexia. Despite extensive research on the phonological deficits observed in dyslexia, it is thought that the theory of a single dominant cause in phonological awareness fails to account for the full range of difficulties that individuals with dyslexia face, such as impairments in fine motor skills and motor coordination where cerebellar dysfunction is implicated (Fawcett, Nicolson, & Dean, 1996). Therefore, the cerebellar theory (Nicolson & Fawcett, 1990) postulates that the cerebellums of individuals with dyslexia are mildly dysfunctional, resulting in the abovementioned phonological and motor deficits.

In terms of phonological deficits, the cerebellar theory postulates that the cerebellum impairment causes difficulties in articulation leading to language-based problems in phonological awareness and rapid processing as emphasised in the phonological theory. Cerebellum impairment was also postulated to affect kinesthetic abilities such as balancing and motor skills (Fawcett et al., 1996; Nicolson, Fawcett, & Dean, 2001; Ramus, 2003). Impairments in motor skills of children with dyslexia are evident through difficulties in performing tasks such as speed of tapping, heel-toe placement, rapid successive finger opposition, accuracy in copying, and learning and

execution of motor sequences (Denckla & Rudel, 1976; Nicolson, Fawcett, & Dean, 2001).

Support for the cerebellar theory comes from research findings indicating deficiency in phonological awareness. In addition, motor skills deficiencies—including motor, time estimation and balance tasks—that are evident amongst some individuals with dyslexia, can be explained by the cerebellar theory but not solely by the phonological theory (Fawcett & Nicolson, 1999; Fawcett et al., 1996; Nicolson & Fawcett, 2006).

However, critics such as Rochelle and Talcott (2006) pointed out that impaired balance, as accounted for by the cerebellar theory, should not be a determinant of dyslexia. The study found that impaired balance in individuals with dyslexia was attributed to the presence of other developmental disorders such as attention-deficit/hyperactivity disorder (ADHD; Rochelle & Talcott, 2006). Additionally, although phonological deficits are established as a core impairment in individuals with dyslexia, it is not well understood if the neurological causes underlying these deficits can indeed be attributed to the impairment in articulation brought about by the dysfunction in the cerebellum. This, in turn, is postulated to lead to language-based difficulties involving phonological processing.

In summary, both behavioural and functional imaging findings have provided substantial evidence documenting differential activation in the cerebellums of individuals with dyslexia. Studies have also established the role of the cerebellum in higher cognitive processes such as language and verbal working memory (E, Chen, Ho, & Desmond, 2012), which have been identified as a core deficit in individuals with dyslexia. However, it remains debatable if deficits in kinesthetic abilities (e.g. motor coordination) should be considered as a core deficit and included into the

theory.

Network Connectivity in Children with dyslexia

Moving beyond the theories of dyslexia, which have attempted to account for both behavioural deficits and neural differences, recent studies have started examining the network connectivity in individuals with dyslexia. Converging behavioural and functional data have suggested a core deficit in phonological processing, rapid automatised naming and verbal working memory in children with dyslexia. Several neuroimaging studies have sought to identify key regions with abnormal activation to tease apart the underlying neural differences between children with dyslexia and children with typical development (Kwok, 2013; Maisog et al., 2008; Richlan et al., 2009, 2011). However, few studies have ventured to examine the functional and effective connectivity in children during phonological processing (Cao, Bitan, & Booth, 2008; Quaglino et al., 2008; Richards & Berninger, 2008). Functional connectivity is defined as the temporal correlations between spatially remote neuropsychological events, while effective connectivity is defined as the influence one neuronal system exerts over another (Friston, 2011).

Studies (Horwitz, Rumsey, & Donohue, 1998; Pugh et al., 2000) have attempted to elucidate the effect of dyslexia on the function connectivity between regions in the adult population. Converging results have indicated impairment in the functional connectivity between the left angular gyrus and regions in the occipital, parietal and temporal lobules.

In pediatric population, a notable study was conducted by Richards and Berninger (2008) where researchers utilised a phonemic task and found that children with dyslexia displayed differential functional connectivity at the left IFG and its connectivity between the bilateral middle frontal gyrus, bilateral supplemental motor

area, left precentral gyrus and right superior frontal gyrus. The findings provided evidence of a dysfunctional phonological connectivity pathway. Notably, the study found children with dyslexia displayed significant differences in connectivity between regions that are involved during verbal working memory processing (i.e. left inferior frontal gyrus to middle frontal gyrus). This is consistent with studies showing impaired verbal working memory architecture in individuals with dyslexia (Beneventi et al., 2010; Gathercole & Baddeley, 1990).

The aforementioned functional connectivity studies provided an understanding of the interrelationships between brain regions in individuals with dyslexia during language processing tasks. However, in order to elucidate the directionality of the task-induced modulatory connectivity between regions of interest, three studies (Cao et al., 2008; Morken, Helland, Hugdahl, & Specht, 2017; Quaglino et al., 2008) went on to examine the effective connectivity in children with dyslexia. In the study by Cao et al. (2008), researchers examined the effective connectivity between three left hemispheric regions, namely the IFG, IPL and FG as well as the bilateral medial frontal gyrus (MeF) during a visually presented rhyming judgment task as illustrated in Figure 2.1.

Figure 2.1. The effective connectivity pathway model tested by Cao et al. (2008), which includes the bilateral medial frontal gyrus (MeF), left inferior frontal gyrus (IFG), left inferior parietal lobule (IPL) and left fusiform gyrus (FG).

Results from the study revealed several interesting findings. Firstly, reduced modulatory connectivity in children with dyslexia was observed from the left FG to the left IPL during conflicting trials. It was suggested by the authors that children with dyslexia have impairment in the connectivity between regions involved in the processing of orthographic information and regions implicated in the mapping between phonological and orthographical information.

Secondly, a positive correlation in modulatory connectivity and task difficulty was observed only in typically developing children. The absence of an increase in modulatory connectivity in relation to task difficulty was suggested to be linked to the functional roles of the left FG, which supports orthographic processing, and the left IPL, which is involved in the mapping between phonological and orthographical information, sub-vocal rehearsal and segmentation of phonological information. As such, during conflicting trials where greater demands were imposed, children with dyslexia failed to effectively recruit the necessary brain regions hence no increase in modulatory connectivity was observed as task difficulty increased.

Thirdly, only children with typical development were found to display an increase in modulatory connectivity from the left IPL to the left IFG in relation to task difficulty. It was postulated that the absence of conflict dependent modulatory connectivity in children with dyslexia is indicative of a dysfunctional connectivity pathway.

Lastly, unlike control children who displayed positive correlation between reading skills and modulatory connectivity from the left IFG to the left IPL and bilateral modulatory connectivity between the left IPL and MFG, children with dyslexia showed no correlation. This suggested an alternate explanation for the phonological deficits observed in children with dyslexia. An indirect connectivity

pathway between the posterior (left IPL) and anterior (left IFG) regions may have been utilised for language processing, especially when the phonological and orthographical information are conflicting. Taken together, the findings from this study provided preliminary indications of a dysfunctional phonological processing connectivity pathway in children with dyslexia.

Subsequently, Quaglino and colleagues (2008) utilised a different connectivity technique, structural equation modeling (SEM), to understand the phonological deficit in children with dyslexia. Using a pseudoword reading task, the effective connectivity between three left hemispheric regions, notably the supramarginal gyrus, fusiform cortex and the inferior frontal cortex, was examined. In general, findings from this study suggested differential modulatory connectivity across all the pathways between children with dyslexia and both reading and age matched children.

Specifically, while both reading and age matched children displayed significant modulatory connectivity between the supramarginal cortex and the inferior frontal cortex on the dorsal temporoparietal pathway, no modulatory connectivity was observed in children with dyslexia. It was suggested that the lack of modulatory connectivity is linked to the phonological deficit documented in children with dyslexia as the pathway between the supramarginal cortex and the inferior frontal cortex has been known to be involved in phonological processing. The finding parallels that of Cao et al. (2008), providing further evidence of a dysfunctional phonological processing connectivity pathway.

In contrast, on the ventrobasal pathway, which is implicated in the processing of lexical semantic information, children with dyslexia displayed greater modulatory connectivity between the fusiform cortex and the inferior frontal cortex via the basal forebrain (uncinate fasciculus) as compared to age matched controls. It was suggested

that children with dyslexia utilised the ventrobasal reading pathway more frequently, and that increasing reading ability may be associated with reduced dependency on this pathway.

More recently, a longitudinal study of effective connectivity was conducted to investigate the literacy development in children with dyslexia (Morken et al., 2017). Participants in the study were followed up in accordance with the reading developmental stages proposed by Frith (1986): Pre-literacy (6 years old), emergent literacy (8 years old) and literacy (12 years old) (Frith, 1986). Using a similar connectivity technique, dynamic causal modeling (DCM), researchers examined the effective connectivity between five cortical regions involved in reading. Connectivity results revealed that children with dyslexia during emergent literacy (the age range of focus for the present dissertation) displayed decrease connectivity from the IFG to the IPL, IFG to precentral gyrus and increased connectivity from the occipital-temporal region to the precentral gyrus. Additionally, results from the study indicated that children with dyslexia displayed a delay in their progression to both the pre-literacy and emergent literacy reading stages. This delay was suggested to be a possible explanation for the reading deficits observed in children with dyslexia.

In summary, findings from both functional and effective connectivity studies have advanced our understanding of the underlying cerebral network connectivity during language tasks. Nevertheless, with studies (Ben-Yehudah & Fiez, 2008; Booth et al., 2007; Chen & Desmond, 2005a, 2005b; Stoodley & Schmahmann, 2009) establishing the role of the cerebellum in language processing, it is pertinent to examine cerebro-cerebellar network connectivity. Previous studies elucidating the differences in connectivity in the phonological pathway prompts our interest to understand whether the differences in dynamics can be generalized to other pathway

models using differential cognitive tasks within the cerebral region. Additionally, the present study seeks to move beyond the cortical regions explored in previous studies to examine the connectivity between cortical and subcortical (cerebellar) regions. In particular, this dissertation is interested in understanding the differences in effective connectivity pathway during a verbal working memory task (a core deficit of individuals with dyslexia). This concept of verbal working memory will be discussed in detail in the next section.

Working memory

The concept of working memory proposes a temporary storage and manipulation of information that is assumed to be necessary for a wide spectrum of complex cognitive tasks such as reading (Baddeley, 1992, 2003a, 2003b). The original model proposed by Baddeley and Hitch (1974) comprised of three components—the central executive, the phonological loop and the visuo-spatial sketchpad. The central executive system was postulated to act as a control system while the phonological loop and the visuo-spatial sketchpad were systems that temporarily maintained the processing of verbal and/or visual information. A widely cited version of the original model is presented in Figure 2.2. Since then, the model has undergone several revisions. The most recent version incorporated an additional component—the episodic buffer (Baddeley, 2000), which is presented in Figure 2.3. The present study will focus on verbal working memory (phonological loop), which will be reviewed in greater depth in the ensuing section.

Figure 2.2. Original working memory model. Figure adapted from Baddeley and Hitch (1974).

Figure 2.3. Baddeley's recent working memory model. Figure adapted from Baddeley (2000).

Verbal Working Memory and Language

The phonological loop functions as a temporary storage for the manipulation of verbal (phonological) information (Baddeley & Hitch, 1974). Since the proposition of the three-component model of working memory by Baddeley and Hitch (1974), the phonological loop was assumed to be responsible for speech (phonological) coding and maintenance within short-term memory. Early behavioural evidence of phonological coding in the working memory dates back to the study on the phonological similarity effect conducted in 1964 by Conrad and Hull. In their study, subjects were shown a string of letters for immediate recall. It was shown that more errors were made if the

letters were phonologically similar (E.g. V, Z, T, D, E, G) as compared to strings of letters that are phonologically dissimilar (E.g. A, W, T, O, R, X) (Conrad & Hull, 1964). A similar study conducted by Baddeley (1966) using words instead of letters also found comparable results. Similar words (E.g. ten, can, man, ran, pan) were recalled significantly less during immediate recall as compared to dissimilar words (E.g. cat, dog, mop, day, can) (Baddeley, 1966).

It was assumed that verbal/auditory stimuli could directly access the phonological store, bypassing the articulatory process, whereas visual information entered the store via the articulatory process (Baddeley, 1986). Evidence for the rehearsal system was provided by the word length effect study conducted by Baddeley et al. (1975). The word length effect study is best exemplified as the immediate recall of a list of short words (e.g. cat, dog, mop, ten, day) in comparison to a list of long words (e.g. technological, sanitisation, international, congratulations, hippopotamus) with similar number of words (Baddeley, Thomson, & Buchanan, 1975). Findings from the study suggested that an individual's ability to sub-vocalise and subsequently recall the words during immediate recall is dependent on the rate of sub-vocalisation of the word, in which anything greater than two seconds was lost through the process of temporal decay (Baddeley, 1986).

The study of the word length effect (Baddeley et al., 1975) led to findings of the effect of articulatory suppression (the process of speaking aloud an irrelevant word while performing an immediate recall task), which ultimately prompted the fractionation of the phonological loop into two subcomponents. In the study, Baddeley et al. (1975) found that if participants underwent articulatory suppression while undergoing the immediate recall test, the effect for visually presented stimuli was negated. Later studies which examined the effect of articulatory suppression on the

phonological similarity effect found similar results (Estes, 1973; Hanley & Bakopoulou, 2003; Salamé & Baddeley, 1986). Findings from the aforementioned studies collectively suggest that articulatory suppression prevented the phonological encoding of visually presented stimuli, but spoken words can be stored directly without phonological encoding. In light of these findings, the phonological loop was revised to consist of two subcomponents—the phonological store that holds speech-based information over a matter of seconds, and the sub-vocal rehearsal system (Baddeley, 1986, 2003a). The sub-vocal rehearsal system not only maintains information within the store, but also serves the function of registering visual information (if items can be named) in the store (Baddeley, 2003a).

The revision of the phonological loop and the postulation of its role in language acquisition (Baddeley et al., 1998) prompted an influx of empirical research that helped further our understanding of verbal working memory in language acquisition. In one of the earlier studies by Gathercole and Baddeley (1989), researchers examined the role of the phonological loop in native language acquisition. Using a group of eight-year-olds with specific language impairment (SLI), a group of children with typical development that were matched for age and nonverbal intelligence, as well as a group of younger children that were matched for language ability, the differences in performance on a non-word repetition task was investigated (Gathercole & Baddeley, 1989). During the non-word repetition task, children were required to repeat sequences of unfamiliar phonemes, which are used as an index of their phonological loop capacity. Results indicated that children with SLI fared much worse than their counterparts in the other two groups, indicating impairment in the phonological storage component of the loop (Gathercole & Baddeley, 1989).

Subsequent studies (Baddeley et al., 1998; Gathercole & Baddeley, 1990; Gathercole, Willis, Emslie, & Baddeley, 1992) were conducted to examine the role of the phonological loop in vocabulary acquisition across age groups (four to thirteen year olds), finding significant correlations between vocabulary scores and non-word repetition. Findings from these studies provided evidence that the learning of new vocabulary is highly dependent on the capacity of the phonological loop.

Moving beyond behavioural studies, neuroimaging techniques have been widely used in the investigation of the role of verbal working memory in language processing. Notably, in the study conducted by Vallar and Papagno (2002) examining patients with short-term phonological deficits, researchers provided a detailed neuroanatomical basis of the phonological loop as seen in Figure 2.4. They postulated that auditory input is analysed and relayed to the short-term store in the inferior parietal lobe. Information in the system can then be passed onto the phonological output buffer in the Broca's area-premotor cortex, which can result in a spoken output or a rehearsal process that recycles information (Vallar & Papagno, 2002).

Figure 2.4. A proposed structure of the phonological loop. STS refers to short term store. Figure adapted from Vallar & Papagno (2002).

Cerebro-cerebellar network during a Verbal Working Memory task

While the cortical regions involved in the processing of language-based tasks (i.e. phonological information) have been elucidated, the role of subcortical regions such as the cerebellum has been less well understood. Nonetheless, with the growing interest in the function of the cerebellum over the past two decades, studies have documented the role of the cerebellum in higher cognitive processing such as that of verbal working memory. In the study by Desmond and colleagues (1997), researchers identified two cerebellar regions involved in verbal working memory processing, namely the bilateral superior cerebellum (lobule VI/ Crus I) and the inferior cerebellum (VIIB). Extending these findings, Chen and Desmond (2005a) proposed a network comprising of both cortical and subcortical regions. Findings from Chen and

Desmond (2005a) provided evidence for two cerebrocerebellar networks for verbal working memory—a frontal/superior cerebellar articulatory control system and a parietal/inferior cerebellar phonological storage system, as presented in Figure 2.5.

Figure 2.5. Verbal working memory cerebro-cerebellar network proposed by Chen & Desmond (2005a). Depicted are the two networks—a frontal/superior articulatory control system (blue) and a parietal/inferior phonological storage system (green).

To validate the established verbal working memory network by Chen and Desmond (2005a), researchers further examined the activations during three distinct verbal working memory phases—encoding, maintenance and retrieval (Chen & Desmond, 2005b). Temporal concordance of activation was found whereby increased activation was observed at both the left parietal regions and the right inferior cerebellum maintenance phase. In contrast, the encoding phase was linked to neural activity at both the left inferior frontal region and the right superior cerebellum (Chen and Desmond, 2005b). Consistently, results from the transcranial stimulation (TMS) study by Desmond and colleagues (2015) also demonstrated the role of the superior cerebellum during verbal working memory. Taken together, the aforementioned studies

provided substantial evidence to support the verbal working memory network established by Chen and Desmond (2005a).

Neurodevelopmental Changes and Verbal Working Memory

The neurodevelopment of mental abilities, including that of verbal working memory, continues to develop through adolescence. Behavioural studies examining verbal working memory have shown that maturation to adult-like level performance occurs around mid-adolescence (Gathercole, 1999; Luna, Garver, Urban, Lazar, & Sweeney, 2004). Likewise, in a functional imaging study by O'Hare and colleagues (2008), researchers examined the neurodevelopmental changes during the Sternberg verbal working memory task across different age groups (children, adolescents and adults). They found that although participants across age groups engaged the cerebro-cerebellar network during the task, the number of linear task-modulated activated regions increased with age (O'Hare, Lu, Houston, Bookheimer, & Sowell, 2008).

Previous studies have established the lengthy maturation process of verbal working memory—which plateaus during mid-adolescence—as well as the establishment of the cerebro-cerebellar network in typical adults (Chen & Desmond, 2005a, 2005b). Therefore, it is pertinent to further examine the effective connectivity network during verbal working memory in typical adults before systematically elucidating the network in typically developing children and children with dyslexia.

Dyslexia and Verbal Working Memory

Converging findings from studies in the field of dyslexia have identified three core deficits: phonological awareness, verbal working memory, and lexical retrieval (rapid automatised naming) (Ramus & Szenkovits, 2008). In a recent paper by Norton and colleagues (2014), researchers provided compelling neuroimaging evidences supporting the double-deficit hypothesis. Findings from the study revealed a unique

neural basis for impairments in phonological awareness and rapid automatised naming. Differential activation observed by Norton et al. (2014) at both the left IPL and left IFG were consistent with previous studies linking the left IPL and IFG to processing of phonological information. Additionally, the right superior cerebellum (lobule VI) was found to be associated with rapid automatised naming. The findings were in line with previous research suggesting deficits in the cerebellum of individuals with dyslexia (Nicolson et al., 2001). Studies examining the right superior cerebellum have also provided evidence supporting its role in motor, linguistic, and working memory processes (Stoodley & Schmahmann, 2009).

Although the study by Norton et al. (2014) was focused on the impairments seen in phonological awareness and rapid automatised naming, the cognitive task administered involved the articulation loop, which is a key component of verbal working memory. Additionally, studies have established the connection between the right cerebellar lobule VI to the left inferior parietal lobule and the inferior frontal gyrus, postulated to function as the phonological store and the articulatory loop respectively (Chen & Desmond, 2005a, 2005b). In light of these, perhaps the three core deficits of dyslexia can be understood as impairments that affect the reading ability of individuals with dyslexia in partially overlapping yet distinct ways.

Reading is a complex process that involves various cognitive processes; among them is verbal working memory. Behavioural and neuroimaging studies examining verbal working memory and reading have shown convergent findings—phonological loop capacity is impaired in individuals with dyslexia (Baddeley, 2003a; Baddeley et al., 1998; Beneventi et al., 2010; de Jong, 1998; Gathercole & Baddeley, 1990). In a more recent study, researchers examined the performance and neural activation of children with dyslexia and their age-matched peers on a version of the n-back verbal

working memory task (Beneventi et al., 2010). Behavioural findings from the study showed that children with dyslexia performed significantly below their peers in the 1-back and 2-back, but not the 0-back level, suggesting a verbal working memory deficit. Functional results displayed similar activation in both groups and that of established cortical network found in adult and child populations.

Despite extensive research in the field of verbal working memory, there is limited knowledge on the effect of dyslexia on the effective connectivity network of verbal working memory network. Therefore, the present study sought to elucidate the contribution of dyslexia on the effective network connectivity during the Sternberg's verbal working memory task.

The Research Framework

In summary, dyslexia is the most common learning disability where the impairment in reading hinders learning and knowledge gathering in the important formative years of a child. The core cognitive deficits in dyslexia are phonological awareness, verbal working memory and lexical retrieval (Ramus & Szenkovits, 2008), which have been associated with neural abnormalities. Functional abnormalities have been found in regions related to language processing such as the left IFG, left IPL, STG, MTG and left FG and more recently, the cerebellum (Eckert et al., 2003; Fawcett & Nicolson, 1999; Richlan et al., 2009, 2011).

Converging evidence from behavioural and neuroimaging studies highlight the impairment of the phonological loop (verbal working memory), which is the part of the working memory that is used for the storage and processing of verbal information (Baddeley, 1979). There is extensive research supporting an impairment of the phonological loop in individuals with dyslexia. However, there are limited studies examining the effects of dyslexia on verbal working memory network. Therefore, the

primary aim of the present study is to systematically understand the underlying neuro-mechanisms of verbal working memory using both behavioural measures and neuroimaging techniques. As the cerebro-cerebellar network has been established in the adult population (Chen & Desmond, 2005a, 2005b), the present study starts off by first establishing the cerebro-cerebellar effective connectivity network during verbal working memory in typical adults. Subsequently, it will then examine this network in typically developing children to understand the cross-sectional neurodevelopmental differences in effective connectivity network. Finally, in line with the main aim, the dissertation will explore how effective network connectivity differs between children with dyslexia and typically developing children. In addition, the study will evaluate how neurocognitive measures correlate with the effective connectivity between the two groups.

Findings from the study will advance our understanding on how the cerebro-cerebellar network of verbal working memory is affected in children with dyslexia. Therefore, the study will not only help to fill the existing knowledge gap, but also establish a platform for possible future research studies to examine the sub-components of intervention methodologies (e.g., through programs that emphasise articulatory awareness, like Lindamood Phoneme Sequencing (LiPS), or through enhancing phonological memory, like Orton Gillingham) that contribute to both behavioural and cognitive improvements. This would ideally translate into intervention methodologies that are more targeted at the underlying deficit, hence increasing its efficacy.

CHAPTER III: STUDY 1

Network connectivity in typical adults during verbal working memory

Introduction

Studies have been examining the role of the working memory in a wide spectrum of cognitive tasks. The present study is interested in the phonological loop (verbal working memory), a subcomponent of the working memory. The phonological loop functions as a temporary storage for the manipulation of verbal information (Baddeley & Hitch, 1974). Studies examining the phonological loop have postulated that the phonological loop comprises of two subcomponents—the phonological store and the phonological output buffer.

The fractionation of the phonological loop and its role in language has generated great interest. Notably, the study conducted by Vallar and Papagno (2002) examining patients with phonological short-term deficit, provided a comprehensive neuroanatomical basis of the phonological loop as seen in Figure 3.3. They postulated that auditory input is analysed and fed into the short-term store in the inferior parietal lobe. Information in the system can then be passed onto the phonological output buffer in the Broca's area-premotor cortex, which can result in a spoken output or a rehearsal process that recycle information (Vallar & Papagno, 2002). With a detailed understanding of the neuroanatomical basis of the phonological loop, studies further examined the cerebrocerebellar network during a verbal working memory task (Chen & Desmond, 2005a, 2005b). Findings from Chen and Desmond (2005a) provided evidence for two cerebrocerebellar networks for verbal working memory—an articulatory control system, which connects the left IFG to right superior cerebellum and a phonological storage system that connects the left IPL to the right inferior cerebellum.

To date, functional neuroimaging studies have predominantly focused on the examination of isolated neuronal regions that are selectively engaged during verbal

working memory tasks. However, network shift could possibly occur due to the connectivity between network components, as opposed to a change in activation at specific cortical or subcortical regions. This is evident in studies showing task-dependent alteration in the interaction between network components, which was postulated to be independent of the level of brain activation (Bitan et al., 2005; Friston, 2011).

Recent research has moved beyond the study of co-activated regions during verbal working memory, and started examining the network connectivity that is typically quantified using functional or effective connectivity analysis techniques. Functional connectivity is defined as the temporal correlations between spatially remote neuropsychological events, while effective connectivity is defined as the influence one neuronal system exerts over another (Friston, 1994).

With the network components involved in verbal working memory established by Chen and Desmond (2005a), further understanding of the functional architecture can be elucidated through the analyses of effective connectivity. Dynamic causal modeling (DCM) and structured equation modeling (SEM) are two commonly used methods of analysing the effective connectivity between co-activated brain regions. In contrast to the SEM approach, DCM models the dynamics between a network of neuronal regions, thereby providing greater clarity on the functioning of neural networks (Daunizeau, David, & Stephan, 2011). Furthermore, DCM is not constrained by the temporal precedence of one time series in a particular area relative to another (unlike multivariate autoregressive models); dependence on time lag may pose difficulties because the use of fMRI data may obscure modeling accuracy (Friston, Moran, & Seth, 2013). Past research used DCM to understand effective connectivity of verbal working memory in the cortical regions (Dima, Jogia, & Frangou, 2014) as

well as to examine the effect of the memory load (Ma et al., 2012) and altered connectivity in patient populations (Campo et al., 2012; Deserno, Sterzer, Wüstenberg, Heinz, & Schlagenhauf, 2012).

Despite heightened interest in cerebellar contributions to higher cognition and the increasing number of studies exploring the role of the cerebellum during verbal working memory (Chen & Desmond, 2005a, 2005b; Desmond & Fiez, 1998; Desmond, Gabrieli, Wagner, Ginier, & Glover, 1997; E et al., 2012; Schmahmann & Pandya, 1997; Stoodley & Schmahmann, 2009), DCM studies of verbal working memory network have not examined cerebellar regions (Dima et al., 2014; Harding, Yücel, Harrison, Pantelis, & Breakspear, 2015). Therefore, it is pertinent to move beyond examining cortical connectivity to understand the cerebro-cerebellar network connectivity using a Sternberg's verbal working memory task. To the best of our knowledge, DCM has predominantly been applied to examine effective connectivity during the N-back task (Dima et al., 2014), and no study has explored the effective connectivity during verbal working memory using the Sternberg task paradigm.

The N-back paradigm involve the continuous presentation of stimuli that requires the participant to respond if the current stimulus presented is similar to the previous stimuli that were presented (1-back) or the second to last (2-back). The Sternberg paradigm, on the other hand, includes a set of stimuli presented (e.g. numbers or letters), followed by a maintenance phase, before the presentation of a single probe stimulus, which requires the participant to decide whether the probe was part of the set presented previously.

Differential activation in the cerebellum during the N-back and Sternberg task paradigms was found in a previous meta-analysis (E, Chen, Ho, & Desmond, 2012). Therefore, the present study employed a Sternberg verbal working memory paradigm

with the aim of better understanding the dynamics of effective connectivity in a cerebro-cerebellar network. As such, it is hypothesised that the Sternberg verbal working memory task utilised in the present study would elicit activation at the left frontal and parietal regions as well as at both the right superior and inferior cerebellum. Additionally, we expect to observe task dependent modulatory connectivity on both the frontal-superior cerebellar articulatory control pathway and the parietal-inferior cerebellar phonological pathway storage. The current study conducted a secondary data analysis on a subset of pre-existing data set collected in a previous study (Ng et al., 2016).

Methodology

Participants

Forty-two typically developing young adults with no previous records of psychiatric and/or neurological conditions were enrolled in this study. Eleven participants were excluded for the following reasons: excessive head motion greater than 3mm ($n = 2$), functional activity not present at one or more of the region of interest when thresholded at $p < 0.05$ (uncorrected; $n = 8$) for the high load versus low load contrast across all run, and dropout ($n = 1$). The mean age of the 31 participants was 22.5 years ($SD = 1.18$ years; range = 21 to 25). Using the Edinburgh Handedness Inventory (EHI), all participants were assessed to ensure right-handedness. Participants scored an average of 95.25 with a standard deviation of 6.65.

Before commencing the experiment, informed consent was administered to all participants. Approval for the study was also obtained from the Nanyang Technological University Institutional Review Board.

Task description

All participants completed two runs of the Sternberg working memory task (see Figure 3.1) presented in a block design whilst undergoing the MRI scan. A Fujitsu Lifebook computer (Fujitsu, Tokyo, Japan) was used to display visual stimuli, while the task was programmed using E-Prime version 2.0 (Psychology Software Tools, Inc, Pittsburgh, US). All participants had a practice session where they had to attain an 80% accuracy rate to demonstrate familiarisation with the experimental procedures prior to the scanning.

Participants were alerted to the commencement of a trial with the display of a red fixation cross at the center of the screen that lasted for 1.2-seconds. This was followed by the encoding phase, which involved the switch of display to either six identical uppercase letters (low load condition) or six non-repeated uppercase letters (high load condition) for three seconds. Similarly, stimuli in both load conditions were presented in a horizontal array in the middle of the screen. Successively, during the maintenance phase, participants saw a centered white fixation cross for 3 seconds. Lastly, a lowercase probe letter was presented for 2 seconds where participants were asked to press the right button once with their middle, if they thought that the probe was presented during the encoding phase. Alternatively, participants could choose to press the left button with their index finger if they do not recall the probe being present during the encoding phase. Participants were instructed to sub-vocally rehearse the letters in consecutive order continuously, throughout the encoding and maintenance phases. Additionally, they were instructed to respond as precisely and as quickly as possible during the probe phase. The stimuli were back-projected onto a screen and viewed via a mirror mounted on the birdcage coil.

Figure 3.1. Sternberg's verbal working memory task paradigm.

Visual stimuli were presented in a block design. Blocks comprised of either two high or two low-load trials. Block duration was 20 seconds and was interleaved by rest intervals of 1.6 seconds. A total of 20 blocks (10 high load; 10 low load) in a run took 400 seconds to complete. A total of 2 runs yielded a total of 80 (40 high load; 40 low load). Task order was counterbalanced across participants.

Image acquisition

A 3-Tesla Siemens MRI scanner (Siemens Trio, Erlangen, Germany), equipped with a 32-channel birdcage head coil was utilised to acquire the whole-brain MRI data. To reduce head movements, foam padding was used to pack the participant's head within the head coil. A combination of localiser, structural and functional scans were acquired. For the structural scans, the MPRAGE sequence was utilised to obtain a high resolution, 1mm isotropic, T1-weighted image in the sagittal plane with the ensuing parameters: TR=2300ms; TE=1.9ms; FOV=256mm; voxel size of 1 x 1 x 1mm³; interleaved; slice thickness=1mm with 0.5mm gap. For the functional scans, T2*-weighted EPI were obtained in the oblique axial plane with the following parameters: TR = 2500 ms; TE = 29 ms; 48 interleaved slices; flip angle = 90°; FOV = 225 mm;

64 x 64 matrix giving an in-plane voxel size of 3.5 x 3.5 mm² and a slice thickness of 3.5 mm. To increase the signal measurements obtained from the subcortical regions, in particular the cerebellum, the acquisition plane was rotated 25° about the posterior vertical axis of the brainstem (Chen and Desmond, 2005a). Additionally, the E-Prime software was utilised to synchronize the collection of MRI data with the behavioural task. Participants were also provided instruction before each run through the intercom system.

Functional data analysis

Functional image analyses and processing was done via the Statistical Parametric Mapping (SPM12), software package, version 6470 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, UK, www.fil.ion.ucl.ac.uk/spm). Images (functional and structural) were all DICOM converted and reoriented to the AC-PC line. Subsequently, preprocessing was done using a protocol comprising of slice timing correction, realignment, co-registration, normalisation and smoothing. High pass filtering at 128s was also used. To correct for temporal lag during image acquisition, slice timing correction was aligned to the middle slice of the EPI images. This was followed by the realignment of images to the first volume. Structural images were then co-registered to the EPI images before they were normalised to the Montreal Neurological Institute (MNI) space. Lastly, images were smoothed using a Gaussian kernel of 8mm full-width at half-maximum (FWHM).

To estimate the experimental effects, general linear model (GLM) within SPM was utilised. Load-dependent contrast images (HL > LL) were computed individually, generating a total of 31 contrast images. All trials (HL and LL) and movement

parameters were included for the calculation and motion parameters were added as covariates of no interest in the GLM.

At the group level, load-dependent contrast images obtained from the one-sample *t*-tests were utilised to perform the random effects analyses. Only clusters of voxels that survived the FWE correction of $p < 0.05$ were reported. Cortical and subcortical activations were overlaid onto the MNI template brains, respectively, and their anatomical labels were determined using the Anatomical Automatic Labelling (AAL) (Tzourio-Mazoyer et al., 2002) within WFU PickAtlas tool (Maldjian, Laurienti, Kraft, & Burdette, 2003).

Analysis of effective connectivity

Based on previous literature (Baddeley, 2003a; Chen & Desmond, 2005a, 2005b; Wu et al., 2014) in the field of verbal working memory and language, eight a priori regions-of-interest (ROI) were selected from the left cerebral and right cerebellum: left inferior occipital gyrus (IOG) (BA 17/18), left fusiform gyrus (FG) (BA 37), left inferior frontal gyrus (IFG) (BA 44/45/47), left inferior parietal lobule (IPL) (BA 40), thalamus, pons, right superior cerebellum (VI/CrusI) and right inferior cerebellum (VIIB/ VIIIA). An anatomical mask was created for each of the ROI using the WFU PickAtlas tool (Maldjian et al., 2003) available in SPM12 (v6470), an anatomical mask was created for each of the aforementioned regions.

To obtain the peak coordinate for each of the ROIs, the anatomical masks were then applied individually to the group activation map with a threshold of $p < 0.001$ uncorrected (see Table 3.1 for group maxima of the ROIs). At the individual level, the activation maps were thresholded at $p < 0.05$ (uncorrected) and the ROI masks were applied. Volumes of interest (VOIs) were then created using 8mm radius spheres centered at the peak coordinates and within the respective ROI masks (see Table 3.1).

Regional responses were extracted based on the eigenvariates of the activated voxels within the respective VOIs. The distance between the centers of the individual VOIs and the peak coordinate was controlled within 10 mm. This criterion was introduced to ensure that the individual VOIs did not fall out of the ROI and were nearby.

Participants ($N = 8$) that did not display significant activations at one or more of the ROIs were not included in the subsequent analyses.

Table 3.1.

MNI coordinates of the group maxima in adults within the selected ROIs for the purpose of DCM

Region	Left/ Right	Cluster Size (voxel)	MNI Coordinates			T
			x	y	z	
Fusiform Gyrus	Left	109	-39	-66	-12	9.00
Inferior Occipital Gyrus	Left	190	-39	-78	-9	8.78
Inferior Frontal Gyrus	Left	229	-42	3	27	10.94
Inferior Parietal Lobule	Left	71	-27	-60	42	11.04
Thalamus	Bilateral	77	-15	-9	6	8.07
Superior Cerebellum (Lobule VI)	Right	327	21	-60	-27	12.87
Inferior Cerebellum (Lobule VII)	Right	136	21	-72	-51	8.56
Pons	Bilateral	5	-6	-42	-42	3.71

Note. Anatomical masks of each of the ROIs were applied individually to the group activation map with a threshold of $p < 0.001$ (uncorrected), to obtain the peak coordinates for the purpose of DCM.

DCM10, as implemented in SPM12 (v6470) (Functional Imaging Laboratory,

UCL, UK), was used for the analysis of effective connectivity. DCM is a non-linear system recognition process, which makes use of Bayesian methods in parameter estimation for drawing inferences about the underlying brain connectivity between neuronal regions, and examining how experimental conditions may alter the neural connectivity. Three sets of parameters were estimated using DCM: intrinsic connectivity between region (A parameters), modulatory connectivity (B parameters) and driving input from the experimental task (C parameters) using the ensuing model specification criteria. Slice timing for each of the VOIs was specified as the middle slice, as per Kiebel and colleagues (2007) recommendation that the slice timing selected should be similar to the reference slice indicated at the slice timing correction step of preprocessing. Echo time was set at 0.03s while bilinear modulatory effects were selected. Other criteria set were such as one state per region and no stochastic effects.

To examine the verbal working memory process, eight modulated pathway models were proposed based on the findings of previous studies (see Fig. 3.2 and Fig. 3.3). For the visual input and analysis, the model postulated that activity in the IOG—involved for primary visual analysis—was modulated by visual stimulation at the driving input region. Intrinsic connectivity between the IOG and the FG, which has a pertinent role in secondary visual analysis, was also proposed in the present model based on the previous findings from Wu et al. (2014). In their study examining age-related effective connectivity during a homophone judgment task, they found clear preferences across age groups for models with driving input on the IOG as opposed to both the IOG and FG. Their study also demonstrated a positive intrinsic connection from the IOG to FG. The remaining portion of the model, which is responsible for the phonological processing, is postulated based on the two cerebro-cerebellar networks—

an articulatory control system, which connects the left IFG to the right superior cerebellum and a phonological storage system that connects the left IPL to the right inferior cerebellum that were established by Chen and Desmond (2005a). The cerebro-cerebellar networks were further validated by a recent study examining the contralateral cerebro-cerebellar white matter pathways for verbal working memory using diffusion spectrum imaging (Sobczak-Edmans, 2016).

Figure 3.2. Base model for verbal working memory model. Cortical regions that were left-lateralised included the IOG, FG, IFG and IPL. Subcortical regions that were right-lateralised comprised of both the superior and inferior cerebellum. Both bilateral pons and thalamus were included.

From the base model (Fig. 3.2), eight possible pathways were considered (Fig. 3.3). Model 1 and model 2 were proposed based on the phonological loop (Baddeley, 2003a)—the models with bilateral modulatory effect from the IFG to the IPL and the IPL back to the IFG (odd-numbered models) and models with only modulatory effects from the IFG to the IPL (even-numbered models). The next six models were postulated based on the two cerebro-cerebellar networks established by Chen and

Desmond (2005a). Here, we considered the modulatory effects of verbal working memory task load on either the frontal/ superior cerebellar articulatory control system (Model 3 and 4) or the parietal/ inferior cerebellar phonological storage system (Model 5 and 6). Lastly, two more models (model 7 and 8) with the combination of modulatory effect on the two cerebro-cerebellar pathways were considered. This resulted in a total of eight models for comparison.

Using the eight postulated pathway models, Bayesian model selection (BMS) (Stephan, Penny, Daunizeau, Moran, & Friston, 2009), was done to compare the different models. Specifically, random-effect analysis (RFX) was utilised as it accounts for between subject variability unlike fixed-effect analysis (FFX). RFX-BMS estimates the parameters of a Dirichlet distribution, which includes the probability for all the models included into the analysis. This allows for the computation of the likelihood that a specific model is representative of the network pathway of a randomly chosen individual, as well as, the exceedance probability (xp) of a particular model having a higher probability than the other models considered in the model space. Based on the exceedance probability of each of the models at group level, the model with the highest exceedance probability was selected as the model that best predicts the data and is referred to hereafter as the most optimal model. For the most optimal model, one-sample *t*-tests, Bonferroni corrected, were conducted to test the significance of the parameter estimates.

Figure 3.3. Proposed networks for verbal working memory model. Black solid lines indicate modulatory connections, whereas dotted lines indicate intrinsic connections and the blue arrow indicates driving input from the visual stimuli

Results

Behavioural data

The effects of load on performance accuracy and reaction time (RT) are displayed in Figure 3.4. Performance accuracy was significantly higher ($t(30) = 4.64$, $p < 0.001$) for the low load condition ($M = 98.97$, $SD = 1.74$) in comparison to the high load condition ($M = 95.26$, $SD = 4.29$). Reaction time was also significantly shorter ($t(30) = 15.5$, $p < 0.001$) for low load condition ($M = 645\text{ms}$, $SD = 112$) as compared to the high load condition ($M = 930\text{ms}$, $SD = 170$).

Figure 3.4. Mean reaction time of accurate responses and reaction time by stimuli load in adults. Error bars represent standard deviation at 95% CI. Significant at $p < .001$ level.

Functional data

In line with the research hypotheses and past research examining the underlying neural network during verbal working memory tasks, similar pattern of activation in the left IFG, left IPL, left thalamus, pons, right inferior cerebellum and right superior cerebellum was found (Baddeley, 2003a; Chein et al., 2003; Chen &

Desmond, 2005a). Results indicated strong left cerebral, right cerebellar dominance (see Figure 3.5 and Table 3.2).

Figure 3.5. Brain activation map for the Sternberg verbal working memory task (High Load > Low Load) in adults. The axial, coronal and sagittal views displayed the activation at the group maxima. Images were thresholded at $p < 0.05$ FWE corrected.

Table 3.2.

MNI peak coordinates within the significant clusters for the effects of load (High load > Low load) in adults

Region	Left/ Right	Cluster Size (voxel)	MNI Coordinates			T
			x	y	z	
Precentral Gyrus	Left	882	-51	3	45	13.00
Precentral Gyrus	Left		-45	3	30	12.09
Insula	Left		-33	24	3	9.21

Superior Cerebellum (Lobule VI)	Right	2808	21	-60	-27	12.87
Superior Cerebellum (Lobule VI)	Right		12	-72	-21	10.97
Medial Occipital Region	Left		-5	-90	0	10.84
Superior Parietal Region	Left	383	-24	-60	42	11.58
Middle Occipital Region	Left		-27	-69	27	8.71
Medial Frontal Region	Left	350	-3	15	45	10.18
Medial Frontal Region	Left		-6	6	57	9.21
Limbic Region	Right		9	21	36	8.79
	Left	608	-21	-6	12	9.56
Caudate Nucleus	Right		15	0	18	8.83
	Right		12	-3	0	8.05

Note. Thresholded at FWE < 0.05 (corrected).

Effective Connectivity

BMS-RFX was done across all eight models. Results indicated that the data obtained from the adult population showed a better fit for model 8 ($x_p = 0.9802$) (see Figure 3.6), in which the connectivity between the following regions were modulated by the verbal working memory task: (1) connections from the IFG to the IPL, (2) IFG to superior cerebellum and (3) IPL to inferior cerebellum. Significantly lower exceedance probability was observed for the other models: Model 1 ($x_p=0.000$), Model 2 ($x_p=0.000$), Model 3 ($x_p=0.008$), Model 4 ($x_p=0.000$) Model 5 ($x_p=0.000$), Model 6 ($x_p=0.000$) and Model 7 ($x_p=0.0189$).

Parameter estimates of the driving input, intrinsic connection and modulatory effects within the most optimal model are summarised in Figure 3.6. One-sample t -

tests, Bonferroni corrected at the alpha level of 0.05 were implemented to determine if the parameter estimates were significant. All of the parameter estimates were found to be significant.

Figure 3.6. DCM parameter estimate for the most optimal model (Model 8) in adults. The number alongside the connections or modulation summarises the M(SD) of parameter estimate (in Hertz). Bolded parameter estimates represent the modulatory parameter estimates. The significance of parameter estimates was examined using one-sample t-tests, with Bonferroni correction for multiple comparisons at the alpha level of 0.05. All parameter estimates were statistically significant. Black dash-arrows indicate modulatory connections, whereas dotted arrows indicate intrinsic connections and the blue arrow indicates driving input from the visual stimuli. FG: left fusiform gyrus; IOG: left inferior occipital gyrus; IFG: left inferior frontal gyrus; IPL: left inferior parietal lobule. Both superior and inferior cerebellum are right lateralised while thalamus and pons are bilateral.

Discussion

The present study extends past investigations of dynamics in effective connectivity during verbal working memory in two ways. Firstly, most studies utilised the n-back task (Dima et al., 2014; Harding et al., 2015). In contrast, the present employed the Sternberg verbal working memory paradigm. Secondly, to the best of our knowledge, the present study was the first to include regions of interest from the cerebellum to examine the cerebrocerebellar connectivity.

Therefore, the current study had the scope to provide novel insights into the effective connectivity underlying the cerebro-cerebellar verbal working memory network. Using the Sternberg verbal working memory task paradigm, unique dynamics in effective connectivity were found both within the cerebral cortex, and between the cerebral cortex and the cerebellum. Results from the Bayesian model selection analysis indicated that the data from the adult population showed a better fit for the model with modulatory effects from the left IFG to the left IPL and right superior cerebellum (via the pons), as well as from the left IPL to the right inferior cerebellum (via the pons).

Visual input from the presentation of the task (driving input) to the left IOG—which is important for primary visual analysis—and bilateral intrinsic connectivity between the left IOG and left FG—which is pertinent for the secondary visual analysis—were found. The positive intrinsic connectivity from the left IOG to the left FG demonstrated that the activation at the left IOG has a concomitant effect on the activation at the left FG. While the parameter estimate from the left IOG to the left FG is positive, negative intrinsic connectivity was found from the left FG to the left IOG. This was interpreted an inhibitory effect whereby the increase of activation at the either the left FG or the left IOG is correlated with the decrease in activation at the

other. These findings are in line with that reported in Wu et al. (2014). In their study examining age-related effective connectivity during a homophone judgment task, data obtained from participants displayed a better fit for models with driving input at the IOG as opposed to driving input at both the IOG and left FG was found. Additionally, Wu et al (2014) found a positive intrinsic connection from the IOG to FG but negative intrinsic connection from the FG to the IOG.

The involvements of both the left IFG and left IPL in verbal working memory have been well documented with studies showing the link to phonological rehearsal and phonological storage respectively (Awh et al., 1996; Jonides et al., 1998; Smith & Jonides, 1998; Vallar & Papagno, 2002). In the present study, neuronal activation was found in both the left IFG and left IPL with positive modulatory connection from left IFG to left IPL. We postulate that the connection from the left IFG to the left IPL is related to the sub-vocal rehearsal of the letters during the encoding phase. This speculation is consistent with studies examining both neuroanatomical and neurological underpinning of the phonological loop (Chen & Desmond, 2005a, 2005b; Vallar & Papagno, 2002). Furthermore, our finding partially replicated the load-dependent bilateral modulatory effect documented in Ma et al. (2012) during an immediate recall working between the parieto-frontal regions. By contrast, negative intrinsic connectivity was observed from left IPL to left IFG, suggesting that the connectivity from IPL to IFG is inhibited. On the basis that the left IPL is linked with the phonological storage (Baddeley, 2003; Chein, Ravizza, & Fiez, 2003; Chen & Desmond, 2005a), we postulate that this could be interpreted as such: after phonological/verbal information is transferred from the left IFG to the left IPL for temporary storage, the activity in the IPL would be inhibited and only important information would be transferred back to the IFG.

Although the cerebellar role in verbal working memory has been less well understood and less investigated than the fronto-parietal network, both the right lobule VI/crusI and right lobule VIIIB have been previously documented to be involved in verbal working memory (Desmond et al., 1997; Chen and Desmond 2005a). Therefore, we included both the right superior and inferior cerebellum as part of the network pathway in the examined models. Positive modulatory effects from the left IPL to the right inferior cerebellum (via the pons) and from the pons to the left inferior cerebellum were observed. However, negative modulatory effects were observed from the inferior parietal lobule (IPL) to the pons.

On the basis that the IFG has been previously linked with the articulatory control, it is likely that superior cerebellum also supports articulatory control during verbal working memory. Similarly, the IPL is involved in functions of phonological storage; therefore, it is possible that the inferior cerebellum, by receiving a positive modulation effect from the IPL, also contributes to this function. This conjecture is in line with past fMRI findings by Chen and Desmond (2005a), that the IFG and the superior cerebellum are co-activated during articulatory rehearsal, whereas the IPL and the inferior cerebellum are co-activated during the phonological storage processing. The superior and inferior cerebellum could enhance these phonological loop functions by providing automation and predictive mechanisms (Caligiore et al., 2016), given that the cerebellum is known to be a key neural structure involved in acquisition and adjustment of learnt information, in order to generate the most economical responses in similar contexts (Koziol, Budding, & Chidekel, 2011).

The inhibitory modulatory effects observed from the IPL to the pons could be postulated as the following: as the difficulty of the task increases, the phonological store (IPL) is required to work harder to inhibit the unnecessary information by

working as a first pass filter before information is transmitted to the pons. Thereafter, excitatory modulatory effects can be observed from the pons to the inferior cerebellum, which continues on to the feedback loop.

The utilisation of the Sternberg verbal working memory task paradigm in the present study elicited differential dynamics in effective connectivity in comparison to previous studies that employed the n-back task (Dima et al., 2014; Ma et al., 2012). This may be attributed to the functional distinction in neural activation elicited during the different task paradigm as seen in E et al (2014) study, which examined differences in brain activation elicited by the different working memory paradigm. For the n-back task, both left and right Crus 1 were found to be activated while the Sternberg task elicited activation in the bilateral Crus 2 and right Lobules VI, VIII and IX.

Likewise, in the Dima et al (2014) and Ma et al (2012) n-back studies, positive bilateral connections between the fronto-parietal regions were found. In contrast, positive connection from IFG to IPL and negative connection from IPL to IFG have been found in our study, which employed the Sternberg task paradigm. We postulate that this could be attributed to difference in task paradigm whereby the Sternberg task only taps on the maintenance component of verbal working memory while the n-back task requires both the maintenance and manipulation components (Veltman, Rombouts, & Dolan, 2003).

Verbal working memory processing can be segregated into various components, which include maintenance and manipulation. As with its variants, the Sternberg task (Sternberg, 1966) has been employed to explicate the role of specific brain regions involved in the different processes associated with working memory. The Sternberg task comprises of three distinct phases. Firstly, the encoding phase,

which involves the presentation of stimuli which participants are instructed to commit to memory. Secondly, the maintenance phase, during which participants are expected sub-vocally rehearse the earlier presented stimuli. Lastly, the probe phase, where participants are required to evaluate whether the probe matched the array of stimuli presented during the encoding phase and make a response typically via button press. In contrast, the n-back generally involves the presentation of a sequence of stimuli after which, participants are instructed to recall if a particular stimulus was displayed n trials before the present one. It is postulated that there are two distinct processes involved when participants perform the n-back task. The first involves a complex updating mechanism in the working memory and the other involves the search and matching of the task stimuli. In a neuroimaging study, Veltman et al. (2003) found that the Sternberg task and n-back task elicited a functional distinction rather than a neuroanatomical difference. This suggests that though both variants of verbal working memory tasks activated similar regions, the functional activation differed between the two tasks. This further illustrates the importance of understanding the dynamics in effective connectivity during a Sternberg task.

Although this study furthered current understanding of the unique dynamics in effective connectivity in typical adults during the Sternberg verbal working memory task, the findings should be considered in light of several limitations. First, the present study utilised a block task paradigm. Hence, it was not possible to distinguish the modulatory effect on specific components during the task such as the encoding and retrieval processes.

Additionally, due to the nature of the standard block design fMRI analysis, responses regardless of its accuracy were included into the analyses. Future studies with event-related task paradigm are warranted to understand the specific components

that are observed during task modulation. Secondly, the present study compared eight possible pathway models based on the cerebro-cerebellar model of verbal working memory. Nonetheless, it is pertinent to highlight that there may be other plausible pathway models for verbal working memory processing that was not explored in the present study that would be interesting for future studies to look into. Lastly, the present study only explored the connectivity within a left cerebral and right cerebellum framework. Future studies are needed to examine homologous brain regions in addition to the specific ROIs included in the present study.

In summary, the study builds substantially upon previous research and provides supplementary evidence for the frontal/superior cerebellar articulatory pathway and the parietal/inferior cerebellar phonological storage pathway.

CHAPTER IV: STUDY 2A

Effective Network connectivity in typically developing children during Verbal
Working Memory: Understanding the Effect of Neurodevelopment

Introduction

Verbal working memory serves as a fundamental building block for complex cognitive processes such as reading, which is pertinent for knowledge gathering. Limited studies have examined the neurodevelopmental changes of the neural substrate during verbal working memory. Nonetheless, Casey and colleagues (1995) provided preliminary understanding of the neuronal regions engaged during verbal working memory in the pediatric population. Also, it is noteworthy that adults and children have been found to display similar patterns of activation at both the inferior and middle frontal gyri. Subsequently, studies by Luciana and Nelson (2000) as well as Luna and colleagues (2004) found that working memory performance improved from childhood to adolescence, and through to early adulthood.

More recently, Crone and colleagues (2006) found that although children exhibited comparable activation profiles in the ventral lateral prefrontal cortex (VLPFC) during the maintenance phase of an object WM task as adults, they failed to recruit the right dorsal lateral prefrontal cortex (DLPFC) and bilateral superior parietal cortex if additional manipulation demands were added on during the delay phase. The finding provided evidence that the fronto-parietal regions in verbal working memory networks are less functionally developed in children relative to adults. Additionally, it raised the likelihood that the neurodevelopmental disparities in brain activity may only be observable in tasks that place greater demands on working memory.

To further understand the effect of working memory demand on the underlying neural network across age groups, O'Hare and colleagues (2008) explored developmental differences in three age groups—children, adolescence and young adults—using the Sternberg verbal working memory task paradigm. They found that participants across all three groups engaged the cerebro-cerebellar network. However,

significant age-related differences were found in relation to working memory load-dependency. This suggests that increases in age are associated with a greater number of brain regions exhibiting linear load-dependency. In particular, while children display increasing activation in the left ventral prefrontal cortex only, this pattern is observed in the right prefrontal, left parietal, superior cerebellum bilaterally (VI/Crus I), and right inferior cerebellum (VHA/VIIB) regions in adolescents and young adults. Results from the study extended the findings of earlier research through demonstrating that the neural basis of verbal working memory load-dependency changes with maturation.

While several studies have evaluated the neurodevelopmental differences of the neural substrate during verbal working memory (Casey et al., 1995; Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006; Luna et al., 2004; O'Hare et al., 2008), Finn and colleagues (2010) went beyond the study of co-activated regions during verbal working memory and examined functional connectivity within the networks associated with verbal working memory. The study evaluated the functional network connectivity differences from mid to late adolescence and documented developmental differences in connectivity in the prefrontal and hippocampal regions (Finn et al., 2010). Using a region of interest approach as opposed to a data-driven approach (Finn et al., 2010), van den Bosch and colleagues (2014) examined neurodevelopmental changes across three groups—children, young adolescents and older adolescents—using a modified Sternberg task paradigm. The seed based functional connectivity analyses found age-related differences between children and adolescents in the first load-dependent network and between children and older adolescent in the second load-dependent network: (i) the left motor and right cerebellum, which have been linked with motor coordination, and (ii) the left

prefrontal cortex, left parietal lobe and right cerebellum, which are regions found to be involved during load-dependent verbal working memory (van den Bosch et al., 2014).

Despite differences in age groups studied, analyses approaches, and regions of interest selected, majority of the studies have demonstrated an age-related increase in activations at regions of interest associated with the load-dependent verbal working memory. To the best of our knowledge, however, no study has attempted to understand the effective network connectivity during verbal working memory in typically developing children. By examining how the different regions involved during verbal working memory interact, a more granular understanding of verbal working memory network in children may be attained.

Therefore, the current study aimed to investigate the effective connectivity network in typically developing children by building upon earlier neurodevelopmental research. Additionally, by using our earlier study on the effective network connectivity in young adults as a framework, this study will focus on the cross-sectional neurodevelopmental changes in effective network connectivity during verbal working memory between children and young adults. Furthermore, it is pertinent to have clear knowledge of the normal developmental trajectory of verbal working memory as a basis before elucidating how developmental disorders such as dyslexia may cause a difference in the network.

Methodology

Participants

Fourteen typically developing children with no prior history of neurological or psychiatric conditions enrolled for the study. All children were between seven to ten years of age and studying in mainstream schools. The children all received compulsory bilingual education in mainstream school, with English as the first

language and their mother tongue (I.e. Chinese, N=7; Malay, N=3; and Tamil, N=0) as second language. Two participants were subsequently excluded from the study due to excessive head motion greater than 5mm. Another two were excluded due to lack of functional activity at one or more of the region of interest when thresholded at $p < 0.05$ (uncorrected). As such, only 10 typically developing children were included in the study.

The mean age of the participants (six males, four females) was 7.8 years ($SD=1.03$ years; range: 7 to 10). All participants were right-handed based on the Edinburgh Handedness Inventory (EHI) score: $M = 100.00$, $SD = 0.00$).

Prior to the start of the experiment, parental informed consent and child assent were obtained from all participants. Ethics approval was also obtained from both the Nanyang Technological University Institutional Review Board and the National University of Singapore Institutional Review Board.

Children underwent two phases of the study: Phase 1 included a brief neurocognitive test battery to assess the child's reading ability as well as a pediatric MRI protocol, designed to decrease dropout rate. Phase 2 comprised of a short recap of the Sternberg verbal working memory task and the functional magnetic resonance imaging (fMRI) scan.

Brief neurocognitive test battery

All participants underwent a brief neurocognitive battery, which provided an indicator of the child's cognitive profile related to reading ability. The battery consisted of: (1) The Raven's Colored Progressive Matrices (CPM), which provides an estimate of children's intellectual functioning, (2) Five subtests of the Comprehensive Test of Phonological Processing – Second Edition (CTOPP-2)—The blending words (BW), phoneme isolation (PI), blending nonwords (BN) and segmenting non-words

(SN), which measure children's phonological awareness/processing skills and the rapid digit naming (RDN) subtest to measure children's rapid automatised naming skill, (3) The number memory forward and number memory reversed subtests of the Test of Auditory Processing Skills—Third Edition (TAPS-3), which assess children's verbal working memory and (4) Two subtests of the Wide Range Achievement Test (WRAT-4)—Word Reading and Sentence Comprehension, which measures an individual's ability to read words and comprehend sentences.

Pediatric MRI protocol

Excessive head movement, anxiety and lack of cooperativeness have been some of the long-standing challenges of pediatric MRI research. In view of these challenges and the lack of access to a mock scanner, a pediatric MRI protocol was developed and piloted for the purpose of the present study. The protocol adapted methods from past studies (Nordahl et al., 2008; Raschle et al., 2012; Thomason, 2009; Yerys et al., 2009), and integrated feedback from participants and their parents during the piloting phase of the protocol development. With that, the finalised pediatric MRI protocol comprised four components (i) Attitudinal and Anxiety Questionnaire, (ii) MRI video, (iii) MRI experience and (iv) VWM task practice session, as depicted in Figure 4.1.

Figure 4.1. Components of the pediatric MRI protocol.

To understand both parents' and children's knowledge about MRI scanning as well as their affective state, an attitudinal and anxiety questionnaire (refer to Appendix A) was administered to both parents and children at the start and end of the protocol. Questions assessing affective state were adapted from the Spence Children's Anxiety Scale (Spence, 1998) while MRI knowledge questions were selected based on reviews and feedback during the protocol development stage to best understand participants' knowledge, experience and assumptions of MRI scans.

A MRI video was also specially created with the use of a family cartoon character "Tigger" from the cartoon, Winnie the Pooh, to guide participants on what to expect on the day of the MRI scan by observing Tigger's MRI experience. Through the video, they will also get to see actual MRI site as well as the MRI spaceship (see Figure 4.2) that they will be entering. The purpose of the MRI video is to help children familiarize themselves with the surrounding that they will be at and the things they would be doing on the day of the MRI scan as well as to alleviate any possible fear or anxiety.

Figure 4.2. 3-T Siemens MRI scanner with the spaceship theme cover designed for the purpose of the study.

After watching the video, participants were brought through a series of interesting activities beginning with the MRI simulation (see Figure 4.3). The MRI simulation makes use of a children play tunnel to resemble the MRI environment by playing the sounds that participants would be hearing during the MRI scan. Through this activity, participants will have a better understanding of the experience of being in an MRI scanner and be accustomed to the MRI noises. Additionally, researchers were instructed to pay attention to any signs of hyperactivity and distress displayed by participants while in the tunnel to screen out possibility of claustrophobia. In comparison to previous studies that utilised mock scanners, using a children play tunnel provided researchers the flexibility to carry out the MRI protocol at any given location and timeslots. To highlight the importance of keeping still during the MRI

scan, the activity—Photo Journey, was created where by children looked at a series of blur and clear photos (see Figure 4.4). Children were then asked to divide the photos into two stacks— “clear” and “blurry”. Thereafter, they were informed that they would be given a photo of their brain in a photo frame that they could decorate and that the photo would only be nice if they stayed still.

Figure 4.3. MRI simulation/ mock scanner

Figure 4.4. Photo journey picture cards. Children were asked to choose the clear photo

Lastly, children were asked to perform the Sternberg Verbal Working Memory task, which they would be doing in-scanner, on a laptop. They first went through a demonstration which explained the task to them. Thereafter, they underwent a practice session—a shorter version of the actual in-scanner task—which is documented in the next section. All participants had to attain an 80% accuracy rate to demonstrate familiarisation with the experimental procedures during the practice session prior to proceeding to the second phase of the study (MRI scan).

Task description

All participants completed four runs of the Sternberg working memory task while being scanned as illustrated in Figure 4.5. Visual stimuli were presented on a

Toshiba Portege computer with E-Prime version 2.0 (Psychology Software Tools, Inc, Pittsburgh, US) software during the MRI scan.

During the task (see Figure 4.5), participants were prompted to the commencement of the trial with the display of a red fixation cross at the center of the screen for one second. This was followed by the encoding phase, which entailed the change in display to either the low load condition with six identical uppercase letters of the high load with six different lower-case letters for three seconds. Similarly, letters were displayed in the center of the screen. Successively, during the maintenance phase, participants were presented a centered white fixation cross for three and a half seconds. Lastly, a lowercase probe letter was presented for two and a half seconds and participants were instructed to respond accordingly—if the letter presented matched any of the letters in the corresponding encoding phase, participants were asked to indicate with a button press corresponding to their right middle finger for a match and their right index finger for a non-match. All participants were requested to sub-vocally rehearse the letters sequentially throughout the three seconds maintenance period. Additionally, they were also instructed to respond as accurately and as quickly as possible during the probe phase. The stimuli were back-projected onto a screen and viewed via a mirror mounted on the birdcage coil.

Visual stimuli were presented in a block design. Blocks comprised either two high- or two low-load trials. Block duration was 20 seconds. A total of 10 blocks (5 high load; 5 low load) in a run took 200 seconds to complete. A total of 4 runs yielded a total of 40 high load and 40 low load trials. Task order was counterbalanced across participants.

Figure 4.5. Sternberg's verbal working memory task paradigm

Behavioural data analysis

Paired-sample *t*-tests were conducted to investigate the effects of stimuli load on accuracy rate and reaction time on the typically developing children subsample. To understand the behavioural differences between children and adult, a two-way repeated measures analysis of variance (ANOVA) with load (low, high) as the within-subjects variable and group (typically developing children, adult) as the between-subjects variable were conducted.

Multiband echo planar imaging

A general limitation in many fMRI studies, especially pediatric studies, is the lack of sufficient statistical power, which decreases the ability of a study to detect true effects. It is pertinent to address this issue given the importance of producing research that is reliable and reproducible when designing a study. Low statistical power may be attributed to factors such as small sample size or small effect size. General recommendations to overcome such limitation is to increase the sample size, which may be challenging due to reasons such as high imaging cost, high drop-out rates (e.g.

pediatric population), or in cases where it is impractical to increase scan time (e.g. patient and pediatric population).

With that in mind, the image acquisition parameter for both pediatric studies (typically developing children and children with dyslexia studies) were set up differently from the adult study, documented in the previous chapter, for optimal acquisition of whole brain data in the pediatric population. Multiband echo planar imaging (EPI) was utilised to reduce scan time and improve statistical power (Feinberg et al., 2010).

Multiband EPI was first introduced by Nunes (Nunes, Hajnal, Golay, & Larkman, 2006). This was followed by a major advancement in the field when the blipped-CAIPI approach was developed (Feinberg & Setsompop, 2013). The approach enabled the simultaneous acquisition of excited slices, which contributes to a significant increase in the temporal resolution as the acceleration factor is obtained from the number of simultaneously excited slices. In the present study, an acceleration of factor of four was utilised to simultaneously acquire four slices at each time point. As such, 200 volumes per subject were obtained in each run, yielding a total of 800 volumes per subject across four runs.

Image acquisition

A 3-Tesla Siemens MRI scanner (Siemens Trio, Erlangen, Germany), equipped with a 32-channel birdcage head coil was utilised to acquire the whole-brain MRI data. To reduce head movements, foam padding was used to pack the participant's head within the head coil. A combination of localizer, structural and functional scans were done as part of the acquisition protocol. For the structural scans, the MPRAGE sequence was applied to obtain a high resolution, 1mm isotropic, T1-weighted image in the sagittal plane with the ensuing parameters: TR=1950ms; TE=3.06ms;

FOV=256mm; voxel size of $1 \times 1 \times 1\text{mm}^3$; interleaved; slice thickness=1mm with 0.5mm gap. For the functional scans, T2*-weighted EPI were obtained in the oblique axial plane with the following parameters: TR = 1000 ms; TE = 30 ms; 52 interleaved slices; flip angle = 90° ; FOV = 200 mm; voxel size of $2.5 \times 2.5 \times 2.5\text{mm}^3$ and a slice thickness of 2.5 mm. To increase the signal measurements obtained from the subcortical regions, in particular the cerebellum, the acquisition plane was rotated 25° about the posterior vertical axis of the brainstem (Chen and Desmond, 2005a). Additionally, the E-Prime software was employed to synchronize the collection of MRI data with the behavioural task. Participants were also provided instruction before each run through the intercom system in the magnet room.

Functional data analysis

Functional image analyses and processing was done via the Statistical Parametric Mapping (SPM12), software package, version 6470 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, UK, www.fil.ion.ucl.ac.uk/spm). Images (functional and structural) were all DICOM converted and reoriented to the AC-PC line. Subsequently, preprocessing was done using a protocol comprising of slice timing correction, realignment, co-registration, normalisation and smoothing. High pass filtering at 128s was also used. To correct for temporal lag during image acquisition, slice timing correction was aligned to the middle slice of the EPI images. This was followed by the realignment of images to the first volume. Structural images were then co-registered to the EPI images before they were normalised to the Montreal Neurological Institute (MNI) space. Lastly, images were smoothed using a Gaussian kernel of 8mm full-width at half-maximum (FWHM).

To estimate the experimental effects, general linear model (GLM) within SPM was utilised. Load-dependent contrast images (HL > LL) were computed individually, generating a total of 10 contrast images. All trials (HL and LL) and movement parameters were included for the calculation. Both correct and incorrect trials were included into the statistical analysis as a two-sample *t*-test was conducted and no significant activation differences were found between children with high accuracy (> 70%) and children with lower accuracy (<70%).

Group-level random effects analyses were conducted on task-specific contrasts with one-sample *t*-tests. Only clusters of voxels that survived the uncorrected thresholding of $p < 0.005$; $k=20$ were reported. According to Lieberman & Cunningham (2009), a combined intensity and cluster thresholding of $p < 0.005$; $k=20$ would be comparable to a false discovery rate (FDR) correction of $p < 0.05$. Additionally, to determine if activations at the regions of interests would still be observed with a more stringent thresholding, a cluster-level thresholding of $p < 0.05$, FWE corrected with a cluster-defining primary threshold of uncorrected $p < 0.001$ was applied (Woo, Krishnan, & Wager, 2014).

Cortical and subcortical activations were superimposed onto the MNI template brains, respectively, and their anatomical labels were determined using the Anatomical Automatic Labelling (AAL) (Tzourio-Mazoyer et al., 2002) within WFU PickAtlas tool (Maldjian et al., 2003).

Laterality index

Verbal working memory has predominately been associated with an activation pattern of left cerebro—right cerebellar in typical adults. In a recent study by Ng and colleagues (2016), researchers utilised the AveLI software (Matsuo, Chen, & Tseng, 2012) to compute the lateralisation of the neural activity during both visual and verbal

working memory in typical adults and replicated a similar pattern of activation during verbal working memory. Although the hemispheric lateralisation during Sternberg verbal working memory task in typical adults has been well established, little is known about the lateralisation in children.

Using the AveLI (Matsuo et al., 2012), the lateralisation of the brain activation during the Sternberg verbal working memory task was analysed in typically developing children. AveLI computes the laterality index (LI) by utilising the task-related positive voxel t-values to compute the laterality index of two homologous regions of interest (ROIs). The subordinate Lis (sub-Lis) are calculated using the task-specific positive beta-values with the following equation:

$$sub - LI = \frac{Lt - Rt}{Lt + Rt}$$

The summations of positive task-specific voxel t-values at and above an arbitrary threshold in the left and right ROIs are represented by Lt and Rt respectively.

Thereafter, the laterality index is calculated by averaging the sub-LIs in the ROI using the following equation:

$$AveLI = \frac{\sum(sub - LI)}{VN}$$

where the total number of positive t-values voxel in the ROIs is represented by VN.

AveLI indicates how consistently lateralised the performance of the subject is across a full range of voxel t-values thresholds.

Analysis of effective connectivity

Using similar regions-of-interest as the adult study, the anatomical masks for all eight ROIs were applied to the activation map. To obtain the peak coordinate for each of the ROIs, the anatomical masks were then applied individually to the group activation map with a threshold of $p < 0.005$ (uncorrected) (see Table 4.1 for group

maxima of the ROIs). At the individual subject level, peak coordinates were obtained by applying the respective ROI masks on the individual subject's activation map, which was thresholded at $p < 0.05$ (uncorrected). Subsequently, volumes of interest (VOIs) were created within 10mm of the peak coordinates (see Table 4.1) using spheres with 8mm radius, and regional responses were extracted based on the eigenvariates of the activated voxels within the respective VOIs. Participants ($N = 2$) that did not display significant activations at one or more of the ROIs were not included in the subsequent analyses.

Table 4.1.

MNI coordinates of the group maxima in typically developing children within the selected ROIs for the purpose of DCM

Region	Left/ Right	Cluster size (voxel)	MNI Coordinates			T
			x	y	z	
Fusiform Gyrus	Left	114	-38	-66	-17	5.54
Inferior Frontal Gyrus	Left	22	-38	9	11	6.86
Inferior Occipital Gyrus	Left	148	-30	-96	-12	5.54
Inferior Parietal Lobule	Left	13	-28	-56	46	4.01
Thalamus	Bilateral	3	0	-14	6	4.87
Inferior Cerebellum (Lobule VII)	Right	202	33	-71	-52	7.95
Superior Cerebellum (Lobule VI)	Right	435	18	-76	-20	6.5
Pons	Bilateral	21	-3	-39	-35	4.52

Note. Anatomical masks of each of the ROIs were applied individually to the group activation map with a threshold of $p < 0.005$ (uncorrected), to obtain the peak coordinates for the purpose of DCM.

Results

Pediatric protocol efficacy

To assess the efficacy of the protocol, a “successful scan” is defined as children completing an anatomical reference scan and all four runs of the fMRI task (regardless of the activation obtained) for the purpose of the present study.

Noteworthy, the evaluation of protocol included participants from study 2a (typically developing children) and study 2b (children with dyslexia).

After completing the pediatric MRI protocol, 83.9% of the participants were able to go through the scan successfully. Twenty-six successful scans were collected out of a total of 31 children (14 typically developing children and 17 children with dyslexia) that participated in Phase 2 (MRI scan) of the study. The main reasons for dropout were: (1) excessive head motion ($n = 3$) and (2) fear of being in the MRI machine ($n = 2$).

Behavioural data

To understand the effects of load on response accuracy and reaction time (RT) for typically developing children, t -test were computed, with results displayed in Figure 4.6. Typically developing children displayed a significantly higher proportion of accurate responses $t(9) = 4.02$, $p = .003$, in the low load condition ($M = .795$, $SD = .175$) compared to the high load condition ($M = .656$, $SD = .121$). In addition, they exhibited significantly shorter reaction times $t(9) = -5.71$, $p < .001$, in the low load condition ($M = 1200$, $SD = 292$) relative to the high load condition ($M = 1510$, $SD =$

188).

Figure 4.6. Mean proportion of accurate responses and reaction time by stimuli load, for typically developing children. Error bars represent standard deviation at 95% CI.

To understand the cross-sectional age-related differences, repeated-measures ANOVA analysis was done to examine the differences in accuracy rates; results are summarised in Table 4.2 and Figure 4.7. When comparing typically developing children to adults (from study 1), an effect of Group on accuracy, $F(1, 39) = 91.8, p < .001$ was found. Adults displayed significantly better accuracy than children. There was an effect of Load on accuracy, $F(1, 39) = 54.8, p < .001$. Both adults and children responded less accurately to high load stimuli than low load stimuli. A significant Group X Load interaction effect was observed, $F(1, 39) = 18.3, p < .001$. Inspection of estimated marginal means revealed that high-load stimuli adversely affected children's response accuracy to a greater degree than that of adults.

Table 4.2.

Repeated-measure ANOVA analysis on accuracy rates.

	<i>df1</i>	<i>df2</i>	<i>F</i>	<i>p</i>	η
Main Effects					
Group	1	39	91.8	.000***	.70
Load	1	39	54.8	.000***	.58
Interaction Effects					
Group X Load	1	39	19.3	.001**	.32

Note. *** $p < .001$; ** $p < .01$. Group represents both adults and children while load refers to high load/ low load.

Figure 4.7. Interaction effect and mean accuracy by stimuli load, for adults and typically developing children. Significant main effects for group ($p < 0.001$) and load ($p < 0.001$), as well as a significant interaction effect ($p < 0.001$) was found. This indicates that the decrease in performance from low to high load is greater for children than for the adult group.

Repeated-measures ANOVA analysis was also done to examine the differences

in reaction time. When comparing typically developing children to adults, an effect of Group on RT, $F(1, 39) = 92.8, p < .001$ was found. Adults displayed significantly shorter reaction times than children. There was an effect of Load on RT, $F(1, 39) = 180, p < .001$. Both adults and children took significantly longer to react to high load stimuli than low load stimuli. No Group X Load interaction effect was observed, $F(1, 39) = .212, p = .65 (ns)$. Table 4.3 and Table 4.8 summarises the results of the ANOVA analysis on RT.

Table 4.3.

Repeated-measures ANOVA analysis on reaction time.

	<i>df1</i>	<i>df2</i>	<i>F</i>	<i>p</i>	η
Main Effects					
Group	1	39	92.8	.000***	.70
Load	1	39	180	.000***	.82
Interaction Effects					
Group X Load	1	39	.212	.65	.05

Note. *** $p < .001$. Group represents both adult and children while load refers to high load/ low load.

Figure 4.8. Interaction and mean reaction time by stimuli load, for adults and typically developing children. Significant main effect for group and for load ($p < 0.001$) was found. However, the interaction effect is not significant. This indicates that the increase in reaction time from low to high load did not differ between the adults and children.

Functional data

In line with previous studies examining the underlying neural activation in children during verbal working memory, the present study found similar load-dependent activation in the left prefrontal region and the right inferior and superior cerebellum (Figure 4.9 and Table 4.4) (O'Hare et al., 2008; Thomason et al., 2009) of typically developing children.

Figure 4.9. Brain activation map for the Sternberg verbal working memory task (High Load > Low Load) in typically developing children. The axial, coronal and sagittal views showed the activation at the group maxima for the ROIs. Activation was thresholded at $p < 0.005$; $k=20$.

Table 4.4.

MNI peak coordinates within the significant clusters for the effects of load (High load > Low load) in typically developing children.

Region	Left/ Right	Cluster Size (voxel)	MNI Coordinates			T
			x	y	z	
Medial Frontal Region	Left	344	-8	4	56	9.41
Medial Frontal Region	Left		-3	17	43	5.08
Cerebellum—Lobule 4-5	Left	3019	-10	-44	-20	8.11
Inferior Cerebellum—Lobule 8	Right		33	-71	52	7.95
Inferior Occipital Region	Left		-15	-66	13	6.62
Insula	Right	121	35	12	3	7.49
	Left	328	-30	-1	38	7.24
Precentral Gyrus	Left		-58	2	38	4.72
	Left		-35	-6	31	4.58
Inferior Frontal Region	Left	88	-38	9	11	6.86
Superior Occipital Region	Left	20	-18	-71	28	5.12
Cerebellum—lobule 9	Left	24	-10	-61	-52	4.83
Inferior Occipital	Right	28	35	-96	-10	4.34
Anterior Limbic Region	Right	75	8	29	28	4.20
Superior Parietal Region	Left	65	-25	-54	46	4.15
Inferior Occipital Region	Right	24	13	-76	16	3.61
Inferior Occipital Region	Right		20	-74	13	

Note. Activation was thresholded at $p < 0.005$ (uncorrected) with minimum cluster $\geq$ 20 voxels.

To examine if the activations of the regions of interests observed when thresholded at $p < 0.005$; $k=20$ would survive more stringent threshold, a cluster-level thresholding of $p < 0.05$, FWE corrected with a cluster-defining primary threshold of uncorrected $p < 0.001$ was applied (Figure 4.10 and Table 4.5). The cerebellar activations were observed to survive this more stringent threshold indicating their robustness despite the small sample.

Figure 4.10. Brain activation map for the Sternberg verbal working memory task (High Load > Low Load) in typically developing children. The axial, coronal and sagittal views showed the activation at the group maxima for the ROIs. Cluster-level thresholding of $p < 0.05$, FWE corrected with a cluster-defining primary threshold of uncorrected $p < 0.001$ was applied. Cerebellar activations were still observed with this more stringent threshold.

Table 4.5.

MNI peak coordinates within the significant clusters in typically developing children for the effects of load (High load > Low load) using a more stringent thresholding.

Region	Right/ Left	Cluster Size (voxel)	MNI Coordinates			T
			x	y	z	
Medial Frontal Region	Left	113	-8	4	56	9.41
Medial Frontal Region	Left		-3	17	43	5.08
Cerebellum—Lobule 4-5	Left	137	-10	-44	-20	8.11
	Left		-8	-24	-10	6.58
	Right		3	-31	-20	6.57
Inferior Cerebellum— Lobule 8	Right	124	33	-71	-52	7.95
Cerebellum—Lobule Crus2	Right		13	-79	-42	4.93
Insular	Right	50	35	12	3	7.49
	Left	60	-30	-1	38	7.24
	Left		-35	-6	31	4.58
Superior Cerebellum— Lobule 6	Right	229	18	-76	-20	6.50
Superior Cerebellum— Lobule 6	Right		30	-64	-27	5.72
Cerebellum—Lobule 7	Bilateral		0	-81	-22	5.47
Inferior Occipital Region	Left	89	-13	-104	-2	5.99

Note. Activation was thresholded at $p < 0.05$, FWE corrected with a cluster-defining primary threshold of uncorrected $p < 0.001$ to examine if activations of the regions of interests would survive more stringent threshold.

Laterality Index

To examine if typically developing children showed similar left cerebro-right cerebellar lateralisation as documented in adults a laterality index analysis was done using AveLI (Matsuo et al., 2012). Results at the cortical regions found left lateralisation at the IFG while the IPL showed bilateral activity tilted towards leftward asymmetry. At the subcortical regions, the inferior cerebellum showed right lateralisation while the superior cerebellum was found to be bilateral with rightward asymmetry (see Table 4.6).

Table 4.6.

Mean and standard deviation of the Laterality Indices (LI) in typically developing children

ROIs	Mean	SD	Laterality
IFG	0.21	0.37	Left
IPL	0.15	0.69	Bilateral (leftward asymmetry)
Inferior Cerebellum	-0.40	0.44	Right
Superior Cerebellum	-0.12	0.27	Bilateral (rightward asymmetry)

Note. Mean of 0.2 and above denotes left lateralised while -0.2 and below denotes right lateralised. SD: Standard deviation.

Effective connectivity

Bayesian Model Selection (BMS) analysis was conducted on all eight models to examine which model best accounted for the data acquired from typically developing children. Data obtained indicated a better fit for model 8 ($x_p = 0.7504$) (see Figure 4.11), in which verbal working memory task modulated the connections from the IFG to the IPL, IFG to superior cerebellum and IPL to inferior cerebellum. The

exceedance probabilities for the other models were as followed: Model 1 ($x_p=0.0122$), Model 2 ($x_p=0.0119$), Model 3 ($x_p=0.0130$), Model 4 ($x_p=0.0594$) Model 5 ($x_p=0.0124$), Model 6 ($x_p=0.0131$) and Model 7 ($x_p=0.1276$) as documented in Figure 4.10.

Figure 4.11. Results of the BMS analysis; exceedance probability (x_p) of all eight models in typically developing children.

Parameter estimates of the driving input, intrinsic connection and modulatory effects within the most optimal model (Model 8) are summarised in Figure 4.12. One-sample t -tests, Bonferroni corrected at the alpha level of 0.05 were performed to examine if the parameter estimates were significant. All of the parameter estimates were significant.

Figure 4.12. DCM parameter estimate for the most optimal model (Model 8) that fits the data obtained from typically developing children. The number alongside the connections or modulation summarises the $M(SD)$ of parameter estimate (in Hertz). Bolded parameter estimates represent the modulatory parameter estimates. The significance of parameter estimates was examined using one-sample t-tests, with Bonferroni correction for multiple comparisons at the alpha level of 0.05. Significant parameter estimates were denoted by an asterisk (*). Black dash-arrows indicate modulatory connections, whereas dotted arrow indicates intrinsic connections and the blue arrow indicates driving input from the visual stimuli. FG: left fusiform gyrus; IOG: left inferior occipital gyrus; IFG: left inferior frontal gyrus; IPL: left inferior parietal lobule. Both superior and inferior cerebellum are right lateralised while thalamus and pons are bilateral.

Discussion

Previous studies such as Finn et al. (2010) and van den Bosch et al. (2014) have demonstrated age-related changes in functional connectivity during verbal working memory. However, the influence that different neuronal systems in verbal working memory network exert over one another has yet to be well understood. In the current study, the Sternberg verbal working memory task paradigm was utilised to explore the neurodevelopmental cross-sectional effective network connectivity changes during verbal working memory. The study aimed to elucidate the effective connectivity pathway model that best fits the child population, and examine the cross-sectional age-related changes on the pathway between adult and children.

In the Sternberg verbal working memory task, both adults and children had lower accuracy rates and slower reaction times during the high load trials as compared to the low load trials, which indicates that the increase in difficulty (high load) was taxing on verbal working memory capacity. Additionally, in line with previous behavioural studies, children made significantly more errors and had significantly longer reaction times as compared to the young adults. This may be accounted for by the reduced verbal working memory capacity where it is thought that the working memory develops gradually through childhood to late adolescents, where it starts to stabilize (Crone et al., 2006; Gathercole, Pickering, Ambridge, & Wearing, 2004; Huizinga, Dolan, & van der Molen, 2006). Consistent with reduced accuracy rate observed in children, load-dependent activation differences were also observed. Decreased functional activation at the regions of interests (left inferior frontal gyrus, left inferior parietal lobule, right inferior cerebellum and right superior cerebellum) was found when comparing children to adults.

The decrease in activation observed in children parallels that of previous studies examining the neurodevelopmental changes during verbal working memory (O'Hare et al., 2008; Thomason et al., 2009; Vogan, Morgan, Powell, Smith, & Taylor, 2016). Although children are found to display decreased activation in regions of interest involved in verbal working memory, they displayed similar hemispheric lateralisation as adults during the task. Verbal working memory tasks, in particular the Sternberg verbal working memory task paradigm, has been characterised to elicit a left cerebral, right cerebellum pattern of activation in the adult population (Chen & Desmond, 2005a; Ng et al., 2016). Existing studies examining the pediatric population have also found similar left lateralisation in the cerebral cortex (Thomason et al., 2009). Novel to the present study was the right lateralisation of the cerebellum, resembling the pattern observed in the adult population.

In addition to hemispheric lateralisation, distinctive dynamics in effective connectivity were also observed between regions within the cerebral cortex and region between the cerebral cortex and the cerebellum via the pons. Using Bayesian model selection analysis, data obtained from the typically developing children indicated a better fit for Model 8—unilateral modulatory effect on three pathways (1) from the inferior frontal gyrus to the inferior parietal lobule, (2) the frontal/superior cerebellar articulatory pathway and (3) the parietal/inferior cerebellar phonological storage pathway. The preference for Model 8 is similar to that of that the adult population, which is consistent with the hypothesis given that children and adults, have been shown to recruit similar regions during verbal working memory (O'Hare et al., 2008; Thomason et al., 2009; Vogan et al., 2016). Noteworthy, the exceedance probability of the adult study ($x_p = 0.98$) provided us a 98% confidence that Model 8 best represents the adult population. Although the exceedance probability for the children group was

slightly lower ($x_p = 0.75$), it still provided a good indicator of the best-fitting model. The lower exceedance probability obtained for the children group may possibly be attributed to the reduced activation and activated voxels observed at the regions of interests.

In comparison to the adults, children showed comparable parameter estimates for both the driving input and the intrinsic connectivity although age related difference was observed in the modulatory connections. On the pathway where the task modulated the connection from the IFG and IPL, positive modulatory effects were found for both adult and children. The role of both IFG and IPL during verbal working memory has been well established in the children population and is postulated to be related to the sub-vocal rehearsal of the letters during the encoding phase, as discussed in the adult study. However, in comparison to adults, reduced modulatory connectivity (parameter estimate in Hertz) was observed in children. It is postulated that the differences observed in modulatory connectivity may be related to the protracted course of brain maturation from childhood to adulthood (Simmonds, Hallquist, Asato, & Luna, 2014). In a longitudinal study by Simmonds and colleagues (2014) examining the development of white matter tracts, it was found that the superior longitudinal fasciculus, which connects the frontal and parietal regions, only matures in adolescence. As such, our findings may be interpreted as the following: weaker connectivity was observed as the superior longitudinal fasciculus is not fully developed in children as such, the modulatory connectivity between the IFG and IPL may have been impeded. However, it is important to note that the present study did not have the scope to verify if the reduced connectivity between the IFG and IPL was indeed due to the developing superior longitudinal fasciculus in our population.

Further study using diffusion tensor imaging (DTI) could be utilised to confirm the aforementioned hypothesis.

Apart from the reduced modulatory connectivity observed between the IFG and IPL, increased modulatory connectivity was observed in children as compared to adults on both the cerebro-cerebellar pathways. This may be explained by the findings of post-mortem studies (Brody, Kinney, Kloman, & Gilles, 1987; Yakovlev & Lecours, 1967) examining the brain maturation process where researchers have provided evidence of an inferior to superior (subcortical to cortical) and posterior to anterior (occipital to frontal) myelination process. It is believed that the developmental process of the cerebellum begins earlier than the cortical regions. As such, we observe comparatively higher modulatory connectivity from the IFG to the superior cerebellum and from the IPL to the inferior cerebellum as compared to both cortical to cortical connectivity (IFG to IPL) and the cortical to subcortical connectivity observed in adults.

Taken together, it is postulated that the Sternberg verbal working memory task is comparably harder for children as compared to adults, as evidenced in the behavioural performance. Hence, children are required to put in more effort to perform the same task, which is postulated to lead to an increase in activation at the regions of interest such as the left IFG, left IPL, right superior cerebellum and right inferior cerebellum. However, as myelination progresses from the subcortical regions to the cortical regions, which is thought to be reflective of the functional maturation (Sowell, Thompson, & Toga, 2004), the cortical regions of interest (i.e. left IFG and left IPL) may not have been fully developed in children. Hence, this may explain why we do not observe the increase in activation at the cortical regions in relation to the increased effort put in by children during the task. Instead, decreased activation was observed as

compared to adults. However, greater activation of both the right inferior and superior cerebellum were found in our study, as opposed to the cortical regions (as seen in Figure 4.9) with the more stringent thresholding, which may further provide evidence of the functional maturation process (subcortical to cortical). In light of these findings, it is postulated that the increased modulatory effective connectivity observed in children in both the cerebro-cerebellar pathway is reflective of both the increased effort in the task as well as the maturation process of both cortical and subcortical regions and white matter pathways.

While the present study has contributed to the deeper understanding of the cross-sectional differences in effective connectivity network between children and young adults during the Sternberg verbal working memory task, several limitations could be addressed in future research. Firstly, despite our best efforts in recruitment, the current study had a humble sample size of ten children. This was due to various factors such as parents' reluctance towards their children undergoing a MRI scan, availability of scanning slots, participant dropout, and the lack of functional activation at one or more regions of interest. However, it is important to note that the effect of the sample size may have been mitigated by the use of the multiband EPI sequence utilised in the study. Notwithstanding this, the present study is the first to provide conclusive evidence that the preferred effective connectivity network in children is similar to that of adults. However, future research with larger sample sizes are recommended for conclusive replicability.

Secondly, the use of block design instead of the event-related design impeded the understanding of the individual components (encoding, maintenance and retrieval) involved during verbal working memory. Additionally, by using block design fMRI analysis, responses regardless of its accuracy were included into the analyses.

However, preliminary event-related analyses were done to ensure that there were no statistically significant functional differences between trials that were answered correctly versus those that were erroneous during the pilot phase. Additionally, block design was used as opposed to event related design so as to minimise the length of the runs and the overall scan time and to maximise the power of the signal for children, where head motion leading to dropout is a major concern. Nonetheless, future studies with event-related task paradigm are warranted to understand the specific components that are observed during task modulation. Thirdly, as the aim of the study was to examine the cross-sectional changes in effective connectivity, the effective network connectivity in adolescence and older adults were not examined. Future studies are required to map out the neurodevelopmental trajectory using effective connectivity to better understand how this network differs across age. Lastly, one could argue about the difficulty of the Sternberg verbal working memory task paradigm that was utilised with the children. To address the plausible concern, prior to conducting the study, pilot testing was done to examine a suitable number of stimuli (4, 5 or 6). Children showed no differential performance statistically across the number of stimuli utilised. As such, six letters were used for the study to make the task more comparable to the adult study. Additionally, timings of the presentation of stimuli, encoding, maintenance and retrieval were examined. Based on the feedbacks from children as well as their performance (reaction and accuracy), the timings for the different components were tweaked slightly to ensure that children could attain an accuracy of above 80%.

In conclusion, the present study contributed significantly to the understanding of the cross-sectional neurodevelopmental changes in the effective network connectivity during verbal working memory. Moreover, it provided added evidence

that both children and young adults not only recruit similar network of regions, but that they also exhibit similar network connectivity.

CHAPTER V: STUDY 2B

Effect of Dyslexia on the effective Network Connectivity in Children during Verbal
Working Memory

Introduction

The ability to read may seem like a natural process for most children. However, for children with dyslexia, the process of learning to read is an arduous one. In hopes of ameliorating dyslexia, researchers have been elucidating the core deficits so as to develop targeted intervention methodologies. Behaviourally, children with dyslexia have been found to show difficulties in phonological processing, verbal working memory and rapid automatised naming (Ramus & Szenkovits, 2008). Imaging modalities such as structural and functional imaging, diffusion tensor imaging (DTI) and electroencephalogram (EEG) have also been utilised to better understand these core deficits.

Imaging studies typically focus on understanding the phonological processing deficit in individuals with dyslexia. Meta-analyses have provided converging evidence of decreased activation in the left inferior frontal, superior and middle temporal, and temporo-parietal regions (Kwok, 2013; Maisog et al., 2008; Fabio Richlan et al., 2009, 2011). Additionally, functional connectivity studies (Cao et al., 2008; Quaglino et al., 2008; Richards & Berninger, 2008) in children, though scarce, provided supplementary evidence of reduced connectivity between regions of interest. However, it is important to note that these studies typically used a variation of phonological processing tasks such as rhyming, pseudoword reading, and phoneme tasks, as opposed to verbal working memory tasks such as the n-back or Sternberg task. Although phonological processing is an important component during verbal working memory, the aforementioned phonological processing tasks typically tap on an individual's ability to map phonemes to graphemes, as well as sub-vocal rehearsal that updates the short-term memory store (STS) for retaining important information.

Despite the growing body of literature documenting observations of behavioural deficits in verbal working memory in children with dyslexia (de Jong, 1998; Peng & Fuchs, 2016; Swanson, Zheng, & Jerman, 2009), little is known about the functional neuroanatomy underlying this impairment in individuals with dyslexia; even less so in children with dyslexia. A pioneering study conducted by Paulesu and colleagues (1996) using positron emission tomography (PET) found that adults with dyslexia showed decreased activation in Broca's area during a verbal working memory task, similar to that of the Sternberg's task paradigm. Subsequently, Beneventi and colleagues (2010) utilised the n-back task with three loads to examine the differences in activation between typically developing 13 year olds and similarly aged children with dyslexia. Results from the study showed that the n-back task elicited activation in similar brain regions for both groups of children but reduced activation was observed in frontal, parietal and cerebellar regions (Beneventi et al., 2010). More recently, a functional connectivity study was done to understand the fronto-parietal connectivity in both adolescents and adults with and without dyslexia (Wolf et al., 2010). Increased connectivity was found in the left lateralised fronto-parietal network related to phonological processing (Wolf et al., 2010).

Despite emerging functional imaging studies being done in the adolescence and adult population to examine the effect of dyslexia on the verbal working memory network, such studies have not been conducted in the child populations. Recent studies have mapped out the cerebro-cerebellar network underlying verbal working memory (Chen & Desmond, 2005a, 2005b). Thus, our first study sought to establish the effective connectivity network in typical adults during verbal working memory. This was further built upon by study 2a, where cross-sectional age-related differences in

verbal working memory network connectivity was examined by exploring the network in typically developing children, and cross comparing it with the adult population.

Therefore, the present study aimed to build upon the findings from the study in the previous chapter by exploring the cerebro-cerebellar regions of interest involved during verbal working memory in children with dyslexia. More importantly, in line with the previous two studies, the main aim of the present study is to elucidate the effective network connectivity during verbal working memory in children with dyslexia. The differences in effective network connectivity between children with dyslexia and their typically developing peers will also be discussed. It is hypothesised that children with dyslexia will display differences in effective network connectivity whereby an absence in modulatory connectivity from the cortical to subcortical pathways would be observed. The prediction is in line with previous studies documenting both functional and structural deficits in the cerebellums of individuals with dyslexia coupled with poorer behavioural performance on tasks that require the involvement of the cerebellum such as verbal working memory, phonological awareness and rapid automatised naming.

Methodology

Participants

Similar recruitment criterion was set for the recruitment of both children with dyslexia and typically developing children. In addition, children with dyslexia had to be formally diagnosed by a registered psychologist with developmental dyslexia, and screened for comorbidities such as attention deficit hyperactive disorder (ADHD) through oral interviews with parents, psychologists who administered the psychological assessment, and the respective educational therapist. With the aforementioned criteria, seventeen children with dyslexia and no prior history of

neurological or psychiatric conditions were enrolled for the study. The children aged within the range of seven to ten years old. Only children studying in mainstream schools where bilingual education was compulsory were recruited. Seven participants were excluded from the study, for the following reasons: excessive head motion greater than 5mm ($n = 1$), functional activity not significant at one or more of the region of interest when thresholded at $p > 0.05$ (uncorrected; $n = 4$), and dropout due to fear of being in the MRI machine ($n = 2$). The mean age of the 10 participants (six males, four females) was 8.2 years ($SD = 0.79$ years; range: 7 to 9). All participants were right-handed based on the Edinburgh Handedness Inventory (EHI) score: Mean = 96.47, $SD = 11.16$).

Prior to the start of the experiment, assent forms were administered to children while informed consent was obtained from the parents of all the participants. Ethics approval was also obtained from both the Nanyang Technological University Institutional Review Board and the National University of Singapore Institutional Review Board.

Brief neurocognitive test battery and pediatric MRI protocol

A similar brief neurocognitive test battery and pediatric MRI protocol was administered to all children (both typically developing and dyslexia group). Details of both the brief neurocognitive test battery and pediatric MRI protocol can be found documented in the methodology section of the previous chapter.

In-scanner task description

Children with dyslexia performed the same in-scanner Sternberg working memory task as their typically developing peers as documented in the “In-scanner task description” segment of the methodology section in previous chapter.

Behavioural data analysis

Brief Neurocognitive test battery. Statistical analyses were conducted using IBM Statistical Package for the Social Sciences Statistics (SPSS) version 23 (IBM Corp, 2015). The scores of five domains – phonological awareness, pseudoword phonological awareness, rapid automatized naming, verbal working memory, and reading – were aggregated scores of their respective subtests. Independent *t*-tests were conducted to examine differences between typically developing children and children with dyslexia across the five domains.

In scanner task. Paired-sample *t*-tests were conducted to investigate the effects of stimuli load on accuracy rate and reaction time on the children with dyslexia subsample. To elucidate the behavioural differences between children with dyslexia and their typically peers, a two-way repeated measures analysis of variance (ANOVA) with load (low, high) as the within-subjects variable and group (children with dyslexia, typically developing children) as the between-subjects variable were conducted.

Image acquisition and functional data analysis

Both groups of children (children with dyslexia and typically developing children) were scanned using the same scanner and similar imaging parameters. Functional data were also analysed using an equivalent pipeline as documented in the methodology section of the previous chapter.

Analysis of effective connectivity

Similar regions-of-interest were selected as those used in the adult and typically developing children study. To obtain the peak coordinates for each of the ROIs, the anatomical masks were then applied individually to the group activation map with a threshold of $p < 0.005$ (uncorrected) (see Table 5.1 for group maxima of the ROIs). At the individual subject level, peak coordinates were obtained by applying

the respective ROI masks on the individual subject's activation map, which was thresholded at $p < 0.05$ (uncorrected). Subsequently, volumes of interest (VOIs) were created within 10mm of the peak coordinates (see Table 5.1) using spheres with 8mm radius and regional responses were extracted based on the eigenvariates of the activated voxels within the respective VOIs. Participants ($n = 4$) that did not display significant activations at one or more of the ROIs were not included in the subsequent analyses. These were part of the seven participants that were excluded from the study.

Table 5.1.

MNI coordinates of the group maxima in children with dyslexia within the selected ROIs for the purpose of DCM

Region	Left/ Right	Cluster Size (voxel)	MNI Coordinates			T
			x	y	z	
Left Fusiform Gyrus	Left	48	-43	-81	-17	8.65
Left Inferior Frontal Gyrus	Left	4	-48	14	33	3.04
Left Inferior Occipital Gyrus	Left	70	-43	-79	-15	6.80
Left Inferior Parietal Lobule	Left	28	-28	-59	48	6.82
Thalamus	Bilateral	3	-13	-9	11	3.37
Right Inferior Cerebellum (Lobule VII)	Right	15	8	-64	-32	5.81
Right Superior Cerebellum (Lobule VI)	Right	98	35	-61	-27	6.21
Pons	Bilateral	6	0	-36	-42	3.13

Note. Anatomical masks of each of the ROIs were applied individually to the group activation map with a threshold of $p < 0.005$ (uncorrected), to obtain the peak coordinates for the purpose of DCM.

Results

Behavioural data

Brief neurocognitive test battery. There were no significant age differences $t(18) = .356, p = .73$ (*ns*) between both groups. Similarly, there were no significant differences in performance on the Raven's Coloured Progressive Matrices (Raven, 2004) $t(18) = 0.00, p = 1.00$ (*ns*). As seen in Table 5.2, participants in the dyslexia

group generally performed worse than participants in the control group across all domains.

Table 5.2.

Descriptive statistics of the five domains in children with dyslexia.

Domain	Dyslexia (N = 10)		Control (N = 10)		<i>t</i>	<i>p</i>
	M	SD	M	SD		
Phonological Awareness	20.5	3.06	20.2	2.77	.268	.79
Rapid Automatized Naming	19.6	5.87	17.8	3.22	.854	.40
Pseudoword Phonological Awareness	12.8	3.88	15.7	3.43	- 1.77	.093
Verbal Working Memory	13.4	2.13	15.7	2.81	- 2.02	.059
Reading	29.6	7.20	41.1	8.38	- 3.12	.007* *

Note. ** $p < .01$. The score of each domain was calculated by taking the mean score of its pair of subtests. M: mean; SD: Standard deviation

Attitudinal and anxiety questionnaire. Results from both pre-MRI and post-MRI questionnaire showed no significant differences in terms of anxiety between both groups, $p = .71$ (*ns*) and $p = .93$ (*ns*) respectively.

In-scanner task. Paired sample *t*-test was done to examine the effects of load on response accuracy and reaction time (RT) for children with dyslexia; results are displayed in Figures 5.1. Children with dyslexia performed significantly better $t(9) = 4.09$, $p = .003$, in the low load condition ($M = .710$, $SD = .153$) compared to the high

load condition ($M = .575$, $SD = .097$). In addition, they exhibited significantly shorter reaction times $t(9) = -2.80$, $p = .021$, in the low load condition ($M = 1251$, $SD = 142$) relative to the high load condition ($M = 1340$, $SD = 133$).

Figure 5.1. Mean accuracy and reaction time by stimuli load, for children with dyslexia. Error bars represent standard deviation at 95% CI.

To understand differences in behavioural performance between typically developing children and children with dyslexia, repeated-measures ANOVA analyses were performed. Table 5.3 and Figure 5.2 summarises the results of the ANOVA analysis on response accuracy. There was no effect of Group on response accuracy, $F(1, 18) = 2.07$, $p = .167$ (*ns*), indicating that there were no differences in accuracy rates between children with dyslexia and typically developing children. There was a significant effect of Load on response accuracy, $F(1, 18) = 32.9$, $p < .001$, indicating that children responded poorer to high load stimuli than to low load stimuli. No Group X Load interaction effect was observed, $F(1, 18) < 1$, $p = .93$ (*ns*).

Table 5.3.

Repeated-measure ANOVA analysis on accuracy rates in children with dyslexia.

	<i>df1</i>	<i>df2</i>	<i>F</i>	<i>p</i>	η
Main Effects					
Group	1	18	2.07	.167	.10
Load	1	18	32.9	.000***	.64
Interaction Effects					
Group X Load	1	18	.007	.93	.00

Note. *** $p < .001$. Group represents both children with dyslexia and typically developing children while load refers to high load/ low load.

Figure 5.2. Interaction effect and the mean accuracy by stimuli load, for typically developing children (TD) and children with dyslexia (RD). No significant main effect for accuracy between TD and RD was observed. However, a main effect for load was found whereby both TD and RD showed better performance for low compared to high load. There was no significant interaction, which indicated that the decrease in performance from low to high load was not significant between the TD and RD.

Repeated-measures ANOVA analysis was also conducted on reaction time (RT); results are summarised in Table 5.4 and Figure 5.3. There was no effect of Group on RT, $F(1, 18) = .478, p = .50$ (*ns*), indicating that children with dyslexia and typically developing children displayed similar reaction times. There was a significant effect of Load on RT, $F(1, 18) = 40.1, p < .001$. Children took longer to respond to high load stimuli than low load stimuli. A significant Group X Load interaction effect was observed, $F(1, 18) = 11.6, p = .003$. Stimuli load had a differential effect on reaction time between the two groups of children. Comparison of marginal means revealed that high-load stimuli adversely affected typically developing children's response accuracy to a greater degree compared to children with dyslexia.

Table 5.4.

Repeated-measure ANOVA analysis on reaction time in children with dyslexia.

	<i>df1</i>	<i>df2</i>	<i>F</i>	<i>p</i>	η
Main Effects					
Group	1	18	.478	.50	.03
Load	1	18	40.1	.000***	.69
Interaction Effects					
Group X Load	1	18	11.6	.003**	.39

Note. *** $p < .001$; ** $p < .01$. Group represents both children with dyslexia and typically developing children while load refers to high load/ low load.

Figure 5.3. Interaction effect and the mean reaction time (RT) by stimuli load, for typically developing children and children with dyslexia. There was no significant main effect for RT between the groups. However, a main effect for slower RT in the high load condition was found. A significant interaction effect ($p < 0.001$) was also found whereby the TD group was much faster than RD in low load, but slower than RD for high load.

Functional data

Results indicated that children with dyslexia displayed neural activity at the left prefrontal region and the right inferior and superior cerebellum, which are involved in verbal working memory network as shown in Figure 5.4 and Table 5.5.

Figure 5.4. Brain activation map in children with dyslexia for the Sternberg verbal working memory task (High load > Low load). The axial, coronal and sagittal views showed the activation at the group maxima for the ROIs. Images were thresholded at $p < 0.005$ (uncorrected) with minimum cluster ≥ 20 voxels

Table 5.5.
MNI peak coordinates within the significant clusters for the effects of load (High load > Low load) in children with dyslexia

Region	Left/ Right	Cluster Size (voxel)	MNI Coordinates			T
			x	y	z	
Superior Parietal Region	Left	480	-25	-59	48	12.87
Medial Parietal Region	Left		-8	-64	53	5.69
	Left		-25	-49	48	5.21
Superior Occipital Region	Left	3780	-10	-94	6	9.15
Inferior Occipital Region	Left		-43	-81	-17	8.65

Inferior Occipital Region	Left		-33	-51	-37	8.13
Medial Frontal Region	Left	581	0	14	61	9.06
	Left		-13	32	21	5.82
Limbic Region	Right		13	21	31	5.39
Precentral Gyrus	Left	140	-48	-1	53	7.64
Precentral Gyrus	Left		-38	-4	48	5.11
	Left		-18	7	41	3.89
Middle Temporal Region	Left	21	-53	-64	13	6.67
Cerebellum—Lobule 6	Right	102	35	-61	-27	6.21
Cerebellum—Crus 1	Right		43	-51	-32	5.82
Cerebellum—Crus 1	Right		43	-74	-25	3.78
Inferior Occipital Region	Right	21	23	-96	-17	4.43
	Left	21	-28	-76	18	4.40
Middle Frontal Region	Right	21	25	62	21	4.38

Notes: MNI Coordinates of the largest T-value within the ROI was selected as the peak coordinate based on the one-sample t-test on all participants in the group. The activation was thresholded at $p < 0.005$ uncorrected with minimum cluster ≥ 20 voxels.

To understand the functional differences between children with dyslexia and typically developing children, a two sample *t*-test with the following two contrasts were conducted: (1) typically developing children > children with dyslexia (TD > RD) and (2) children with dyslexia > typically developing children (RD > TD). For the first contrast (TD > RD), significant activation difference was found at the left temporal-parietal region and both the right inferior and superior cerebellum as displayed in

Figure 5.5 and Table 5.6. For the second contrast examining RD > TD, no voxel survived the Liebermann recommended threshold of $p < 0.005$, $k = 20$.

Figure 5.5. TD > RD brain activation map for the Sternberg verbal working memory task (High Load > Low Load). The axial, coronal and sagittal views showed the activation at the group maxima for the ROIs. Activation was thresholded at $p < 0.005$ (uncorrected) with minimum cluster ≥ 20 voxels.

Table 5.6.

MNI peak coordinates within the significant clusters for the effects of group (TD > RD) and load (HL > LL)

Region	Right/ Left	Cluster Size (voxel)	MNI Coordinates			T
			x	y	z	
Cerebellum—Lobule 8	Right	102	25	-66	-49	4.39
Cerebellum—Lobule 6	Right	96	15	-71	-22	3.95
Cerebellum—Lobule 6	Right		28	-64	-25	3.77
	Left	29	-3	-19	-5	3.78
	Left		-8	-26	-12	3.07
Precentral Gyrus	Left	24	-55	-2	41	3.54

Notes: MNI Coordinates of the largest T-value within the cluster was selected as the peak coordinate based on the two-sample t-test with a threshold of $p < 0.005$ uncorrected with minimum cluster ≥ 20 voxels.

Effective connectivity

Bayesian Model Selection (BMS) analysis was conducted on all eight models to examine which model best accounted for the verbal working memory pathway in children with dyslexia. Data obtained from the children with dyslexia indicated a slightly better fit for model 2 ($x_p = 0.29$) (see Figure 5.6), in which the verbal working memory task modulated the connections from the IFG to the IPL. The exceedance probabilities for the other models were as follows: Model 1 ($x_p=0.0962$), Model 3 ($x_p=0.1098$), Model 4 ($x_p=0.2055$), Model 5 ($x_p=0.0828$) Model 6 ($x_p=0.0944$), Model 7 ($x_p=0.0614$) and Model 8 ($x_p=0.1615$) as documented in Figure 5.6.

Figure 5.6. Results of the BMS analysis; exceedance probability (xp) of all eight models in children with dyslexia.

Parameter estimates of the driving input, intrinsic connection and modulatory effects within the most optimal model are summarised in Figure 5.7. One-sample *t*-tests, Bonferroni corrected at the alpha level of 0.05, were performed to examine if the parameter estimates were significant. All of the parameter estimates were significant with the exception of the intrinsic connectivity from the left IPL to the left IFG, the left IPL to the right inferior cerebellum via the pons and the left IFG to the right superior cerebellum via the pons.

Figure 5.7. DCM parameter estimate for the model (Model 2), which showed a slightly better fit for the data obtained from the children with dyslexia. The number alongside the connections or modulation summarises the $M(SD)$ of parameter estimate (in Hertz). Bolded parameter estimates represent the modulatory parameter estimates. The significance of parameter estimates was examined using one-sample t-tests, with Bonferroni correction for multiple comparisons at the alpha level of 0.05. Significant parameter estimates were denoted by an asterisk (*). Black dash-arrows indicate modulatory connections, whereas dotted arrows indicate intrinsic connections and the blue arrow indicates driving input from the visual stimuli. FG: left fusiform gyrus; IOG: left inferior occipital gyrus; IFG: left inferior frontal gyrus; IPL: left inferior parietal lobule. Both superior and inferior cerebellum are right lateralised while thalamus and pons are bilateral.

To understand if the data obtained from children with dyslexia fitted better with the models that only have cortical modulatory connectivity (i.e. model 1 and 2) or models with both cortical-cortical as well as cortical-subcortical modulatory connectivity (i.e. model 3, 4, 5, 6, 7 and 8), model space partitioning was utilised to compare two different families of models. Result indicated that the data obtained from the children with dyslexia had a better fit for the models with cortical modulatory connectivity ($x_p = 0.61$) as opposed to the models with both cortical-cortical and cortical-subcortical modulatory connectivity ($x_p = 0.38$).

Discussion

In the present study, the Sternberg verbal working memory task paradigm was applied to examine the underlying neural network in children with dyslexia during verbal working memory and how these regions involved in the verbal working memory network modulate each other during the task. Both the functional activation disparity and the differences in effective connectivity network between children with dyslexia and children with typical development were evaluated. Additionally, behavioural differences between both groups will be discussed.

Behaviourally, the study explored differences between children with dyslexia and their typically developing peers on both the brief neurocognitive test and the in-scanner Sternberg verbal working memory task paradigm. For the brief neurocognitive test, children with dyslexia generally demonstrated poorer reading ability than typical children. Compared to the latter, children with dyslexia performed significantly more poorly in the reading domain, and marginally more poorly in the pseudoword phonological awareness and verbal working memory domains. These results indicate a generalised reading deficit and specific impairments in phonological awareness and verbal working memory in children with dyslexia. This finding is in line with the

imaging data obtained in this study, whereby children with dyslexia displayed decreased activation at the left fronto-parietal regions and right superior and inferior cerebellum, which are linked to the processing of various reading domains such as phonological awareness, verbal working memory and rapid automatised naming. Noteworthy, there were no differences in reading ability between children from the different ethnicity group ($p = .73$)

Additionally, findings from the present study overlap partially with the results obtained by Norton and colleagues (2014). Specifically, results from this study reveal trends of weaker phonological awareness and verbal working memory—albeit only marginally significant—evidenced by decreased activation at the left fronto-parietal regions and right inferior and superior cerebellum. In comparison, Norton and colleagues documented a decrease in activation in correlation with the observed impairments in children with dyslexia whereby children with double deficit in phonological awareness and rapid automatised naming show less activation as compared to children with a single deficit. Taken together, findings from both studies highlighted the importance of both the superior and inferior cerebellum in verbal working memory and rapid automatised naming.

For the in-scanner verbal working memory task, children with dyslexia and their typically developing peers were found to show only significant differences in reaction time but not accuracy. Noteworthy, children with dyslexia tended to have lower mean accuracy rates and higher mean reaction time. Additionally, the repeated measures multivariate analyses showed response accuracy in children with dyslexia to be less adversely affected by the effect of load as compared to typically developing children. Similarly, the increase in load affected typically developing children's reaction time to a greater degree than children with dyslexia. It is thought that the

reduced performance caused by increases in load on both accuracy rate and reaction time in children with dyslexia is reflective of the reduced phonological loop capacity (Majerus & Cowan, 2016) documented in individuals with dyslexia. This deficit in verbal working memory capacity may account for the reduced effects of load observed as the performance (both accuracy and reaction time) of children with dyslexia may have already reached its capacity during the low load condition hence plateauing into the high load condition. Additionally, in terms of reaction time, although children with dyslexia took longer as compared to their typically developing peers during the low load condition, they had shorter reaction during the high load condition relative to their typically developing peers. It is believed that the reduced reaction time observed during the high load condition could be attributed to difficulty with task mastery, as evidenced by the low response accuracy rates for children with dyslexia—close to chance levels (57.5%). As such, the condition of load (high load or low load) did not significantly affect children with dyslexia as much as their typically developing peers.

Consistent with the verbal working memory deficit observed in the behavioural task, children with dyslexia displayed aberrant cerebro-cerebellar activation. Whole brain analysis revealed similar pattern of activation, whereby children with dyslexia activated a similar network of regions as the typically developing controls. This included the regions sub-serving the frontal/superior cerebellar articulatory control system and the parietal/inferior cerebellar phonological storage system (Chen & Desmond, 2005a), which have been established in the cerebro-cerebellar verbal working memory network of typical adults. Although similar regions were activated, children with dyslexia showed decreased activation as compared to their typically developing peers at the left temporo-parietal region and both the right inferior and superior cerebellum. In particular, we found the typical children to have marked

increased activation in the right inferior cerebellum that is linked to the phonological processing loop in the cerebral-cerebellar circuitry for verbal working memory. This finding is consistent with the behavioral results that showed a tendency for better verbal working memory performance in the typical children compared to the dyslexia group.

To the best of our knowledge, the current study is the first to examine the neural networks involved during verbal working memory by using the Sternberg task paradigm. Although few studies have been done to examine the differences in the cerebro-cerebellar circuitry of children with dyslexia, these studies utilised different task paradigms such as word generation task (Baillieux et al., 2009), word-rhyme task (Norton et al., 2014) and phonological task (Feng et al., 2017). Findings from these studies taken together with a meta-analysis (Linkersdörfer, Lonnemann, Lindberg, Hasselhorn, & Fiebach, 2012), consistently demonstrated a decreased in functional activation in the left inferior frontal gyrus (IFG). Additionally, Linkersdörfer and colleagues (2012) also found convergent grey matter reduction in the temporo-parietal region. The left IFG have been thought to be involved in the mapping of grapheme to the associated phoneme. As such, the aberrant activation found at the left IFG together with robust evidence of phonological deficit observed in children with dyslexia findings formed the basis of the phonological deficit theory.

In contrast, mixed findings pertaining to activations at the right inferior and superior cerebellum have been found. Specifically, in a recent study by Norton and colleagues (2014), reduced activation at the right superior cerebellum (lobule VI) in children with dyslexia during written word rhyming task was found. Similarly, in the study by Baillieux and colleagues (2009), using a silent word generation task, researchers found that children with dyslexia displayed a more widespread and

reduced activation as compared to their typically developing peers. In contrast, increased activation in the cerebellum of individuals with dyslexia during reading tasks was found in a meta-analysis review (Linkersdörfer et al., 2012). Likewise, in a recent study examining the cerebro-cerebellar activation in children with dyslexia, increased cerebellar activation was found during a phonological task (Feng et al., 2017). However, it is important to note that the study by Feng and colleagues (2017) was conducted on children who were native Mandarin speakers. Differential functional activation between dyslexia in alphabetic words and Chinese characters have been reported in our recent meta-analysis (Kwok, 2013). Nevertheless, the discrepancy in cerebellar activation findings could also potentially be attributed to the differences in experimental design such as the selected participant population, task paradigms and scanning parameters. In light of the findings from previous studies, results from the present study provide supporting evidence for the deficit in verbal working memory in children with dyslexia as evidenced by the reduced activation at the left temporal-parietal region and both right inferior and superior cerebellum.

Moving beyond the functional activations and in line with the main aim of the study, the effective connectivity network during verbal working memory in children with dyslexia was elucidated. In contrast to both typical adults and children, data obtained from the children with dyslexia displayed a slightly better fit for Model 2, which includes the unilateral modulatory effect from the left IFG to the left IPL. The finding is in contrast with an effective connectivity study conducted by Cao et al (2008) using a rhyming task. In the study, the authors found that typically developing children showed positive correlation between reading skills and the increasing unilateral modulatory effect from the inferior frontal gyrus to the inferior parietal lobule, which was not observed in children with dyslexia (Cao et al., 2008). The

authors interpreted the findings as children with better reading ability are more proficient in top-down modulation involving the integration of orthographic and phonological information (Cao et al., 2008). Nonetheless, it is important to note that the mean age of the participants from both groups (dyslexia and typically developing) included in the study by Cao and colleagues (2008) was 12.4 years (range: 8.9—14.11) as compared to 8 years (range: 7.8-10.2). As such, in line with literature documenting the trajectory of brain maturation, the four years age gap may have contributed to the activation differences observed.

However, despite the differences found in the modulatory connection between the left IFG to the left IPL, it is important to note that the data obtained from the children with dyslexia did not indicate a clear fit for model 2 as the exceedance probability for the other models were all within a narrow range. In light of this finding, it may be argued that children with dyslexia have yet to develop a specialised verbal working memory pathway. Taken together, although data obtained from the present study indicated a slightly better fit for model 2, it does not negate the possibility that children with dyslexia could have utilised other network pathways.

Although the data obtained from the children with dyslexia did not show a clear fit for any particular model, further analysis using model space partitioning analysis indicated that the data obtained from the children with dyslexia displayed a better fit for models with cortical-cortical modulatory connectivity as opposed to models with both cortical-cortical and cortical-subcortical modulatory connectivity. The aforementioned finding coincides with the reduced activation observed in both the right superior and inferior cerebellum of children with dyslexia. In line with the findings from the present study, a recent study documented reduced gray matter in the right lobule VI and right Crus II of the cerebellum, which have been found to be

mapped to the frontoparietal and default mode network respectively (Stoodley, 2014). Similarly, in the meta-analysis done by Linkersdörfer and colleagues (2012), grey matter reduction was observed in the superior cerebellum (lobule VI) of children with dyslexia. Evidence from the structural imaging of children with dyslexia overlaps significantly with the reduced activation observed at the cerebellum as well as the lack of modulatory connectivity from the cortical to subcortical regions during verbal working memory.

In summary, based on current published literature, the current study is the first to utilise the Sternberg verbal working memory task paradigm to elucidate both the cerebro-cerebellar functional activation pattern during verbal working memory as well as the effective connectivity network in children with dyslexia. Consistent with earlier research, this study found reduced verbal working memory capacity in children with dyslexia as evidenced through the analyses of behavioural performance. Similarly, in line with the behavioural performance, reduced activation was found predominantly in the left inferior parietal lobule and both right superior and inferior cerebellum. Additionally, a difference in effective connectivity network was observed between children with dyslexia and typically developing children whereby the data obtained from the children with dyslexia showed a better fit for models without the cortical-subcortical modulatory connections.

While findings from the present study furthered the understanding of the underlying network connectivity during verbal working memory in children with dyslexia, several limitations should be considered. The first limitation would be the small sample size ($N = 10$), which may have contributed the lack of activation found in children and the variability in preferred connectivity model pathway. Future studies with larger samples are warranted to verify the consistency of the both the aberrant

functional activation as well as the effective network connectivity. Second, as the present study is the first to provide valuable insights into the cerebro-cerebellar network during verbal working memory, comparison with other studies was not possible. Hence, more research is required to draw a conclusive understanding of this network in children with dyslexia. Lastly, as mentioned previously (see pg. 94), the use of block design instead of the event-related design hampered the possibility of having an in-depth understanding of the individual components involved during verbal working memory and the inclusion of erroneous trials into the analyses. As such future studies with event-related task paradigm are warranted to understand the specific components that are observed during task modulation.

Despite these limitations, findings from the current study provided novel insights into the understanding of the underlying neural network connectivity of dyslexia. It is hoped that the present findings would serve as a platform to spearhead future research to continue to focus on the cerebro-cerebellar circuitry and further understand verbal working memory deficits in children with dyslexia. It is hoped that the present study could provide a framework for future studies to develop more targeted intervention methodologies to ameliorate dyslexia.

CHAPTER VI: GENERAL DISCUSSION

Verbal working memory is an important aspect of reading as it is involved in both the phonological processing and storage of word forms. Studies examining individuals with dyslexia have constantly reported a verbal working memory deficit. Although past research has documented aberrant activation during phonological tasks, very little is known about how the cortical and subcortical network of regions involved during verbal working memory modulate each other in the typically developing population, and much less in individuals with dyslexia. It is thought that a better understanding of verbal working memory, and how the network differs in children with dyslexia, would provide a basis for the development of more targeted intervention methodologies. The current dissertation utilised functional magnetic resonance imaging (fMRI) to examine the underlying neural substrates and the effective network connectivity during verbal working memory in three distinct populations. This systematic investigation further showed how the task modulated the functional connectivity within the respective age-groups and differed in dyslexia.

The thesis elucidated the aberrant effective network connectivity during verbal working memory in children with dyslexia through three distinct but integrated studies as illustrated in Figure 6.1. Study 1 helped set the stage for the thesis by establishing the cerebro-cerebellar effective network connectivity involved during verbal working memory in typical adults. Study 2a investigated cross-sectional age-related differences during verbal working by examining the same network in typically developing children, and comparing it with findings from Study 1. Study 2b explored the functional roles of both the cortical and subcortical regions in children with dyslexia during verbal working memory. It furthered the understanding of the underlying neural network by elucidating the effective network connectivity as well as the network differences between typically developing children and children with dyslexia.

Figure 6.1. Research Framework.

Summary of findings

The first study applied effective network connectivity analysis to investigate the cerebro-cerebellar network during verbal working memory established previously by Chen & Desmond (2005a) and Desmond & colleagues (2005) in young adults. Using the Sternberg verbal working memory task paradigm, activations at both the cortical and subcortical regions were consistent with previous findings (Chen & Desmond, 2005a; Desmond et al., 2005; Ng et al., 2016). Notably, we observed a pattern of left-cerebro and right-cerebellar activation, which has been characterised as a signature pattern of activation elicited by the Sternberg verbal working memory task. The pattern of activation found was inclusive of the neural activation at the eight regions of interest included in the hypothesised verbal working memory model. This model was subsequently evaluated using Bayesian model selection analysis to elucidate how the regions within the network modulate each other during verbal

working memory. Results indicated that the data obtained from the typical adults showed a better fit for the model where the connectivity pathway from the left IFG to the left IPL was modulated. This is in addition to the modulatory effects on both the frontal/superior cerebellar articulatory control system and the parietal/inferior cerebellar phonological storage system.

Next in study 2a, using the same task paradigm, the underlying neural network during verbal working memory in typically developing children was investigated. Consistent with previous studies, reduced activation was observed across all the regions of interest. Importantly, similar to that in adults, left-cerebro-right-cerebellar lateralisation was observed in typically developing children. Moving beyond functional activation, unique dynamics in effective connectivity was observed between both cortical-to-cortical regions as well as cortical-to-subcortical regions via the pons. In line with our hypothesis, results indicated that the data obtained from the typically developing children displayed a better fit for the model with unilateral modulatory effect on three distinct pathways (1) from the inferior frontal gyrus to the inferior parietal lobule, (2) the frontal/superior cerebellar articulatory pathway and (3) the parietal/inferior cerebellar phonological storage pathway, similar to that of the adults. In addition to the similar effective connectivity network used by both children and adults, comparable parameter estimates for both the driving input and the intrinsic connectivity were found. Nonetheless, age-related differences were observed in the modulatory connections. The reduced cortical-to-cortical connectivity between the left IFG and left IPL observed in children was suggested to be related to the protracted course of brain maturation (Simmonds et al., 2014). In contrast, increased connectivity were observed on the cortical-to-subcortical pathways which was postulated to be related to the brain maturation process whereby evidence has suggested that

neurodevelopment progresses from the inferior to the superior regions. As such, increased connectivity between the cortical and subcortical networks is interpreted as an increased effort to compensate for the reduced activation and connectivity in the cortical regions (both the left IFG and left IPL).

While Study 2a elucidated both the specialised network of regions involved during verbal working memory and the effective connectivity network, Study 2b examined how this network may be influenced by a neurodevelopmental learning disorder, specifically, dyslexia. Although verbal working memory have been consistently documented as a core deficit found in individuals with dyslexia, little is known about the underlying neural network in this population. Using the same Sternberg verbal working memory task paradigm as the previous two studies, neural activation was found in all eight regions of interest during verbal working memory in dyslexia. However, in comparison to typically developing children, children with dyslexia shown significantly reduced activation at both the inferior and superior cerebellum. Consistent with the functional activation, Bayesian model selection showed that the data obtained from children with dyslexia indicated a slightly better fit for the model with only modulatory effects from the left IFG to the left IPL. Further analysis revealed that the data from the children with dyslexia had a better fit for models without modulatory connectivity from the cortical-to-subcortical regions. It was hypothesised that the better fit for models without modulatory connectivity from the cortical-to-subcortical regions may be related to the reduced grey matter at both the right lobule VI and right Crus II of the cerebellum in children with dyslexia.

Importance of understanding network connectivity

The brain is an intricate and ever-changing organ that is perpetually engaged in activity. Neurons with similar functions combine to form malleable networks that are

bounded by structural pathways directly involving the brain. These functional networks are capable of governing high-order cognitive processes; a feat which cannot be achieved by individual elements of the nervous system working in isolation. The advent of functional and effective connectivity techniques played a crucial role towards understanding how these functional networks operate. Specifically, functional connectivity measures the association between isolated neurophysiological events, while effective connectivity assesses the interaction between multiple neural systems. Collectively, these methods have afforded new insights pertaining to the interplay between various networks within the brain.

Increasingly, researchers have been employing connectivity techniques to better understand the processes involved in brain development. Although verbal working memory plays a vital role in the ability to read, little is known about the neurodevelopmental changes that occur during verbal working memory, particularly, in terms of network connectivity. Using dynamic causal modeling, the ephemeral process of task-induced influence that one region of verbal working memory network exerts over another was elucidated in both typical adults and children in Study 1 and Study 2a respectively. Findings from both studies provided novel insights into the activity of the neural network underlying verbal working memory.

Existing functional neuroimaging studies have documented that neural activity during verbal working memory increases as a function of age and plateaus in adulthood (O'Hare et al., 2008). Although children have been found to show reduced activation, the network of regions involved was similar compared to that observed in adults. Using analyses of effective connectivity, the present study found that both adults and children utilised a similar verbal working memory pathway. This suggests that the verbal working memory pathway is established during childhood. Although

the pathway is developed in childhood, differences in modulatory connectivity provided insights of the importance of the cortical to subcortical connectivity. Brain maturation follows a protracted pathway—whereby maturation begins from the subcortical regions and extends upwards to the cortical regions.

In light of the above, it is postulated that the cerebro-cerebellar connectivity may play an especially important compensatory role during verbal working memory tasks, as cortical regions may not be as well developed as the cerebellum. It is therefore postulated that dysfunction of this cerebro-cerebellar pathways may lead on to verbal working memory deficits observed. Given the aforementioned findings of the pathway, it is thought that the dynamic systems framework established in both Study 1 and Study 2a may provide valuable theoretical principles for conceptualising and understanding the complex neural network involved during verbal working memory.

In addition to advancing our understanding of the developing brain, effective connectivity techniques such as dynamic causal modeling can also be utilised to explicate changes in the effective connectivity pathway caused by neurodevelopmental learning disorders. Study 2b of the dissertation investigated the presence of deviations in the verbal working memory pathway in children with dyslexia. Results indicated a difference in the pathways between typically developing children and children with dyslexia. Specifically, data obtained from the children with dyslexia displayed a better fit for pathway models without modulatory connectivity from the cortical to subcortical regions. This provided novel insights into the possible causes underlying verbal working memory deficit documented in children with dyslexia. The cerebro-cerebellar connectivity was postulated to be a crucial compensatory pathway for verbal working memory in children, with increased modulatory connectivity observed in children when compared to adults. As such, it is evident that the lack of modulatory

connectivity between the cortical and subcortical regions may be accountable for verbal working memory deficits observed in children with dyslexia. Additionally, Study 2b reinforced the importance of understanding the effective network connectivity to elucidate the otherwise unknown aberrant network connectivity. Knowledge of the effective network connectivity can provide valuable insights into understanding the underlying neural network of clinical population.

Taken together, the dissertation utilised dynamic causal modeling and provided unique insights into the understanding of the underlying neural network connectivity. Throughout this thesis, the effective connectivity during verbal working memory was systematically elucidated in three distinct populations. This paved the way for investigating how the effective connectivity pathway is affected by age as well as dyslexia. More importantly, it highlighted the importance of understanding the effective network connectivity in addition to existing functional and structural findings, so as to have a more holistic understanding of the underlying neural network. This may be particularly important when trying to understand how neurodevelopmental disorders such as dyslexia can be associated with a change in the network pathways.

The cerebro-cerebellar network connectivity theory of dyslexia

Developmental dyslexia is traditionally defined as a disorder in children who, despite having normal intelligence and conventional classroom experiences, display below average reading abilities (American Psychiatric Association, 2013). Researchers in the field of dyslexia have postulated various theories to account for the deficits observed in dyslexia, as documented in the literature review section of the dissertation. In a nutshell, the most widely accepted theory is the phonological deficit theory (Stanovich, 1988), which holds that the difficulties children have in the mapping of

grapheme to phoneme is accountable for the reading deficits observed. This was subsequently expanded upon with the postulation of the double-deficit theory (Wolf & Bowers, 1999) that suggests that both phonological deficit and rapid automatised naming are independent core deficits associated to the reading deficits in children with dyslexia. The theory posits that children with dyslexia may have either or both of these deficits; children with both deficits would display more pronounced reading difficulties. Separately, the cerebellar theory of dyslexia (Nicolson et al., 2001) tried to account for a wider range of deficits, such as automatization and motor skills in addition to phonological awareness, which was thought to be related to the dysfunction of the cerebellum.

The aforementioned theories tried to account for the behavioural deficits observed in children with dyslexia with studies providing both supportive behavioural and functional imaging findings. However, despite the extensive research in the field, little is known about the network connectivity, particularly the effective network connectivity in children with dyslexia. It is thought that an understanding of the differences in effective network connectivity would provide a more in-depth understanding of the underlying neural network, which would translate into the development of a better-encompassed theory. Therefore, the dissertation had the scope to present the case for an alternate hypothesis that incorporates the changes observed at the network connectivity level. The cerebro-cerebellar network connectivity theory of dyslexia postulates that the core deficits of dyslexia such as phonological awareness, verbal working memory, rapid automatising as well as the less wide spread deficits such as motor deficits may be accountable for by the differences in the cerebro-cerebellar effective connectivity in children with dyslexia.

Connectivity between cortical regions.

Neuroimaging studies examining developmental dyslexia have consistently documented aberrant activations in the left perisylvian language areas such as the temporal-parietal cortex, which is involved in the mapping of graphemes to phonemes for the purpose of phonological processing; the occipital-temporal cortex, which supports orthographic processing and the inferior frontal cortex that is important for the articulatory process of phonological components. However, few studies (Cao et al., 2008; Morken et al., 2017; Quaglino et al., 2008), went beyond the understanding of functional activation at an individual brain region to investigate the effective connectivity within regions of the cerebral cortex to provide valuable insights on how in addition to the aberrant activation previously documented, the differences in connectivity with a network of may also play a pertinent role in explaining the behavioural deficits observed in children with dyslexia.

In summary (refer to literature review section on network connectivity in children with dyslexia for more details pertaining to the three effective connectivity studies discussed), Cao et al. (2008) utilised dynamic causal modeling during a rhyming task and found reduced modulatory connectivity in children with dyslexia from the left FG to the left IPL during conflicting trials. Additionally, unlike typically developing children who displayed positive correlation between reading skills and modulatory connectivity between regions of interest, children with dyslexia showed no correlation. It was suggested the aforementioned findings might be a possible explanation for the phonological deficits observed. This is because children with dyslexia may have utilised an indirect connectivity pathway between the posterior (left IPL) and anterior (left IFG) language processing region especially when the phonological and orthographical information are conflicting. The findings from the

study provided preliminary indications of a dysfunctional phonological processing connectivity pathway in children with dyslexia. More importantly, it lent support for the cerebro-cerebellar connectivity network theory of dyslexia by providing evidence indicating that the phonological deficits observed in children with dyslexia go beyond the aberrant neuronal activation involved in isolated regions involved in the task and can be more holistically understood by the differences in connectivity pathways.

Separately, in the study by Quaglino et al. (2008), the authors utilised a different connectivity technique, structural equation modeling (SEM), to understand the phonological deficit in children with dyslexia. Using a pseudoword reading task, no modulatory connectivity was found between the supramarginal cortex and the inferior frontal cortex in children with dyslexia. This is in contrast to both reading-matched and age-matched controls, where modulatory connectivity was observed. It was suggested that the lack thereof modulatory connectivity reflects the phonological deficit in children with dyslexia, as the pathway between the supramarginal cortex and the inferior frontal cortex is known to be involved in phonological processing. In line with the finding from Cao et al. (2008), dysfunction of the phonological processing connectivity pathway was elucidated. Furthermore, results from the present study provided further support to the proposed theory through the investigation of the phonological processing deficits in children with dyslexia using a different connectivity technique and task paradigm, which indicates the robustness of the theory.

More recently, Morken and colleagues (2017) conducted a longitudinal study of effective connectivity to investigate the literacy development in children with dyslexia. Using a similar connectivity technique as the present dissertation and Cao et al. (2008), researchers found reduced connectivity in eight year old children with

dyslexia from the IFG to the IPL, IFG to precentral gyrus and increased connectivity from the occipital-temporal region to the precentral gyrus as compared to their age matched peers. Effective connectivity findings from the alphabetic processing task reiterated the findings from both Cao et al. (2008) and Quaglino et al. (2008), revealing a dysfunctional phonological processing connectivity pathway.

Using a different task paradigm from previous studies, the present dissertation utilised the Sternberg verbal task paradigm to understand the effective connectivity network during verbal working memory in children with dyslexia. Unilateral modulatory connectivity was observed in both typically developing children and children with dyslexia from the IFG to the IPL. However, children with dyslexia displayed reduced modulatory connectivity as compared to children with typical reading development. This finding is consistent with Cao et al. (2008), which suggested that this might be understood as children with better reading ability being more proficient in top-down modulation that involved the integration of both phonological and orthographic information. By examining the verbal working memory network connectivity pathway in children with dyslexia, the findings from the present dissertation provided further validation for the postulated cerebro-cerebellar network connectivity theory of dyslexia. It demonstrated that the specific network connectivity pathways of cognitive deficits observed in children with dyslexia could be attributed to dysfunctional connectivity pathways in addition to the aberrant neuronal activation observed.

Taken together, these studies indicate a difference in network connectivity, evidenced by a reduced/increase in modulatory connectivity, in children with dyslexia when compared to the children with typical reading development. More importantly, it highlighted the importance of understanding brain functions collectively as a network

together with its connectivity, as opposed to the identification of neuronal activations at isolated brain regions. With the recent shift in view towards a more holistic approach in understanding developmental disorders, dyslexia has been recognised as a multifaceted disorder where the expression of deficits differs from individual to individual. Hence, it is important to not only consider the connectivity between cortical regions, which may account for some of the deficits observed in children with dyslexia, but also the connectivity between cortical and subcortical regions.

Connectivity between cortical and subcortical regions.

Over the past two decades, our understanding of the human cerebellum has undergone significant modification. Previously known as a region involved in motor control, the cerebellum has now been shown to be involved in a wider range of higher cognitive functions such as language, working memory, timing, music and emotion (E et al., 2012). Previous studies examining the aberrant neural activation in children with dyslexia rarely included the cerebellum into the analysis until approximately two decades ago when Fawcett and colleagues (1996) showed impaired performance on a series of cerebellar tasks. However, to date, no detailed understanding of the connectivity of between cortical and subcortical regions in children with dyslexia has been published in the literature.

Closed loop circuitries with contralateral connections from the cerebellum to most parts of the cerebral cortex via the pons and through the ventrolateral nucleus of the thalamus have been well documented (Kelly & Strick, 2003; Schmahmann & Pandya, 2008). These circuitries are involved in distinct functions dependent on the input and output (Ramnani, 2006), whereby different regions of the cerebellum have been found to be elicited in different higher cognitive task domains (E et al., 2012). The functions governed by different regions of the human cerebellum are determined

by its physical associations with the spinal cord and cerebral cortex: lobules I-V and VIII are largely sensorimotor, lobules VI and VIII form linkages with the cortex in the parietal and frontal regions, lobule IX is involved in several cortical networks—such as the default mode network—and lobule X encompasses the vestibulocerebellum (Stoodley & Schmahmann, 2010). More recently, Fernandez and colleagues (2016) elucidated the white matter integrity of the cerebro-cerebellar tracts in children with dyslexia and found increased fractional anisotropy as compared to typical readers in tracts connecting the cerebellum to both the temporal-parietal and the inferior frontal regions of the cerebral cortex.

With anatomical connections elucidated, the present dissertation investigated the cerebro-cerebellar effective connectivity network in children with dyslexia using the Sternberg verbal working memory task paradigm. Results indicated a difference in the pathway during verbal working memory in children with dyslexia, compared to typically developing children. Although differential activation has been documented in cerebellums of children with dyslexia, the present study was the first to document a difference in verbal working pathway whereby data obtained from the children with dyslexia were found to show a better fit for pathway without the cortical to subcortical connectivity. These results, coupled with previous anatomical connectivity findings, provide substantial evidence pointing towards a differential connectivity pathway between the cortical and subcortical regions, which is postulated to be accountable for verbal working memory deficits observed in children with dyslexia.

Empirical evidence

The postulation of the cerebro-cerebellar network connectivity theory was motivated by findings from previous studies establishing the cerebellar – cortical tracks in children with dyslexia as well as the functional and effective connectivity

between cortical regions. The present dissertation provided further evidences for the theory by elucidating the effective connectivity between cortical and subcortical regions using an established cerebro-cerebellar verbal working memory network (Chen & Desmond, 2005a).

The case for the cerebro-cerebellar network connectivity theory was systematically elaborated in the aforementioned two sections: (i) the connectivity between cortical regions and (ii) the connectivity between cortical and subcortical regions. In general, the theory postulates that the differential connectivity pathways utilised by children with dyslexia as compared to typically developing children may provide justifications for the various behavioural deficits observed. However, it is important to note that the numerous deficits observed tap on differing cognitive domains, of which, certain tasks may elicit connectivity between regions within the cerebral cortex while others induce connectivity between cortical and subcortical regions. Therefore, the theory postulates that the deficits observed in individuals with dyslexia can be accounted for by the differences in network connectivity pathway specific to the task (see Figure 6.2).

Figure 6.2. An illustration of the effective connectivity pathways during verbal working memory in children with dyslexia. Green arrows denote connectivity between the cortical regions while red dashed arrows denote the dysfunctional connectivity between the cortical to the sub-cortical regions. IFG (pink): left inferior frontal gyrus; IPL (green): left inferior parietal lobule; iCERE (blue): right inferior cerebellum; sCERE (red): right superior cerebellum.

Limitations and Future Directions

While the present study provided novel insights into the understanding of the effective connectivity network during verbal working memory, it is not without limitations. Methodological limitations pertaining to the individual studies have been addressed in the previous three chapters. Here, the discussions will emphasise on broader issues that have yet to be addressed in the dissertation and require future investigation.

Firstly, the cerebro-cerebellar network connectivity theory cannot yet fully account for all of the behavioural deficits observed in children with dyslexia, such as motor skills and coordination, as not all of the deficits have been thoroughly examined using network connectivity techniques. Despite this, the theory provided a more comprehensive understanding and hypothesis to account for both the aberrant

activation as well as the atypical network connectivity pathway during the processing of two of the core deficits in dyslexia. In addition, findings from the present dissertation and previous studies (Cao et al., 2008; Morken et al., 2017; Quaglino et al., 2008) have elucidated the dysfunctional network in verbal working memory and phonological awareness respectively. Nonetheless, future studies are required to investigate the differences in network connectivity during other cognitive domains, such as rapid automatised naming, to provide support for the cerebro-cerebellar network connectivity theory of dyslexia.

Second, to understand the preferred connectivity pathway in all three populations, the current dissertation compared eight candidate models focusing on the dynamics elicited by verbal working memory processing during task modulation. Although it is believed that the proposed network model is representative of the verbal working memory network, it is arguable that an alternative network may be possible. The present network model (Figure 3.2) was substantiated through anatomical connectivity studies documenting prefrontal to subcortical connectivity (Schmahmann & Pandya, 2008) and the functional activation documented by Chen and Desmond (2005a), which was further validated by a diffusion spectrum imaging study documenting contralateral cerebro-cerebellar white matter pathways during verbal working memory (Sobczak-Edmans et al, 2016). However, as noted in the earlier chapters of the dissertation, functional activation observed during verbal working memory processing is dependent on the task paradigm utilised (E et al., 2012). As the network model utilised in the present dissertation is based on the activation patterns elicited by the Sternberg verbal working memory task paradigm, alternate network models can possibly be examined.

Third, participants from all three populations included in the present dissertation were examined with the English language network and participants spoke English as their first language. Hence, it is unknown if the cerebro-cerebellar network connectivity theory of dyslexia can be applicable beyond the scope of alphabetic language speakers. However, a recent study by Feng and colleagues (2016) provided insights into the functional connectivity in Chinese children with dyslexia during both a phonological and orthographic task. During the rhyming judgment tasks where participants are required to decide if two Chinese characters rhymed, children with dyslexia in comparison to their typically developing peers, displayed an increase in connectivity between the left cerebellum and the left supramarginal gyrus. Additionally, it was also found that children with dyslexia showed increased functional activation at the bilateral cerebellum lobule VI. It was suggested that both the increase in activation at the bilateral superior cerebellum as well as the increased connectivity between the left cerebellum and the left supramarginal gyrus might be a form of compensatory mechanism during reading. Thus, the Feng et al. (2016) study provided insights into the probable differences in network connectivity pathways during both phonological and orthographic processing in Chinese speaking children with dyslexia. However, as functional connectivity technique was utilised in Feng et al. (2016) study, the direction of the modulatory effects between regions could not be inferred. Consequently, this raises a need for future studies to investigate the differences in effective network connectivity pathway in Chinese speaking children with dyslexia across a range of cognitive tasks documented to show impairment.

Additionally, while Study 1 and Study 2a provided novel insights into the age-related changes in dynamics within the effective connectivity network during verbal working memory, the cross-sectional design of the study may have interfered with a

more holistic understanding of age-dependent changes across the lifespan. At a neurocognitive level, it has become increasingly evident that a thorough understanding of the differences in effective connectivity pathways during cognitive tasks provides an important perspective for elucidating the human brain developmental trajectory. In a study by Sowell and colleagues (1999), researchers found that maturation of the parietal, temporal and occipital lobules is almost complete by the end of adolescence. However, post-adolescent brain development was documented in the frontal and striatal regions in addition to a reduction of grey matter observed at the frontal cortex (Sowell, Thompson, Holmes, Jernigan, & Toga, 1999). The differing course of maturation across both cortical and subcortical regions may be indicative of possible differences at the network connectivity level across the developmental span. More recently, using a sentence processing task, Morken and colleagues (2017) found that by age 12, there was no statistically significant differences in effective connectivity between children with dyslexia and typical readers even though there were still significant differences in terms of reading abilities. As this study employed a cross-sectional design, it was not possible to tease apart changes in brain activity due to ageing from other individual differences. Longitudinal follow-up of participants may overcome this limitation, as it allows the tracking of changes in neural activity as the brain matures. In addition, between-group individual differences in brain maturity can be tracked and accounted for. Alternatively, future studies could also include another age group of adolescents (i.e. 12-15) to examine if reading differences do indeed stabilise by age 12.

Finally, although the findings from the present study elucidated the importance of the cortical to subcortical connectivity during verbal working memory and its implication in reading, cerebellar dysfunction is observed in clinical populations

beyond that of individuals with dyslexia and extends to populations such as that of ADHD and autism. As such, it is plausible that the cerebellar disconnectivity observed in children with dyslexia may be generalised to other clinical populations. However, as the scope of the dissertation was limited to children with dyslexia, future studies are warranted to examine the generalisability of the importance of the cortical to subcortical connectivity in other clinical population.

The aforementioned limitations and possible future research may not be all encompassing, but they provide an interesting avenue for further investigation, which is beyond the scope of the present dissertation.

Conclusion

The current dissertation elucidated the two main hypotheses, namely the cross-sectional changes in effective connectivity between adults and children during verbal working memory as well as the differences in effective connectivity pathway in children with dyslexia. Results from the former provided valuable insights into the developmental changes in dynamics within the effective connectivity network during verbal working memory. Likewise, findings from the latter provided substantial evidence for the postulation of the cerebro-cerebellar network connectivity theory of dyslexia. For the past few decades, in line with a shift towards a more holistic understanding of developmental disorders, researchers have investigated the full range of deficits observed in children with dyslexia. Theories have been postulated to account for the various deficits documented through neuroimaging analysis of the cerebral cortex. More recently, a shift in interest to examine the role of the cerebellum has resulted in the postulation of the cerebellar theory of dyslexia. However, despite studies validating the role of the cerebellum in higher cognitive tasks, the function of the cerebellum has not been fully appreciated by the various postulated theories of

dyslexia. Conversely, the theory postulated in the present dissertation provided significant contributions to not only the role of cerebellum in verbal working memory but also to how the differences in the cerebro-cerebellar network connectivity pathway may be an added dimension to the deficits observed in children with dyslexia.

Taken together, the current investigations have important practical implications. First, the examination of age-related changes in dynamics in effective connectivity provided a more holistic understanding of the neurodevelopmental changes. In particular, findings suggest that the conceptualisation of the trajectory of brain maturation should move towards a more multidimensional approach that is beyond primarily focusing on structural and functional activation but to include the network connectivity changes observed. Secondly, findings from the present study furthered the understanding of dyslexia holistically. More importantly, the postulation of the cerebro-cerebellar network connectivity theory of dyslexia opens the avenue for developing more targeted intervention methodologies to alleviate the difficulties faced by children with dyslexia. Specifically, in addition to current intervention methodologies—which focus on phonological awareness—training could be administered to help improve verbal working memory while early stimulation of the cerebellum through coordination training could also aid in closing up the gap in terms of the delayed cerebellum development. Nonetheless, future studies are required to examine the efficacy of such intervention strategies in order for it to be evidence-based.

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Appendix A

Anxiety and Attitudinal Questionnaire (Children_Pre)

A number of statements that people have used to describe their feelings about entering an MRI scanner are given below. Read each statement and then circle the most appropriate number to the right of the statement to indicate how you feel right now. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

Child version: There are a few statements about how people feel about going into a machine that takes photographs of their brain. Please circle the number that is closest to how you feel now. There are no right or wrong answers.

	NOT AT ALL	A LITTLE BIT	A LOT
1. I feel excited	1	2	3
2. I feel scared	1	2	3
3. I feel sad	1	2	3
4. I feel happy	1	2	3
5. I feel worried	1	2	3
6. I feel comfortable	1	2	3
7. I feel relaxed	1	2	3
8. I feel afraid	1	2	3
9. I feel amazed	1	2	3
10. I feel panic	1	2	3
11. I feel ok in small places (E.g. toilet cubicle, lift, etc.)	1	2	3
12. I know about the machine that takes photographs of people's brains	1	2	3
13. I would like to go into the machine to take photographs of my brain	1	2	3
14. I want to see how my brain looks like	1	2	3

15. I want to help people understand more about the brain	1	2	3
16. I think going into the machine will be fun	1	2	3
17. I think I can do the computer task	1	2	3
18. I feel like I will have lots of fun doing all the activities in this study	1	2	3
19. I think I can stay still and not move for a long time	1	2	3

Anxiety and Attitudinal Questionnaire (Children_Post)

A number of statements that people have used to describe their feelings about entering an MRI scanner are given below. Read each statement and then circle the most appropriate number to the right of the statement to indicate how you feel right now. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

Child version: There are a few statements about how people feel about going into a machine that takes photographs of their brain. Please circle the number that is closest to how you feel now. There are no right or wrong answers.

	NOT AT ALL	A LITTLE BIT	A LOT
1. I feel excited	1	2	3
2. I feel scared	1	2	3
3. I feel sad	1	2	3
4. I feel happy	1	2	3
5. I feel worried	1	2	3
6. I feel comfortable	1	2	3
7. I feel relaxed	1	2	3
8. I feel afraid	1	2	3
9. I feel amazed	1	2	3
10. I feel panic	1	2	3
12. I know more about the machine that takes photographs of people's brains	1	2	3
13. I would like to go into the machine to take photographs of my brain	1	2	3
14. I want to see how my brain looks like	1	2	3
15. I want to help people understand more about the brain	1	2	3

16. I think going into the machine will be fun	1	2	3
17. I had lots of fun doing the computer task	1	2	3
18. I think I can stay still and not move for a long time	1	2	3
19. I think the video help me understand more about the brain	1	2	3
20. Please rate the activities (1-3) on how much it helped you feel more excited. 1 – very little 2 – average 3 – a lot	Video watching	Computer task	Balancing game

Anxiety and Attitudinal Questionnaire (Parents_Pre)

A number of statements that people have used to describe their feelings about their child entering an MRI scanner are given below (Item 1-10). The other 4 items (Item 11-14) are MRI specific questions. Read each statement (Item 1-14) and then circle the most appropriate number to the right of the statement to indicate how you feel right now. Item 15 is an open-ended question. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	NOT AT ALL	A LITTLE BIT	A LOT
1. I feel comfortable	1	2	3
2. I feel worried	1	2	3
3. I feel enthusiastic	1	2	3
4. I feel scared	1	2	3
5. I feel unsure	1	2	3
6. I feel secure	1	2	3
7. I feel relaxed	1	2	3
8. I feel tense	1	2	3
9. I feel unsure	1	2	3
10. I feel at ease	1	2	3
11. I have knowledge about MRI scanner	1	2	3
12. I am interested for my child to do a MRI scan for research purposes	1	2	3
13. I am glad that my child's participation will help researchers understand more about the brain	1	2	3
14. I think it will be a good experience for my child	1	2	3

Anxiety and Attitudinal Questionnaire (Parents_Post)

A number of statements that people have used to describe their feelings about their child entering an MRI scanner are given below (Item 1-10). The other 4 items (Item 11-14) are MRI specific questions. Read each statement (Item 1-14) and then circle the most appropriate number to the right of the statement to indicate how you feel right now. Item 15 is an open-ended question. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	NOT AT ALL	A LITTLE BIT	A LOT
1. I feel comfortable	1	2	3
2. I feel worried	1	2	3
3. I feel enthusiastic	1	2	3
4. I feel scared	1	2	3
5. I feel unsure	1	2	3
6. I feel secure	1	2	3
7. I feel relaxed	1	2	3
8. I feel tense	1	2	3
9. I feel unsure	1	2	3
10. I feel at ease	1	2	3
11. I have knowledge about MRI scanner	1	2	3
12. I am interested for my child to do a MRI scan for research purposes	1	2	3
13. I am glad that my child's participation will help researchers understand more about the brain	1	2	3
14. I think it will be a good experience for my child	1	2	3

15. I think the video helped me feel more assured in consenting my child to participate in a MRI research	1	2	3
16. I think the brochure will be useful in helping me talk to my child about participating in a MRI research	1	2	3
17. Seeing my child go through the activities smoothly helps me feel more comfortable about allowing my child participate in a MRI research	1	2	3
18. What could have been done to help you feel more comfortable about your child's participation in a MRI research study?			

Appendix B

IRB Approval for the behavioural component of Study 2

Research Support Office

Reg. No. 200604393R

IRB-2014-08-041

13 October 2014

Associate Professor Chen Shen-Hsing Annabel
School of Humanities and Social Sciences

NTU INSTITUTIONAL REVIEW BOARD APPROVAL
Project Title: Helping Children with Dyslexia through Neuroimaging

I refer to your application for ethics approval with respect to the above project.

The Board has deliberated on your application and noted from your application that your research involves collecting behavioral data from participants through digital video recording of the subjects performing MRI procedure.

You have also confirmed that informed consent will be obtained from the participants and you have guaranteed the confidentiality of your participants' biodata obtained from them.

The documents reviewed are:

- a) NTU IRB application form dated **29 August 2014**
- b) Participant information sheet and consent form: version 1 dated **29 August 2014**
- c) Data collection form: version 1 dated **29 August 2014**

The Board is therefore satisfied with the bioethical consideration for the project and approves the ethics application under **Full Board** review. The approval period is from **13 October 2014** to **30 September 2015**. The NTU IRB reference number for this study is **IRB-2014-08-041**. Please use this reference number for all future correspondence.

The following protocol and compliances are to be observed upon NTU IRB approval

1. All research involving procedures greater than minimal risk on minors (individuals who are less than the legal age of 21 years old) requires IRB approved written Parental Consent and assent from the participant to be obtained before any research protocols can be administered. Minimal risk refers to an anticipated level of harm and discomfort that is no greater than that ordinarily encountered in daily life, or during the performance of routine educational, physical, or psychological examination.
2. Only the approved Participants Information Sheet and Consent Form should be used. It must be signed by each subject prior to initiation of any protocol procedures. In addition, each subject should be given a copy of the signed consent form.

Blk N2.1, B4-01, 76 Nanyang Drive, Singapore 637331 Nanyang Avenue, Singapore 639798
Tel : +65 6791 9857, Fax: 6793 2019
www.ntu.edu.sg

Research Support Office

3. Consent forms are important documents therefore they should be stored in the strictest arrangement. Loss of consent form would result in disciplinary action.
4. No deviation from, or changes of, the protocol should be initiated without prior written NTU IRB approval of an appropriate amendment.
5. The Principal Investigator should report promptly to NTU IRB regarding:
  - a. Deviation from, or changes to the protocol.
  - b. Changes increasing the risk to the subjects and/or affecting significantly the conduct of the trial
  - c. All serious adverse events (SAEs) which are both serious and unexpected.
  - d. New information that may affect adversely the safety of the subjects of the conduct of the trial.
  - e. Completion of the study.
6. Continuing Review Request/ Notice of Study completion form should be submitted to NTU IRB for the following:
  - a. Annual review: Status of the study should be reported to the NTU IRB at least annually using the Continuing Review Request/ Notice of Study completion form.
  - b. Study completion or termination: Continuing Review Request/ Notice of Study completion form is to be submitted within 4 to 6 weeks of study completion or termination.

A handwritten signature in black ink, appearing to read "Althee".

Professor Lee Sing Kong,
Chair, NTU Institutional Review Board
encl.

cc Chair, School of Humanities and Social Sciences
Members, NTU Institutional Review Board

IRB Approval for the imaging component of Study 2

Research Support Office

Reg. No. 200504353R

IRB-2014-11-005

02 January 2015

Associate Professor Chen Shen-Hsing Annabel
School of Humanities and Social Sciences

NTU INSTITUTIONAL REVIEW BOARD APPROVAL

Project Title: Investigating the neural substrates of verbal working memory in children with dyslexia: A multi-modal neuroimaging study

(Amount Approved: SGD\$89.910; to be funded by AcRF Tier 1 program)

I refer to your application for ethics approval with respect to the above project.

The Board has deliberated on your application and noted from your application that your research involves collecting behavioral data from through a battery of tasks.

You have also confirmed that informed consent will be obtained from the participants and you have guaranteed the confidentiality of your participants' biodata obtained from them.

The documents reviewed are:

- a) NTU IRB application form dated **05 November 2014**
- b) Participant information sheet and consent form: version 1 dated **05 November 2014**
- c) Data collection form: version 1 dated **05 November 2014**

The Board is therefore satisfied with the bioethical consideration for the project and approves the ethics application under **Expedited** review. The approval period is from **02 January 2015** to **31 October 2017**. The NTU IRB reference number for this study is **IRB-2014-11-005**. Please use this reference number for all future correspondence.

The following protocol and compliances are to be observed upon NTU IRB approval

1. All research involving procedures greater than minimal risk on minors (individuals who are less than the legal age of 21 years old) requires IRB approved written Parental Consent and assent from the participant to be obtained before any research protocols can be administered. Minimal risk refers to an anticipated level of harm and discomfort that is no greater than that ordinarily encountered in daily life, or during the performance of routine educational, physical, or psychological examination.
2. Only the approved Participants Information Sheet and Consent Form should be used. It must be signed by each subject prior to initiation of any protocol procedures. In addition, each subject should be given a copy of the signed consent form.

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5. The Principal Investigator should report promptly to NTU IRB regarding:
  - a. Deviation from, or changes to the protocol.
  - b. Changes increasing the risk to the subjects and/or affecting significantly the conduct of the trial
  - c. All serious adverse events (SAEs) which are both serious and unexpected.
  - d. New information that may affect adversely the safety of the subjects of the conduct of the trial.
  - e. Completion of the study.
6. Continuing Review Request/ Notice of Study completion form should be submitted to NTU IRB for the following:
  - a. Annual review: Status of the study should be reported to the NTU IRB at least annually using the Continuing Review Request/ Notice of Study completion form.
  - b. Study completion or termination: Continuing Review Request/ Notice of Study completion form is to be submitted within 4 to 6 weeks of study completion or termination.

A handwritten signature in black ink, appearing to read "Lee", is positioned above the printed name.

Professor Lee Sing Kong,
Chair, NTU Institutional Review Board
encl.

cc Chair, School of Humanities and Social Sciences
Members, NTU Institutional Review Board