Statistical analysis and machine learning in multimodal brain imaging of neuropsychiatric disorders

Hu, Mengjiao

2021

Hu, M. (2021). Statistical analysis and machine learning in multimodal brain imaging of neuropsychiatric disorders. Doctoral thesis, Nanyang Technological University, Singapore.
<https://hdl.handle.net/10356/153263>

<https://hdl.handle.net/10356/153263>

<https://doi.org/10.32657/10356/153263>

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0).

Downloaded on 26 Apr 2023 23:23:13 SGT

**NANYANG
TECHNOLOGICAL
UNIVERSITY**

SINGAPORE

**STATISTICAL ANALYSIS AND MACHINE LEARNING
IN MULTIMODAL BRAIN IMAGING OF
NEUROPSYCHIATRIC DISORDERS**

Hu Mengjiao
Interdisciplinary Graduate School
NTU Institute for Health Technologies

STATISTICAL ANALYSIS AND MACHINE LEARNING IN MULTIMODAL BRAIN IMAGING OF NEUROPSYCHIATRIC DISORDERS

Hu Mengjiao

**Interdisciplinary Graduate School
NTU Institute for Health Technologies**

A thesis submitted to the Nanyang Technological University in
partial fulfillment of the requirement for the degree of
Doctor of Philosophy

2021

Statement of Originality

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

2021Nov2

.....

Date

NTU NTU NTU NTU NTU NTU NTU NTU NTU NTU
NTU NTU *Hu Mengjiao* NTU NTU NTU NTU NTU NTU NTU NTU NTU NTU
NTU NTU NTU NTU NTU NTU NTU NTU NTU NTU NTU NTU
NTU NTU NTU NTU NTU NTU NTU NTU NTU NTU
.....

Hu Mengjiao

Supervisor Declaration Statement

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

2021Nov2

.....

Date

Jiang Luobang

Jiang Xudong

Authorship Attribution Statement

This thesis contains material from 3 papers published/will be published in the following peer-reviewed journals where I was the first and/or corresponding author.

Chapter 2 is published as Hu, M., Cheng, H. J., Ji, F., Chong, J. S. X., Lu, Z., Huang, W., ... & Zhou, J. H. (2021). Brain functional changes in stroke following rehabilitation using brain-computer interface-assisted motor imagery with and without tDCS: a pilot study. *Frontiers in human neuroscience*.

The contributions of the co-authors are as follows:

- Prof Zhou, Prof Guan and Prof Jiang supervised me on the overall project direction and edited the manuscript drafts.
- I prepared the manuscript drafts. The manuscript was revised by Dr Cheng, Dr Ji, and Dr Chong.
- I co-designed the study with Prof Juan (Helen) Zhou and performed all the data analysis.
- Dr Chew provided the data. Dr. Lu, Dr. Huang, Dr. Ang AND Dr. Chuang assisted in data processing.

Chapter 3 is published as Hu, M., Qian, X., Liu, S., Koh, A. J., Sim, K., Jiang, X., ... & Zhou, J. H. (2021). Structural and diffusion MRI based schizophrenia classification using 2D pretrained and 3D naive Convolutional Neural Networks. *Schizophrenia research*.

The contributions of the co-authors are as follows:

- Prof Zhou, Prof Guan and Prof Jiang supervised me on the overall project direction and edited the manuscript drafts.
- I prepared the manuscript drafts. The manuscript was revised by Dr Qian and Dr Liu.
- I co-designed the study with Prof Juan (Helen) Zhou and developed the algorithms.

- Prof Zhou, Prof Guan and Prof Jiang supervised me on the overall

- o-designed the study with Prof Jiang and developed the algorithms.

.....

Hu Mengjiao

Acknowledgement

I would like to express sincere gratitude to my main supervisor, Professor Xudong Jiang, co-supervisors, Professor Cuntai Guan, and Professor Juan (Helen) Zhou, who provided me with the opportunity to pursue graduate study and guided me every step of the way during this tremendous journey. I would not have made it without the invaluable guidance, kind encouragement and enormous support from three supervisors. Professor Jiang inspired me to build deep interest in image processing with his immense knowledge and perpetual enthusiasm. Professor Guan lead me into the field of medical imaging and encouraged me to explore the frontiers of the field with his deep insights. Professor Zhou revealed the fascinating side of neuroscience to me and helped me to work on every details of study design, algorithm development and manuscript writing. I would like to thank my three supervisors from the bottom of my heart for being a defining influence in how I approach scientific research.

I would like to especially thank my mentor Dr. Effie Chew for her support, valuable advice, insightful comments and for being so generous with her feedback about my work. I would also like to thank collaborator Dr. Kang Sim, Dr. Weimin Huang, and Dr. Zhongkang Lu for providing me the data and generous feedback on my research results.

My appreciation also extends to my laboratory colleagues in Media Technology Laboratory, Brain Computing Research Laboratory and Multimodal Neuroimaging in Neuropsychiatric Disorders Laboratory. The amazing members of three labs has offered great advice and encouragement to me and also provided fantastic company and friendships. A special thanks to the research assistant Ms. Amelia Jialing Koh and Mr. Marcus Qin Wen Ong who were always ready with a helping hand with any IT issues

I may have. I would also like to thank my seniors Dr. Joanna Su Xian Chong, Dr. Qian Xing and Dr. Hsiao-Ju (Rita) Cheng for their valuable advice and encouragement on my research.

Finally, I would like to thank my parents, my husband and all other family members for their unconditional love and support to me. They have always been there to encourage me to the best I can be and this thesis would not be possible without them.

Table of Contents

Statement of Originality.....	3
Supervisor Declaration Statement.....	4
Authorship Attribution Statement.....	5
Acknowledgement	7
Table of Contents.....	9
List of Tables	13
List of Figures	14
Abstract.....	15
Chapter 1 Introduction	19
1.1 Background	19
1.1.1 Introduction to Neuropsychiatric Disorders	19
1.1.2 Introduction to MRI.....	24
1.1.3 Statistical Analysis and Machine Learning	27
1.2 Aims and Motivations	31
1.2.1 Differential Neuroimaging Re-normalization Pattern in MI-BCI Stroke Rehabilitation with and without tDCS	31
1.2.2 Structural and diffusion MRI based schizophrenia classification 3D naive Convolutional Neural Networks	32
1.2.3 Decomposing 3D Neuroimaging into 2+1D Processing for Classification of Schizophrenia Patients and Controls	33
1.3 Research Contribution.....	33
1.4 Thesis Outline	35
Chapter 2 Brain Functional Changes in Stroke following rehabilitation using Brain- computer interface-assisted motor imagery with and without tDCS	36
2.1 Introduction	36
2.2 Methodology	39

2.2.1 Participants	39
2.2.2 MI-BCI and tDCS study design	41
2.2.3 Image Acquisition	41
2.2.4 Image Analyses	42
2.2.5 Statistical Analysis	44
2.3 Results	45
2.3.1 Improved Motor Function	45
2.3.2 Abnormal ALFF/ReHo in the SMN and DMN in stroke patients at baseline	46
2.3.3 Differential changes in ALFF/ReHo in the MI-BCI and MI-BCI+tDCS groups post-intervention	48
2.3.4 Functional connectivity changes between the SMN and DMN	49
2.3.5 Association between brain functional measures and motor function improvement.....	50
2.4 Discussion	52
2.4.1 Compensation effect of the contralesional SMN after MI-BCI	52
2.4.2 Re-normalization of brain activity and connectivity after MI-BCI.....	54
2.4.3 Differential Mechanisms of MI-BCI and MI-BCI+tDCS	55
2.4.4 Limitations.....	57
2.5 Summary	57
Chapter 3 Structural and diffusion MRI based schizophrenia classification using 2D pre-trained and 3D naive Convolutional Neural Networks	59
3.1. Introduction	59
3.2. Methods.....	63
3.2.1 Participants	63
3.2.2 Image acquisition.....	64
3.2.3 Image processing	65

3.2.4 Study design	66
3.3. Results	72
3.3.1 Nested cross-validation results on the NUSDAST dataset with sMRI models	72
3.3.2 Independent testing results on the IMH dataset with sMRI models.....	76
3.3.3 Nested cross-validation results on the IMH dataset with sMRI+dMRI models	79
3.3.4 Interpretation of the trained CNN models	80
3.4. Discussion	82
3.4.1 CNN performed better than handcrafted feature-based machine learning ..	82
3.4.2 3D naïve CNN performed better than deep feature based on pre-trained 2D CNN.....	83
3.4.3 Multimodal inputs and complex topologies improved classification accuracy	84
3.4.4 Gradient class activation map identified critical regions for classification.	86
3.4.5 Limitations.....	87
3.5 Summary	88
Chapter 4 Applying Pre-trained 2D Networks to 3D Neuroimaging for Classification of Schizophrenia Patients and Controls	90
4.1. Introduction	90
4.2. Related studies.....	91
4.3. Methodology	93
4.3.1 Image decomposition, feature extraction and feature maxpooling.....	94
4.3.2 Remove redundant information via global pooling in the slice and channel dimensions	95
4.3.3 Channelwise & slicewise convolution and multi-brain metric & multi-view fusion	97

4.4. Experimental settings and results	98
4.4.1 Experimental settings	98
4.4.2 Compare with handcrafted feature-based machine learning	101
4.4.3 Compare with transfer learning approach with direct SVM.....	102
4.4.4 Compare with 3D CNN models trained from scratch	102
4.5. Discussion	103
4.6. Summary	108
Chapter 5 Conclusions and Future Work.....	109
5.1 Conclusions	109
5.2 Future Directions.....	110
5.2.1. Prediction of clinical high-risk state for psychosis.....	111
5.2.2. Prediction of Alzheimer’s disease	112
Bibliography	115
Appendix.....	145
Appendix A: Supplementary Materials.....	145
Appendix B: Publications and Manuscripts	162

List of Tables

Table 1. 1 Prevalence of neuropsychiatric disorders in 2017 (James et al., 2018).....	20
Table 2. 1 Subject demographics.	40
Table 3. 1 Subject demographics of the two datasets.	63
Table 3. 2 Single modal (sMRI) cross-validation results on the NUSDAST dataset. .	74
Table 3. 3 Single modal (sMRI) independent testing results on the IMH dataset.	77
Table 3. 4 Multimodal (sMRI and dMRI) cross-validation results on the IMH dataset.	79
Table 4. 1 Subject demographics of the dataset.....	99
Table 4. 2 Channelwise and slicewise convolutional neural network architecture. ..	100
Table 4. 3 Comparison with previous methods.	103
Table 4. 4 Results for ablation study.	107

List of Figures

Figure 2. 1 Motor recovery after MI-BCI intervention with and without tDCS.....	46
Figure 2. 2 Functional disruptions in stroke patients.	47
Figure 2. 3 ALFF changes in contralesional SMN and posterior DMN in stroke patients along with motor function recovery.....	49
Figure 2. 4 ReHo changes in DMN in stroke patients along with motor function recovery.....	50
Figure 2. 5 Differential correlation between FC changes and behavioural outcome changes using different intervention methods.	51
Figure 3. 1 Study Design.	67
Figure 3. 2 Architectures of the naïve 3D CNN models.....	70
Figure 3. 3 Classification Accuracy in cross-validation and independent testing across all models.	75
Figure 3. 4 Prediction probability distribution of schizophrenia and controls in cross- validation and independent testing across all approaches.....	78
Figure 3. 5 Gradient class activation mapping for schizophrenia classification.....	81
Figure 4. 1 Framework of the proposed method.	93
Figure 4.2 Accuracy and ROC-AUC curve comparisons with previous methods. ...	101

Abstract

Neuropsychiatric disorders are the leading causes of mortality and disability. Specifically, the high prevalence of stroke and high rate of disability due to stroke results in huge socioeconomic burdens. Schizophrenia causes profound effects to patients, their families and the society with its early onset of the disease and its incurable nature with persisting symptoms. Multimodal neuroimaging techniques plays an essential role in investigating brain functional and structural changes in neuropsychiatric disorders. In this thesis, the first study utilized functional magnetic resonance imaging (MRI) to examine the brain alteration post stroke and rehabilitation effect of Brain-computer interface-assisted motor imagery (MI-BCI) or transcranial direct current stimulation (tDCS); the second study utilized structural MRI and diffusion MRI for classification of schizophrenia patients and healthy controls with 3D convolutional neural networks trained from scratch; the third study utilized structural MRI for classification of schizophrenia patients and healthy controls using pre-trained 2D convolutional neural networks.

MI-BCI and tDCS have been proven effective in post-stroke motor function enhancement, yet whether the combination of MI-BCI and tDCS may further benefit the rehabilitation of motor functions remains unknown. The first study investigated brain functional activity and connectivity changes using amplitude of low-frequency fluctuation (ALFF), regional homogeneity (ReHo), and functional connectivity (FC) from resting-state functional magnetic resonance imaging (fMRI) data pre- and post- a two-week MI-BCI and tDCS combined intervention in 19 chronic subcortical stroke patients. At baseline, stroke patients had lower ALFF in the ipsilesional somatomotor network (SMN), lower ReHo in the contralesional insula, and higher ALFF/Reho in the

bilateral posterior default mode network (DMN) compared to age-matched healthy controls. After the intervention, the MI-BCI only group showed increased ALFF in contralesional SMN and decreased ALFF/ReHo in the posterior DMN. In contrast, no post-intervention changes were detected in the MI-BCI+tDCS group. Furthermore, higher increases in ALFF/ReHo/FC measures were related to better motor function recovery (measured by the Fugl-Meyer Assessment scores) in the MI-BCI group while the opposite association was detected in the MI-BCI+tDCS group. Taken together, the findings suggest that brain functional re-normalization and network-specific compensation were found in the MI-BCI only group but not in the MI-BCI+tDCS group although both groups gained significant motor function improvement post-intervention with no group difference. MI-BCI and tDCS may exert differential or even opposing impact on brain functional reorganization during post-stroke motor rehabilitation; therefore, the integration of the two strategies requires further refinement to improve efficacy and effectiveness.

The ability of automatic feature learning makes CNN potentially suitable to uncover the complex and widespread brain changes in schizophrenia. Despite that, limited studies have been done on schizophrenia identification using interpretable deep learning approaches on multimodal neuroimaging data. In the second study, I developed a deep feature approach based on pre-trained 2D CNN and naive 3D CNN models trained from scratch for schizophrenia classification by integrating 3D structural and diffusion magnetic resonance imaging (MRI) data. I found that the naive 3D CNN models outperformed the pretrained 2D CNN models and the handcrafted feature-based machine learning approach using support vector machine during both cross-validation and testing on an independent dataset. Multimodal neuroimaging-based models accomplished performance superior to models based on a single modality. Furthermore,

I identified brain grey matter and white matter regions critical for illness classification at the individual- and group-level which supported the salience network and striatal dysfunction hypotheses in schizophrenia. The findings underscore the potential of CNN not only to automatically uncover and integrate multimodal 3D brain imaging features for schizophrenia identification, but also to provide relevant neurobiological interpretations which are crucial for developing objective and interpretable imaging-based probes for prognosis and diagnosis in psychiatric disorders.

Deep learning has been successfully applied to the classification of both natural images and medical images. However, there remains a gap for applying pre-trained 2D networks to the classification of 3D neuroimaging data, especially for diseases without visible alteration in specific slices such as schizophrenia and depression. In the third study, I propose to process the 3D data by a 2+1D framework so that I can exploit the powerful deep 2D networks pre-trained on huge ImageNet dataset for 3D neuroimaging classification. Specifically, 3D volumes of MRI metrics (grey matter, white matter, and cerebrospinal fluid) are decomposed to 2D slices according to neighbouring voxel positions and input to 2D CNN models pre-trained on ImageNet to extract feature maps from three views (axial, coronal, and sagittal). Global pooling is applied to remove redundant information based on sparsely distributed activation patterns from the feature maps. Channelwise and slice-wise convolution aggregate the contextual information in the third view dimension unprocessed in the 2D CNN network. Multi-view and multi-metric information are fused for final prediction. The proposed approach outperforms handcrafted feature-based machine learning, deep feature approach with a support vector machine SVM classifier and 3D CNN models trained from scratch with better cross-validation results on publicly available Northwestern University Schizophrenia Dataset and independent testing results on a private dataset.

In overall, this thesis illustrated multiple advanced analytic techniques for investigating brain alterations in patients with neuropsychiatric disorders. Statistical analysis examined group-level brain functional activity and connectivity changes and associations with behavioural changes. Machine learning approaches not only constructed conventional classifiers and naïve 3D CNN models for classification of schizophrenia patients and healthy controls but also proposed an efficient framework for applying pre-trained 2D CNN on 3D neuroimaging data. The proposed models and framework lay the foundation for objective imaging-based assays for individual-level classification in neuropsychiatric disorders.

Chapter 1 Introduction

1.1 Background

1.1.1 Introduction to Neuropsychiatric Disorders

Neuropsychiatry involves the application of neuroscientific principles to the study of disorders in cognition, emotion and behaviour associated with neural processes (Sachdev and Mohan, 2017). While neurology and psychiatry developed as different disciplines during the 20th century, there is an increasing need to deal with conditions and disorders from both perspectives (Arzy and Danziger, 2014). Neuropsychiatry is defined as a border discipline attempting to bridge the gulf between psychiatry and neurology (Miyoshi et al., 2010; Sachdev and Mohan, 2017).

The International Neuropsychiatric Association classified neuropsychiatric symptoms and syndromes as follows (Arciniegas et al., 2006): 1) major neuropsychiatric syndromes such as delirium, the dementias, and the major primary psychiatric disorders; 2) neurological conditions with cognition, emotional, behavioural features such as dementias, movement disorders, stroke, epilepsy, multiple sclerosis, traumatic brain injury; 3) comorbid neuropsychiatric and neurological conditions such as Down's syndrome and Alzheimer's disease, obsessive-compulsive disorder and Tourette's syndrome, Huntington's disease and alcohol abuse. In general, almost all organic cerebral diseases cause neuropsychiatric symptoms. Stroke and schizophrenia are the two focuses in this study.

Neuropsychiatric disorders have high prevalence and long years lived with disability (Table 1.1) (James et al., 2018; Reynolds et al., 2009). According to the World Health Organization, at least 20% of illness-related disability can be accounted by neuropsychiatric disorders (Murray et al., 1996). Specifically, some

neuropsychiatric disorders begin in early life. Around 40% medical burden for young people (15-44 years) in the United States and Canada can be contributed by early neuropsychiatric disorders (Guilbert, 2003). Mental disorders are a major source of not only morbidity but mortality (Insel, 2009). More than 90% of suicides in the United States may be associated with mental disorders (Goldsmith et al., 2002).

Table 1. 1 Prevalence of neuropsychiatric disorders in 2017 (James et al., 2018).

Disorder	Prevalence (thousands) 2017 counts	Incidence (thousands) 2017 counts	YLDs (thousands) 2017 counts
Stroke	104178.7	11931.1	18695.4
Alzheimer's disease and other dementias	44988.8	7300.6	6570.4
Parkinson's disease	8525.4	1025.9	1219.0
Epilepsy	27 288.3	2470.8	8561.9
Multiple sclerosis	1761.1	54.9	456.6
Motor neuron disease	237.1	57.3	50.4
Headache disorders	3072812.1	995374.9	54341.8
Migraine	1331364.6	112933.5	47245.4
Schizophrenia	19776.9	1130.5	12657.9
Depressive disorders	264455.6	258164.5	43099.9
Bipolar disorder Anxiety	45549.4	4525.2	9293.8
Anxiety disorders	284360.1	42340.0	27121.4
Eating disorders Anorexia	15801.7	9589.7	3351.9
Autism spectrum disorders	31179.7	670.7	4731.3

(YLDs=years lived with disability)

1.1.1.1 Stroke

Stroke typically refers to a neurological deficit caused by an accurate focal injury of the central nervous system. The Stroke Council of the American Heart Association/American Stroke Association updated the definition of stroke for the 21st century to an episode of neurological dysfunction caused by cerebral, spinal, or retinal

infarction attributed to ischemia, intracerebral hemorrhage and subarachnoid hemorrhage with or without detectable symptoms (Sacco et al., 2013). Ischemia is a deficiency of blood in a tissue that is caused by constriction or obstruction of local blood vessels and results in a reduced supply of oxygen to the tissue (Mak et al., 2014). Intracerebral hemorrhage refers to the results caused by bleeding into the brain substance from an arterial source (Kase et al., 2004). Subarachnoid hemorrhage refers to the results of bleeding into the subarachnoid space, the space between the pia mater covering the brain and the dura mater lining the skull (Fuller and Manford, 2010).

Ischemic strokes attribute for around 87% of all strokes (Virani et al., 2020). The majority of ischemic strokes origin from arterial. Occlusion of a feeding artery caused by a thromboembolic process lead to reduction in tissue perfusion and results in ischemic cascade. Ischemic cascade is a complex series of neurochemical processes involving cellular bioenergetics failure and causing neuron dysfunction. If blood flow is not restored timely, the tissue damage becomes irreversible (Liberato and Krakauer, 2007; Mansfield et al., 2018). According to an quantified estimation, around 2 million neurons die in one minute when an artery is occluded and the brain “ages” 3.6 years every hour (Saver, 2006). The degree of damage depends on the location, severity, and duration of the stroke.

Stroke is one of the leading causes of death and disability worldwide (Mansfield et al., 2018). American Heart Association reported around 795,000 people experience new or recurrent stroke onset in the United States every year (Virani et al., 2020). On average, every 40 seconds there is someone experiencing stroke and every 215 seconds, there is someone died of stroke in the United States (Virani et al., 2020). More people as stoke survivors suffer from long-term disability (Mansfield et al., 2018). The stroke sequalae not only cause motor impairment (Braun et al., 2017; Raghavan, 2015),

somatosensory dysfunction (Brown et al., 2018), dysfunction in language expression and comprehension (El Hachoui et al., 2017; Rohde et al., 2018; Spencer and Brown, 2018), cognitive decline (Rohde et al., 2019; Fanfan Zheng et al., 2019), but also result in psychiatric disorders (Ferro et al., 2016; Robinson and Jorge, 2016) and secondary neurodegeneration leading to recurrent stroke or dementia (Hachinski, 2018; Kalaria et al., 2016). As a chronic disorder, stroke causes great burdens to patients, their families and the society (Feigin et al., 2016).

Numerous methods have been proposed for stroke rehabilitation. Motor Imagery (MI) provides a practical, accessible way to modulate brain activity in the motor network post stroke by stimulating an action without actual physical movements (Dodakian et al., 2014; Sharma et al., 2006; H. Wang et al., 2019). EEG-based Brain Computer Interface (BCI) detects and uses a patient's neural signals as inputs to provide real-time feedback, effectively enabling users to modulate their brain activity (Bockbrader et al., 2018; Buch et al., 2008; Daly and Wolpaw, 2008; Ono et al., 2014). By combining robot-assisted MI and BCI, MI-BCI system enables stroke patients to move the impaired limb driven by a robotic arm via neural signals from the motor imagery of the arm and provides multisensory feedback to patients to enhance the motor learning and recovery (Ang et al., 2009; Ang and Guan, 2015; Buch et al., 2008; Teo and Chew, 2014). Numerous studies reported the clinical efficiency and feasibility of MI-BCI therapy in motor improvements (Ang et al., 2009; Ang and Guan, 2015; Foong et al., 2020; Pichiorri et al., 2015; Ramos-Murguialday et al., 2019; H. Wang et al., 2019). Transcranial direct current stimulation (tDCS) is another promising technique for stroke rehabilitation. TDCS is a non-invasive brain stimulation technique that uses constant, low direct current delivered via electrodes (anode and cathode) on the head to provide a reversible and focal way for neuroplasticity modulation (Nitsche and Paulus,

2001, 2000). TDCS has been shown to modulate activity in both the motor and visual cortices and more recently has been shown to directly influence the excitability of the spinal cord (Butler et al., 2013; Elsner et al., 2018; Zaghi et al., 2010). Furthermore, tDCS has been reported to have a long-term effect lasting beyond the time of stimulation which might indicate the ability to improve motor function through network reorganization and modulation of brain plasticity (Allman et al., 2016; Kashiwagi et al., 2018; A. Liu et al., 2018; Reidler et al., 2011). Although the mechanism of tDCS is not fully revealed yet, meta-analysis and review papers summarized the promising results of tDCS therapy in stroke with motor function improvements (Allman et al., 2016; Butler et al., 2013; Elsner et al., 2018; Hordacre et al., 2018; Lindenberg et al., 2010; Madhavan et al., 2011; Reidler et al., 2011). Given the benefits of MI-BCI and tDCS, it is meaningful to examine the effect of both approaches and whether combination of two approaches will further enhance the rehabilitation process from the neuroimaging perspective.

1.1.1.2 Schizophrenia

Schizophrenia is a complex psychiatric disorder that could originate from genetic, developmental, and environmental factors (Radaic and Martins-de-Souza, 2020). The key features are characterized into three classes: positive (delusions and hallucinations; lose contact with the reality), negative symptoms (reduction in spontaneous speech, and social withdrawal), and cognitive impairment (poorer performance on multiple cognition tests) (Owen et al., 2016). The first episode of psychosis could occur in early adulthood or adolescence. A prodromal phase often occur first, which is called at-risk mental state (Addington and Heinssen, 2012).

Schizophrenia is one of the top 25 causes of global disease burdens (Vos et al., 2015). Despite the relatively low prevalence (Table 1.1) (Saha et al., 2005), there are

profound effects to patients, their families and the society. More than half of the diagnosed individuals have long-term psychiatric disorders and around 20% have chronic symptoms and disability (Owen et al., 2016). 80%-90% patients with schizophrenia are unemployed (Kooyman et al., 2007; Marwaha and Johnson, 2004) and have reduced life expectancy by 10-20 years (Chesney et al., 2014). More importantly, the economic burdens to the society are tremendous. It is estimated that the annual cost of schizophrenia range from US\$94 million to US\$104 billion in the world (Chong et al., 2016). The substantial burden imposed by schizophrenia is related to the early onset of the disease and its incurable nature with persisting symptoms (Chong et al., 2016). The long-term psychiatric problems and disability are associated with presenteeism, unemployment, and early retirement for both patients and caregivers (Phanthunane et al., 2010).

Early and accurate diagnosis of schizophrenia is critical to facilitate treatment planning and improve the outcome of the illness. Yet there is no diagnostic tests or biomarkers (Owen et al., 2016). The clinical diagnosis of schizophrenia is typically based on interviews with examination of the mental states according to the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Del Barrio, 2016). Due to the complex and heterogeneous symptom presentations, the diagnosis could be challenged by sex, race, disease duration, medication and many other confounders (Fanous et al., 2012; Kennedy et al., 2014). Therefore, it is important to incorporate neuroimaging data and establish an objective approach for accurate diagnosis which determines appropriate subsequent treatment.

1.1.2 Introduction to MRI

Advanced neuroimaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) allow us to investigate the structural and functional changes

in the human brain in vivo. MRI has become a primary diagnostic imaging approach with its advantage of non-ironic and high resolution and has been widely utilized in clinical and research applications since its introduction into the field in early 1980s (Yousaf et al., 2018).

The basic principle of MRI is the nuclear magnetic resonance phenomenon, when certain atomic nuclei are placed in a magnetic field and stimulated by a weak oscillating radio waves, they will re-emit the absorbed energy in the form of radio signals. MRI scanner generates a uniform strong magnetic field and causes the rich hydrogen nuclei in human body to align to the field, creating a magnetic moment. A radiofrequency pulse is then applied to deviate the magnetic moment from the field. When the radiofrequency is removed, hydrogen nuclei realign to the direction of the magnetic field (i.e. relaxation) and generate signals that can be detected by a receiver coil (Pykett et al., 1982; Van Geuns et al., 1999).

MRI signals contain wealthy information with regard to the biochemistry and structural properties of the tissue. Therefore, MRI could provide high-resolution images of white matter tracts, lesions and arteries based on the analytic techniques. Furthermore, multimodal MRI techniques involving multiple MRI types such as T1-weighted MRI, functional MRI, diffusion MRI, and continuous arterial spin labeling allow researchers to understand the brain from different perspectives. In this study, structural MRI, functional MRI, and diffusion MRI were utilized and typical analysis approaches for such modalities were discussed.

1.1.2.1 Structural MRI

Different tissues with different water molecules moving patterns have different relaxation time. Biological fluids such as blood and cerebrospinal fluids (CSF) have no

restrictions on the movement of their water molecules and thus have long longitudinal relaxation time (T1) and transverse relaxation time (T2). On the other hand, solid tissues such as grey matter and white matter have shorter relaxation times as macromolecules stopping water molecules from unrestricted movements. Difference in relaxation rates produce signal contrast and therefore leading to different types of structural MRI. For example, CSF with longer T2 than grey matter and white matter appear brighter on a T2-weighted image. On contrast, ventricles on a T1-weighted image appear darker than grey matter and white matter. Various types of structural MRI provide high-resolution images for different tissues in the brain.

Voxel-based morphometry (VBM) is one of the most commonly used technique for analysis of structural MRI. Statistical parametric mapping (SPM; <http://www.fil.ion.ucl.ac.uk/spm>) software provide a VBM pipeline for segmenting the brain images into different compartments including grey matter, white matter and cerebrospinal fluid probability maps by a Bayesian image segmentation algorithm (Kurth et al., 2015). The probability maps are then smoothed and registered to the standard space with linear and nonlinear registration (Jesper L R Andersson et al., 2007). VBM has been used to investigate many disorders such as schizophrenia, Alzheimer's disease, multiple system atrophy and so on. VBM can be used for group-level statistical analysis which compares the difference in patients and healthy controls as well as for machine learning algorithms which use VBM as extracted features for classification (Arbabshirani et al., 2017; Winterburn et al., 2019).

1.1.2.2 Functional MRI

Functional MRI (fMRI) measures the blood oxygenation level-dependent (BOLD) signals which reflects the functional information based on flow changes or blood oxygenation. Echo planar imaging sequence is used to measure the BOLD sensitivity

upon brain activation (Logothetis, 2008; Ogawa et al., 1990).

Using fMRI, there are a few techniques to characterize the spontaneous brain activity. The most widely applied one is to derive the functional connectivity which exploits the relationships between different brain regions. Seed-based analysis, independent component analysis and graph theory are proposed to derive functional connectivity (Biswal et al., 1995; Sporns, 2003; van de Ven et al., 2004). Another popular technique to analyse the brain activity is to measure specific regional activity and connectivity. Amplitude of low-frequency fluctuations and fractional amplitude of low-frequency fluctuations characterize the brain local activity while regional homogeneity characterizes the brain local connectivity (Zang et al., 2004, 2007; Zou et al., 2008).

1.1.2.3 Diffusion MRI

Diffusion tensor imaging (DTI) measures the water diffusion rate within the tissues. Diffusion speed and direction of water molecules vary with tissue types, architectures and presence of barriers. DTI therefore provides information regarding quantitative anisotropy and orientation (Mori and Zhang, 2006).

DTI analysis are in general based on the voxel-based properties of diffusion. Fractional anisotropy indicates the microstructural integrity, mean diffusivity indicates the membrane density, axial diffusivity measures the diffusion rate along the principal axis, and radial diffusivity measures the diffusion rate in the transverse direction (Feldman et al., 2010).

1.1.3 Statistical Analysis and Machine Learning

Statistical analysis is widely utilized in neuropsychiatric studies to investigate the group-level differences among patients and healthy controls, intervention effects at

different time points or under different circumstances. Machine learning approaches, on the other hand, investigate neuropsychiatric disorders from the individual-level to provide individual diagnosis or predictions. Conventional machine learning approaches involving handcrafted features were used for classification of many neuropsychiatric disorders such as Alzheimer's disease, schizophrenia, brain tumour, lung nodule and so on. Deep learning approaches with automatic feature learning is a new trend for 2D and 3D image processing and even achieving superior performance than handcrafted feature-based machine learning.

1.1.3.1 Statistical Analysis

Statistical tests are frequently used in medical and biological studies. Hypothesis tests provide a framework to weigh different hypothesis on an objective basis. A statistical hypothesis is a statement on a probability distribution or its parameters, or a statement about the relationship between probability distributions and their parameters. Null hypothesis, denoted as H_0 is always stated in the null form, suggesting no difference or no relationship between the probability distributions and their parameters. Statistical tests examine sets of sample data based on the null hypothesis H_0 and makes a decision whether to reject H_0 . The null hypothesis is rejected if and only if there are strong and sufficient evidence to support an alternative hypothesis which contradicts the null hypothesis H_0 .

The one sample T test determines whether the sample mean is statistically different from a known or hypothesized population mean, which is commonly used when comparing statistical difference between the sample mean of the test variable and chance or statistical difference between a change score and zero. Two samples from the same object or individuals at different time points or under different conditions can be compared using the paired samples T test. If two samples are from two independent

groups, the independent samples T test can determine whether the associated population means are statistically different. Analysis of variance (ANOVA) compares two or more independent groups to determine whether their means are significantly different. Besides above parametric tests, the Chi-Square test compares whether categorical variables are related or independent.

Correlation and regression analysis investigate the relationships among a set of variables. The most commonly used correlation relationship is Pearson's correlation coefficient which is derived as the quality of least squares fitting to the original data. By taking the ratio of the covariance of two variables and the product of their standard deviation, I obtain a normalized measurement of the covariance in range -1 to 1. A positive or negative association between two sets of variables can be determined depending on the sign of derived Pearson's correlation coefficient.

1.1.3.2 Handcrafted feature-based machine learning

Machine learning approaches have begun to demonstrate its potential in complementing the clinical diagnosis of psychiatric disorders using neuroimaging data (Arbabshirani et al., 2017; Rashid and Calhoun, 2020). Previous work on computer-aided classification of neuropsychiatric disorders mainly focused on handcrafted feature-based machine learning approach, which requires feature extraction and reduction before classification. Cortical thickness and voxel-based morphometry via structural MRI and white matter microstructures via diffusion MRI are common features for many disorders such as dementia and schizophrenia. Traditional classifiers like support vector machine (SVM), random forest, and logistic regression are the most widely used methods. However, the subtle, mixed, and widespread brain anatomical changes in neuropsychiatric disorders limit the performance of handcrafted machine learning approaches. Pre-selected features might not be efficient and generalizable across

different patient cohorts with differing duration of illness, causing the accuracy to vary across datasets, features, and hyperparameter settings.

1.1.3.3 Deep Convolutional Neural Networks

Deep learning has achieved remarkable performance in natural image classification tasks and among different deep learning approaches, convolutional neural networks (CNN) showed superior performance on image processing tasks for their shared-weights architecture and translation invariance characteristics. As a data-driven deep learning method, CNN is capable of automatic feature learning which mitigates the subjectivity and variability in pre-selecting relevant features. This is especially important for psychiatric disorders like schizophrenia which has subtle, complex, and widely distributed brain alterations. Deep model architecture with nonlinear layers also allows efficient mapping of complicated data patterns.

There are two ways to train new CNN models from scratch with 3D MRI images: to train 2D models with 2D slices extracted from MRI and to train 3D models with 3D inputs. 3D CNN models employ 3D convolutional kernels to fully utilize the context information of 3D images. However, development of 3D CNN was limited to simple architecture and small image size due to the high computational cost. Shallow 3D CNN models were proposed for classification of lung nodule and pulmonary (Dou et al. 2017; Liu and Kang 2017). Small patches were utilized for quantification of perivascular spaces and classification of Alzheimer's disease (Asl et al. 2018; Dubost et al. 2019).

Besides training CNN models from scratch, it is critical to utilize successful models pre-trained on other large datasets. Two strategies were applied on medical image classification: fine-tune method and off-the-shelf deep feature method (Razavian et al. 2014; Yosinski et al. 2014). Fine-tune method initialize the model using weights

pre-trained on other datasets and then fine-tune the weights using the data at hand, which is ideal for datasets sharing similar data formats and features with the datasets used for pre-training. Fine-tune method has been successfully applied on classification of brain tumor, breast cancer and skin cancer (Ahmed et al. 2017; Y. Yang et al. 2018; Yu et al. 2019). Off-the-shelf deep feature method extracts features from pre-trained CNN models and then uses traditional classifiers such as SVM and LR to classify obtained features. Deep feature method has been applied to classification of retinal diseases and breast cancer.

1.2 Aims and Motivations

As neuropsychiatric disorders are the leading causes of disability and causing great burdens to patients, their families, and the society, it is important to investigate the brain changes using multimodal neuroimaging data with advanced analytic approaches. In this thesis, functional MRI was used to examine the brain alteration post stroke and rehabilitation effect of MI-BCI and tDCS (chapter 2), structural MRI and diffusion MRI were used for classification of schizophrenia patients and healthy controls with 3D convolutional neural networks trained from scratch (chapter 3) and a 2+1D framework exploiting powerful pre-trained 2D convolutional neural networks (chapter 4).

1.2.1 Differential Neuroimaging Re-normalization Pattern in MI-BCI Stroke Rehabilitation with and without tDCS

Both MI-BCI and tDCS have been reported beneficial for motor function recovery in stroke rehabilitation, but the mechanism related to brain changes from neuroimaging perspective have not been illustrated and whether the combination of MI-BCI and tDCS could further enhance the effectiveness of stroke rehabilitation therapy remains unknown. This study aimed to examine 1) the brain functional activity and connectivity changes in stroke patients at baseline; 2) the brain functional activity and connectivity

changes pre- and post-intervention in the MI-BCI only group and MI-BCI combined with tDCS group; 3) association between the alterations in the brain functional activity and connectivity post-intervention and motor function recovery measured by Fugl-Meyer Assessment scores.

1.2.2 Structural and diffusion MRI based schizophrenia classification

3D naïve Convolutional Neural Networks

Given the subtle, complex, and widely distributed brain atrophy patterns in schizophrenia, the ability of automatic feature learning across levels makes deep learning algorithms such as CNN a powerful tool for schizophrenia classification. Moreover, multimodal brain images provide a complementary understanding of the human brain abnormalities in illness. Yet, limited studies have utilized CNN for classifying schizophrenia and controls using neuroimaging data and most of them are based on a single neuroimaging modality. Importantly, little has been done to evaluate whether CNN could localize the critical brain regions for classification in schizophrenia. Here, I aimed to develop deep feature approach based on pre-trained 2D CNN and naïve 3D CNN models trained from scratch for schizophrenia classification by integrating 3D structural and diffusion MRI. I aimed to develop Naïve 3D CNN models with different architectures and depths and evaluate the models on two independent datasets for accuracy and generalizability. Moreover, this study aimed to interpret the 3D CNN models by visualizing the critical regions for classification and thus illustrate the pathology of schizophrenia from the difference between patients and healthy controls for classification.

1.2.3 Decomposing 3D Neuroimaging into 2+1D Processing for Classification of Schizophrenia Patients and Controls

Deep learning has been successfully applied to the classification of both natural images and medical images. However, there remains a gap for the classification of 3D neuroimaging data, especially for diseases without visible alteration in specific slices such as schizophrenia and depression. In this study, I aimed to process the 3D data by a 2+1D framework so that I can exploit the powerful deep 2D networks pre-trained on huge ImageNet dataset for 3D neuroimaging classification.

1.3 Research Contribution

Advanced neuroimaging techniques are essential for understanding the brain changes in neuropsychiatric disorders. This study utilized different approaches on multimodal neuroimaging data to investigate the brain alteration and developed innovative approaches on applying 2D networks to 3D neuroimaging data. The main contributions are stated as follows:

- This thesis utilized statistical analysis to investigate the brain activity and connectivity alterations in stroke patients with motor dysfunction before and after MI-BCI and MI-BCI combined with tDCS rehabilitation therapy. Reorganization of brain local activity and connectivity were identified in MI-BCI group and divergent association between global connectivity and clinical outcomes were identified in MI-BCI group and MI-BCI combined with tDCS group. The results validated the efficacy of both MI-BCI approach and MI-BCI combined with tDCS approaches while illustrating possible differential mechanisms between the two approaches. This study is published as Hu, M., Cheng, H. J., Ji, F., Chong, J. S. X., Lu, Z., Huang, W., ... & Zhou, J. H. (2021).

Brain functional changes in stroke following rehabilitation using brain-computer interface-assisted motor imagery with and without tDCS: a pilot study. *Frontiers in human neuroscience*.

- This thesis developed multimodal 3D CNN models with different architectures and utilized deep feature approach based on 2D pre-trained CNN for classifying patients with schizophrenia and healthy controls using 3D brain MR images. It demonstrated the superiority of using 3D CNN models and multimodal deep learning features extracted from sMRI and dMRI data over approaches using handcrafted feature-based method and single neuroimaging modality. Based on the learned 3D CNN models, the crucial regions for classification which consisted of grey matter volume in insula, orbital prefrontal cortex, striatum, thalamus, FA in cortico-subcortical fiber tracts, and enlarged ventricles were identified, which were in agreement with previous literature and supported the salience network/striatum dysfunction hypothesis in schizophrenia. This thesis highlighted the potential of CNN for automatic and efficient feature extraction from 3D brain structural imaging data and multimodal imaging information integration, providing an interpretable framework for objective imaging-based assays for individual-level classification in psychiatric disorders. This study is published as Hu, M., Qian, X., Liu, S., Koh, A. J., Sim, K., Jiang, X., ... & Zhou, J. H. (2021). Structural and diffusion MRI based schizophrenia classification using 2D pretrained and 3D naive Convolutional Neural Networks. *Schizophrenia research*.
- This thesis proposed an efficient framework for 3D neuroimaging classification with pre-trained 2D networks to address the classification problem of neuropsychiatric disorders which have no representative slice and limited

number of training samples. The framework consists of image decomposition, feature extraction, feature maxpooling, global pooling in slice and channel dimension, channelwise convolution and slicewise convolution. With promising results obtained, this study highlights the possibility of utilizing pre-trained deep 2D CNN for 3D neuroimaging classification and lays the foundation for computer-aid diagnosis of psychiatric disorders utilizing deep learning approaches. This study is submitted as Hu, M., Jiang, X., Zhou, J.H., Sim, K., Guan, C. Decomposition of 3D Neural Image to 2+1D for Feature Extraction for Schizophrenia Detection. IEEE Transactions on Biomedical Engineering.

1.4 Thesis Outline

There are five chapters in this thesis. Chapter 1 introduces neuropsychiatric disorder, different modalities of MRI, statistical analysis approaches and machine learning. Chapter 2 presents the statistical analysis findings on functional MRI of stroke and stroke rehabilitation. Chapter 3 demonstrates the multimodal 3D CNN models developed for classifying patients with schizophrenia and healthy controls using 3D brain MR images. Chapter 4 presents a 2+1D framework for 3D neuroimaging classification with pre-trained 2D networks for neuropsychiatric disorders which have no visible alterations on specific slices. Chapter 5 summaries the findings of this thesis and identifies the future work.

Chapter 2 Brain Functional Changes in Stroke following rehabilitation using Brain-computer interface-assisted motor imagery with and without tDCS

2.1 Introduction

Robot-assisted motor imagery (MI) and brain-computer interface (BCI) system is an advanced technique for improving motor function recovery in post-stroke rehabilitation. Motor imagery allows the imagination of movements without physical execution, and electroencephalography-based brain-computer interfaces (EEG-BCIs) enables interaction with the environment using brain signals (Bockbrader et al., 2018; Dodakian et al., 2014). By combining robot-assisted MI and BCI, the brain-computer interface-assisted motor imagery (MI-BCI) system enables stroke patients to move the impaired limb driven by a robotic arm via neural signals from the motor imagery of the arm and provides multisensory feedback to patients to enhance motor learning and recovery (Ang et al., 2009; Ang and Guan, 2015; Foong et al., 2020; Wang et al., 2019)

Transcranial direct current stimulation (tDCS) is another promising technique for stroke rehabilitation. tDCS is a noninvasive brain stimulation technique that uses constant, low direct current delivered via electrodes (anode and cathode) on the head to provide a reversible and focal way for neuroplasticity modulation (Nitsche and Paulus, 2001, 2000). tDCS has been shown to modulate activity in both the motor and visual cortices and more recently has been shown to directly influence the excitability of the spinal cord (Butler et al., 2013; Elsner et al., 2018; Zaghi et al., 2010). Furthermore, tDCS has been reported to have a long-term effect lasting beyond the time of stimulation which might indicate the ability to improve motor function through network

reorganization and modulation of brain plasticity (Allman et al., 2016; Kashiwagi et al., 2018; A. Liu et al., 2018; Reidler et al., 2011). Although the mechanism of tDCS has not been fully revealed yet, converging evidence demonstrated the efficacy of tDCS for motor function improvements in stroke (Allman et al., 2016; Butler et al., 2013; Elsner et al., 2018; Hordacre et al., 2018; Lindenberg et al., 2010). Given the benefits in motor function recovery from both MI-BCI and tDCS, it is unclear whether the combination of MI-BCI and tDCS would further enhance functional motor recovery in post-stroke rehabilitation. The underlying neural mechanisms of combined MI-BCI and tDCS are also largely unknown.

Resting-state functional magnetic resonance imaging (rs-fMRI) provides an indirect measure of neuronal activity and connectivity based on regional blood-oxygen-level-dependent (BOLD) signal fluctuations without any imposed task (Biswal et al., 1995). Various analytic methods have been proposed to derive complementary measures of brain functional dynamics from rsfMRI data (Lv et al., 2018). Amplitude of Low-Frequency Fluctuation (ALFF) measures the total power of the BOLD signal within the low-frequency range between 0.01 and 0.1 Hz, which represents local brain activity (Zang et al., 2007). Regional Homogeneity (ReHo) is a voxel-based measure of the similarity between the time-series of a given voxel and its nearest neighbors, which represents local connectivity as calculated by the Kendall coefficient of concordance of the BOLD time-series (Zang et al., 2004). Seed-based functional connectivity (FC) approach measures the temporal correlations between the activity in a seed region and BOLD signals across the brain (Biswal et al., 1995). Canonical functional networks such as the default mode network (DMN) and the executive control network (ECN) have been consistently derived from FC mapping in rs-fMRI (Cheng et al., 2021; Chong et al., 2019, 2017a; Ng et al., 2016). These measurements provide

important insights into the brain functional dynamics, disease mechanisms, and brain-behavior associations (Chen et al., 2019; Chong et al., 2017b; Puig et al., 2018; Wang et al., 2016; Zhang et al., 2020; Zhao et al., 2018). The combination of different measurements incorporates both regional and global information and thus complements each other to build an efficient model for brain analysis.

Nevertheless, little work has been done to examine the brain functional changes in stroke after MI-BCI and tDCS-based intervention. Most of the previous work focused on cross-sectional brain ALFF/ReHo/FC changes in stroke patients in comparison with healthy controls. In terms of regional activity, some studies reported lower ALFF in the motor cortex and lower ALFF/ReHo in the default mode network (DMN) in stroke patients compared to healthy controls (La et al., 2016; Tsai et al., 2014; Zhu et al., 2015) while others reported no differences or contradictory results in the DMN (Liu et al., 2015). On the other hand, disrupted FC in the motor cortex and DMN were widely reported in stroke patients with motor function impairment and cognitive impairment (De Bruyn et al., 2018; Ding et al., 2014; Golestani et al., 2013; Lee et al., 2019; Park et al., 2011, 2014; Puig et al., 2018; Tuladhar et al., 2013). Among the limited work on brain functional changes post-intervention in stroke, emerging evidence demonstrated enhancement of FC in the motor and sensory-related networks after motor imagery training (Sun et al., 2013; Wang et al., 2018). To my knowledge, no study has directly compared the brain functional changes between stroke rehabilitation using MI-BCI and tDCS and how these brain measures relate to clinical outcomes such as motor recovery.

In this study, I examined the alterations in brain functional activity and connectivity in chronic subcortical stroke patients using ALFF, ReHo, and FC. The changes in the neural function of stroke patients pre- and post-intervention were investigated in the MI-BCI only group and MI-BCI combined with tDCS group

separately. I hypothesized that 1) lowered ALFF/ReHo and disrupted FC in the motor cortex and DMN would be observed in stroke patients compared to healthy controls at baseline; 2) stroke patients would have higher ALFF/ReHo/FC in the motor cortex and DMN post-intervention, the degree of which would differ between the MI-BCI and the MI-BCI+tDCS groups. Lastly, I investigated whether these alterations in ALFF/ReHo/FC post-intervention would correlate with motor function recovery measured by Fugl-Meyer Assessment (FMA) scores.

2.2 Methodology

2.2.1 Participants

Forty-two stroke patients aged from 21-70 years with moderate to severe motor impairments and eleven age-matched healthy controls were recruited in this study. The inclusion criteria for stroke patients were 1) first-ever subcortical stroke > 9 months before the study enrolment; and 2) unilateral moderate to severe upper extremity motor impairment measured by the upper extremity component of the FMA (score range 11 – 45). The exclusion criteria for stroke patients were 1) epilepsy, neglect, cognitive impairment, and other neurological or psychiatric diseases; 2) severe arm pain; 3) severe spasticity measured by the Modified Ashworth Scale in the shoulder or elbow (score >2); 4) contraindications to tDCS; 5) weak grip strength measured by a dynamometer (weight < 10 kg); and 6) participation in other interventions or trials that target post-stroke motor recovery. Twenty-three stroke patients were excluded because they either declined to participate in the study or failed to meet the inclusion or BCI performance criteria. Detailed demographics of the remaining nineteen patients and eleven healthy controls who completed the training and scans were provided in Table 2.1. This study was conducted in accordance with the Code of Ethics of the World Medical Association and approved by the National Healthcare Group Domain-Specific

Review Board. It was also registered on ClinicalTrials.gov (Clinical Trial Registration Unique Identifier: NCT01897025, date of registration: July 8, 2013; <https://clinicaltrials.gov/ct2/show/NCT01897025>). Written inform consent was obtained from all participants.

Table 2. 1 Subject demographics.

	HC (N=11)	Stroke Patients		
		Total (N=19)	MI-BCI +tDCS (N=10)	MI-BCI (N=8^a)
Age (Years)	56.7±4.5	54.1±10.6	52.1±11.7	54.6±8.5
Gender (M/F)	6/5	14/5	6/4	8/0
Handedness (R/L)	11/0	17/2	9/1	7/1
Affected Hemisphere (R/L)	-	11/8	5/5	5/3
Stroke Type (I/H)	-	13/6	6/4	6/2
Stroke Location (C/S)	-	1/18	1/9	0/8
Stroke Onset to Therapy (Days)	-	1037±598	1052±721	1076±466
BCI Screening Performance (%)	-	76.5±10.4	79.1±9.4	73.3±10.3

Note:

^a One subject was involved in analysis of baseline comparisons but excluded for intervention effects as the second scan did not pass quality control.

No significant difference was found between any groups for all variables listed here.

Abbreviations:

M: Male F: Female R: Right L: Left I: Infarction H: Hemorrhage C: Cortical S: Subcortical HC: Healthy Controls

2.2.2 MI-BCI and tDCS study design

Nineteen stroke patients were randomized into the MI-BCI+tDCS group ($n = 10$) and MI-BCI group ($n = 9$) with matching pre-training FMA scores. The MI-BCI+tDCS group received 20-min real tDCS, in which direct current was applied using a saline-soaked pair of surface sponge electrodes at an intensity of 1mA with the anode placed over the M1 motor cortex of the ipsilesional hemisphere and the cathode placed over the contralesional M1 while the MI-BCI group received 20-min sham tDCS, in which current ramped up and down to give subjects the sensation of the stimulation. Both groups completed 10 sessions of MI-BCI training within two weeks. Each MI-BCI training was 40 minutes and consisted of 160 trials. In each trial, subjects were prepared with a visual cue and instructed to perform motor imagery by an instruction cue. The EEG segment of 0.5 to 4.5 seconds from the instruction cue was then extracted to classify the EEG segment to perform online detection of MI or the idle condition using the Filter Bank Common Spatial Pattern (FBCSP) algorithm (Ang et al., 2012). The MIT-Manus robot provided movement feedback if the motor imagery was detected. More details of the study design can be found in Ang et al., 2015.

Motor function was assessed by the upper extremity component of the FMA, which is a stroke-specific, performance-based impairment index to assess motor functioning, balance, sensation and joint functioning in patients with post-stroke hemiplegia (Fugl-Meyer et al., 1975). Motor function assessments were conducted 1) one week before training, 2) immediately after training, and 3) four weeks after training.

2.2.3 Image Acquisition

All stroke patients completed three MRI scans: at screening, one week before training, and four weeks after training. Healthy controls underwent two MRI scans: at screening and three weeks after screening. The MRI scans conducted one week before training

for patients and three weeks after screening for healthy controls were considered as baseline. For patients, the MRI scans conducted one week before training and four weeks after training were regarded as pre- and post-intervention respectively.

MRI data were collected using a 3T scanner (TIM Trio, Siemens, Germany) with a 32-channel head array coil. The scan protocol included a T1-weighted magnetization prepared rapid gradient-echo (MPRAGE) sequence (inversion time = 900 ms, repetition time = 1900 ms, echo time = 2.5 ms, flip angle = 9° , field of view = $256 \times 256 \text{ mm}^2$, 176 sagittal slices, matrix size = 256×256 , and voxel size = 1 mm^3 isotropic), and a resting state T2*-weighted echo planar imaging (repetition time = 1750 ms, echo time = 30 ms, flip angle = 74° , field of view = $220 \times 220 \text{ mm}^2$, voxel size = 3.4 mm^3 isotropic, slice thickness = 3.4 mm, 33 axial slices). During the 7-min rs-fMRI, participants were instructed to remain relaxed and awake with their eyes closed and not engage in any specific activity

2.2.4 Image Analyses

2.2.4.1 fMRI preprocessing

Preprocessing of fMRI images was performed using FMRIB software library (FSL) and analysis of functional neuroimaging (AFNI) following the standard protocol (Chong et al., 2017a; Cox, 1996; Ng et al., 2016; Wang et al., 2016). The preprocessing steps consist of: (i) removal of first six volumes for magnetic field stabilization; (ii) slice-time correction; (iii) motion correction, (iv) despiking; (v) spatial smoothing (6-mm FWHM Gaussian kernel); (vi) grand mean scaling; (vii) band-pass temporal filtering (0.009 – 0.1 Hz); (viii) detrending (removal of first and second order); (ix) use of Boundary-Based Registration (BBR) for co-registration of T1 image (Greve & Fischl, 2009) and nonlinear registration tool (FNIRT) for subsequent registration to the Montreal Neurological Institute (MNI) 152 space. Specifically, the left hemisphere was

defined as the ipsilesional hemisphere and all images with lesions at the right hemisphere were flipped to investigate the effect of lesion location. Additionally, regression of nuisance signals (white matter, cerebrospinal fluid (CSF), whole-brain global signals, and six motion parameters) and motion scrubbing were performed for analysis of FC to avoid spurious connectivity (Power et al., 2014, 2012).

Quality of co-registration and normalization were visually inspected. One post-intervention image with movement more than 4mm was discarded. Thus after quality control, data of 19 stroke patients and 11 healthy control remained at baseline. Data of 10 subjects in the MI-BCI+tDCS group and 8 subjects in the MI-BCI group remained for pre- and post-intervention analysis.

2.2.4.2 Derivation of voxelwise amplitude of low frequency fluctuation maps

The ALFF was calculated using a toolbox for Data Processing & Analysis for Brain Imaging (DPABI) (Yan et al., 2016). For each voxel, a discrete Fourier transform was performed on the resting-state time series. The ALFF was computed by measuring the average square root of the total power spectrum between 0.01 and 0.10 Hz on a voxel-by-voxel basis.

2.2.4.3 Derivation of voxelwise regional homogeneity maps

The ReHo maps were also produced using DPABI toolbox. ReHo was calculated in a voxel-wise manner using Kendall's concordance coefficient (KCC) across the time series of a centered cubic cluster of 27 voxels. A large ReHo value for a given voxel indicates a high local synchronization of rs-fMRI signal among neighboring voxels and vice versa.

2.2.4.4 Derivation of default mode and somatomotor network FC

FC analysis was performed for two networks, default mode network and somatomotor network, which were previously reported to show changes in ALFF and ReHo analysis in my study. DMN and SMN were defined using Region of Interest (ROI) from a FC-based 114-node parcellation (Buckner et al., 2011). 24 ROIs were included for DMN and 10 ROIs were included for SMN (ROI names and peak coordinates in supplementary Table 2.1). BOLD time series of each ROI were extracted for every subject and Pearson's correlation between the mean time series of every pair of ROIs were computed. An FC matrix was produced for every subject by Fisher's r-to-z transformation of correlation coefficients. FC within the DMN and SMN, as well as between the DMN and SMN were consequently derived by averaging the corresponding cells in the matrix.

2.2.5 Statistical Analysis

Baseline differences in ALFF, ReHo, and FC between stroke patients and healthy controls were examined using two-sample t-tests. Voxelwise analyses (i.e., ReHo and ALFF) were thresholded using a height threshold of $p < 0.01$ (uncorrected) and extent threshold of $p < 0.05$ (familywise-error (FWE) corrected).

To examine the effects of intervention as well as interaction effects between intervention and group on FMA scores, ALFF and ReHo maps, I conducted mixed-effect Analyses of Variance (ANOVA) with intervention as within-subjects factor and group as between-subject factor. Post-hoc tests were subsequently performed to examine intervention effects in each group separately. Voxelwise analyses (i.e., ReHo and ALFF) were thresholded using a height threshold of $p < 0.01$ (uncorrected) and extent threshold of $p < 0.05$ (FI corrected).

Finally, associations between functional activity/connectivity and clinical outcomes (motor function improvement measured by FMA scores) were examined using Pearson's correlation. Eight-mm spheres created in MARSBAR (Brett et al., 2002) with peak coordinates extracted from the above interaction effect maps were selected as ROIs for ALFF and ReHo. ALFF/ReHo changes in the ROIs were correlated with changes in FMA. FC changes within DMN/SMN and between DMN and SMN were associated with changes in FMA.

2.3 Results

2.3.1 Improved Motor Function

There was no difference between the MI-BCI group and MI-BCI+tDCS group at baseline in terms of age, post-stroke time, or FMA scores (Table 2.1). A 3 (intervention: baseline, immediately after training, 4 weeks after training) x 2 (group: MI-BCI, MI-BCI+tDCS) mixed effects ANOVA performed on FMA scores indicated significant intervention effect ($p=0.002$) but no interaction effect between intervention and group ($p=0.450$), suggesting that both groups gained significant motor function improvement post-intervention with no group difference observed either immediately or 4 weeks after training. Post-hoc tests further showed that significant FMA gains compared to baseline were only found at 4 weeks after training (MI-BCI group: 5.8 ± 6.0 , $p=0.030$; MI-BCI+tDCS group: 5.0 ± 4.4 , $p=0.006$) but not immediately post-training (MI-BCI group: 2.9 ± 4.2 , $p=0.096$; MI-BCI+tDCS group: 0.9 ± 3.0 , $p=0.362$) (Figure 2.1). Furthermore, the MI-BCI group showed greater motor function improvement than the MI-BCI+tDCS group at week 2, although this was not statistically significant (MI-BCI group: 2.9 ± 4.2 vs. MI-BCI+tDCS group: 0.9 ± 3.0 , $p=0.130$).

Figure 2. 1 Motor recovery after MI-BCI intervention with and without tDCS.

FMA scores at Baseline and post intervention. Significant FMA gains comparing to baseline were only found at 4 weeks after training for both MI-BCI and MI-BCI+tDCS group (MI-BCI group: 5.8 ± 6.0 , $p=0.030$; MI-BCI+tDCS group: 5.0 ± 4.4 , $p=0.006$) but not immediately post training (MI-BCI group: 2.9 ± 4.2 , $p=0.096$; MI-BCI+tDCS group: 0.9 ± 3.0 , $p=0.362$). No significant intergroup differences were observed at any time point during the study. $**p<0.01$; $*p<0.05$. Error bars indicate $\pm$ (1SD)

2.3.2 Abnormal ALFF/ReHo in the SMN and DMN in stroke patients at baseline

Cross-sectional comparisons conducted at baseline indicated abnormal ALFF and ReHo patterns in stroke patients compared to healthy controls. Stroke patients showed lower ALFF in the ipsilesional precentral gyrus and postcentral gyrus and higher ALFF in the precuneus, posterior cingulate gyrus, angular gyrus, middle frontal gyrus, and contralesional insula (Figure 2.2A). Thus, these findings suggest that stroke patients had lower ALFF in ipsilesional SMN and higher ALFF in the DMN and contralesional SAN compared to healthy controls.

Stroke patients had higher ReHo in the precuneus and posterior cingulate gyrus and lower ReHo in the ipsilesional superior temporal gyrus and insula (Figure 2.2B). Collectively, the results indicate that stroke patients had higher ReHo in the DMN and lower ReHo in the ipsilesional SAN compared to healthy controls.

Figure 2. 2 Functional disruptions in stroke patients.

A) ALFF comparison between HC and patients at baseline. At baseline, stroke patients showed reduced ALFF at ipsilesional SMN and increased ALFF at DMN and salience network comparing to healthy controls. B.) ReHo comparison between HC and patients at baseline. At baseline, stroke patients showed increased ReHo at DMN and decreased ReHo at insula comparing to healthy controls. Colour bars indicate t-scores.

Abbreviations: L: Ipsilesional Hemisphere, DMN: Default Mode Network, SMN: Somatomotor Network, HC: Healthy Control, Precg: Precentral Gyrus, SMA: Supplementary Motor Area, IPL: Inferior Parietal, PCUN: Precuneus, PCG: Posterior Cingulate Gyrus, MFG: Middle Frontal Gyrus, ANG: Angular Gyrus, ORBsup: Superior Frontal Gyrus, Orbital Part, INS: Insula, MTG: Middle Temporal Gyrus.

2.3.3 Differential changes in ALFF/ReHo in the MI-BCI and MI-BCI+tDCS groups post-intervention

Significant interaction effects between intervention (pre-training, post-training) and group (MI-BCI group, MI-BCI+tDCS group) were found in ALFF and ReHo based on mixed-effect ANOVA, suggesting differential brain functional activity and connectivity changes in the MI-BCI group and MI-BCI+tDCS group. Specifically, differential ALFF patterns post-intervention were found in the contralesional regions within the DMN and SMN, including supplementary motor area, contralesional precentral gyrus, middle frontal gyrus, precuneus, and angular gyrus (Figure 2.3A). On the other hand, differential ReHo patterns were found in the precuneus and posterior cingulate gyrus (Figure 2.4A), suggesting that the MI-BCI group and MI-BCI+tDCS group exhibited differential ReHo patterns in the DMN post-intervention.

Post-hoc analyses revealed that the MI-BCI group showed increased ALFF in the contralesional supplementary motor area and precentral gyrus post-intervention and decreased ALFF in the precuneus, inferior parietal lobule, and middle occipital gyrus (Figure 2.3B). The regions that showed changes post-intervention were very similar to regions that showed abnormal ALFF comparing to healthy controls at baseline (Figure 2.2A). Increased ALFF at baseline in the DMN was reduced post-intervention. Decreased ALFF in the ipsilesional SMN at baseline were not increased after training but increased ALFF was observed in the contralesional SMN. Similarly, decreased ReHo at bilateral precuneus and posterior cingulate gyrus was observed in the MI-BCI group post-intervention (Figure 2.4B). The altered regions were identical to the regions that showed abnormal ReHo changes in stroke patients at baseline comparing to healthy controls (Figure 2.2B). Higher ReHo in the DMN at baseline was reduced post-intervention.

In contrast, the MI-BCI with tDCS group had no significant changes in ALFF/ReHo post-intervention.

Figure 2.3 ALFF changes in contralesional SMN and posterior DMN in stroke patients along with motor function recovery.

A.) Interaction between time and group. MI-BCI group and MI-BCI+tDCS group showed divergent intervention effect at contralesional SMN and DMN. B.) Intervention effect in MI-BCI group. MI-BCI group showed increased ALFF at contralesional SMN and decreased ALFF at DMN. No such effect was observed in MI-BCI+tDCS group. C.) Correlation between FMA changes and ALFF changes in MI-BCI group. Positive correlation was observed between FMA changes and ALFF changes post intervention in MI-BCI group at precentral gyrus. No such correlation was observed at MI-BCI+tDCS group.

(L: Ipsilesional Hemisphere, DMN: Default Mode Network, SMN: Somatomotor Network, HC: Healthy Control, Precg: Precentral Gyrus, SMA: Supplementary Motor Area, PCUN: Precuneus, PCG: Posterior Cingulate Gyrus, MFG: Middle Frontal Gyrus, ANG: Angular Gyrus, INS: Insula, MTG: Middle Temporal Gyrus)

2.3.4 Functional connectivity changes between the SMN and DMN

Given the above ALFF/ReHo patterns mainly in the SMN and DMN, I then investigated if the FC in these two networks was disrupted in stroke patients and whether there was

any intervention effect. As expected, stroke patients showed lower FC within the SMN at baseline compared to healthy controls ($p=0.03$) (Figure 2.5A) while no differences were found for FC within the DMN and FC between the SMN and DMN. Furthermore, no intervention effect (interaction or post-hoc effects) was found.

Figure 2. 4 ReHo changes in DMN in stroke patients along with motor function recovery.

A.) The interaction effect between group and time. The MI-BCI group and MI-BCI+tDCS group showed divergent intervention effects at DMN. B). The intervention effect in the MI-BCI group. The MI-BCI group showed decreased ReHo at DMN. No such effect was observed in the MI-BCI+tDCS group. C). Correlation between FMA changes and ReHo changes in MI-BCI group. A negative correlation was observed between FMA changes and ReHo changes post intervention in the MI-BCI group at precuneus. No such correlation was observed in the MI-BCI+tDCS group.

(L: Ipsilesional Hemisphere, DMN: Default Mode Network, PCUN: Precuneus, PCG: Posterior Cingulate Gyrus, ACG: Anterior cingulate and paracingulate gyri)

2.3.5 Association between brain functional measures and motor function improvement

To find the association between changes in brain functional activity/connectivity and motor function post-intervention, I investigated the correlation between the ALFF/ReHo/FC changes and FMA changes.

A positive correlation ($r = 0.639$, $p = 0.044$) between ALFF changes in the precentral gyrus and FMA changes was observed in the MI-BCI group (Figure 2.2C), which indicated that patients who obtained higher ALFF increase post-intervention gained greater motor function improvement.

A negative correlation ($r = -0.675$, $p = 0.035$) between ReHo changes at precuneus and FMA changes was found in the MI-BCI group (Figure 2.3C). The association between decreased ReHo changes and increased FMA changes indicated that patients who had larger ReHo reduction gained greater motor function improvement.

Differential associations of the FC changes between SMN and DMN and FMA changes were observed in the MI-BCI group and MI-BCI+tDCS group. I found a positive correlation ($r = 0.750$, $p = 0.016$) between inter SMN-DMN FC changes and FMA changes in the MI-BCI group (Figure 2.5B) while a negative correlation ($r = -0.714$, $p = 0.010$) was reported in the MI-BCI+tDCS group. The contradictory association in the two groups indicated that patients who obtained higher SMN-DMN FC increase would gain greater motor function improvement in the MI-BCI group while stroke patients in the MI-BCI+tDCS group would gain lower motor function improvement.

Figure 2. 5 Differential correlation between FC changes and behavioural outcome changes using different intervention methods.

A). Stroke patients showed lower FC at SMN comparing to healthy controls at baseline ($p=0.030$). B). Correlation between FC changes and FMA changes in MI-BCI group. Positive correlation was observed between FMA changes and interconnectivity changes of DMN and SMN. C). Correlation between FC changes and FMA changes in MI-BCI+tDCS group. Negative correlation was observed between FMA changes and interconnectivity changes of DMN and SMN.

2.4 Discussion

This study investigated the brain functional activity and connectivity changes in chronic subcortical stroke patients pre- and post-intervention with MI-BCI and tDCS. I found that stroke patients had lower ALFF in the ipsilesional SMN at baseline and had increased ALFF in the contralesional SMN in the MI-BCI group, providing new evidence for the compensation effect. Furthermore, the higher ALFF/ReHo in the DMN at baseline were decreased after MI-BCI training, illustrating the re-normalization of brain activity and connectivity post-intervention. More importantly, the divergent associations between SMN-DMN FC changes and FMA changes in the MI-BCI group and MI-BCI+tDCS group suggested differential mechanisms in the two approaches.

2.4.1 Compensation effect of the contralesional SMN after MI-BCI

The ALFF findings suggest the possible beneficial effect of brain activity in the contralesional motor cortex after MI-BCI-based intervention. Stroke patients had lower ALFF in the ipsilesional SMN at baseline; and then the MI-BCI group showed increased ALFF in the contralesional SMN post-intervention. Importantly, increased regional brain activity in the contralesional motor cortex was positively associated with motor function improvement, suggesting a compensation effect of the contralesional SMN.

A predominant hypothesis of interhemispheric interaction - the motor cortex of one hemisphere inhibits the contralateral homologue (Dancause et al., 2015; Di Lazzaro et al., 1999; Ferbert et al., 1992; Gerloff et al., 1998; Liepert et al., 2000; Lotze et al., 2006; Lüdemann-Podubecká et al., 2016). In line with this hypothesis, studies have reported persistent contralesional sensorimotor cortex hyperexcitability in patients post-stroke (Bütefisch et al., 2003; Liepert et al., 2000). Such hyperexcitability in the contralesional hemisphere might be harmful to recovery as it inhibits the excitability of the ipsilesional hemisphere (Loubinoux et al., 2003; Manganotti et al., 2008). Repetitive transcranial magnetic stimulation (rTMS) and tDCS have also been employed to inhibit the contralesional motor cortex to improve motor function recovery (Lüdemann-Podubecká et al., 2016; Matsuura et al., 2015; Nowak et al., 2008; Song et al., 2014; Takeuchi et al., 2005).

In parallel, recent BCI-related researches have shown contradictory results against the predominant hypothesis. Patients were reported to gain significant motor function improvement by utilizing the contralesional motor cortex in BCI therapy (Bundy et al., 2017; Song et al., 2014; Young et al., 2014). Although the role of the contralesional motor cortex is still unclear, evidence showed that the contralesional motor cortex excitability is positively correlated with recovery from stroke in chronic stroke patients (Lotze et al., 2006; Schaechter and Perdue, 2008; Young et al., 2016). One hypothesis on the function of the contralesional motor cortex is that it may provide additional neural resources for compensation of ipsilesional damages (Butler et al., 2013; Nowak et al., 2009; Touvykine et al., 2016). My findings provide new evidence supporting the compensation effect of the contralesional SMN after MI-BCI stroke rehabilitation. Nevertheless, more effort should be made to study the role of the contralesional motor cortex in stroke rehabilitation, which could possibly depend on

lesion size, stroke type, stroke stage, and BCI experiment design (Buetefisch, 2015; Dodd et al., 2017).

2.4.2 Re-normalization of brain activity and connectivity after MI-BCI

Stroke patients showed lower ALFF/FC in SMN and higher ALFF/ReHo in the DMN compared to healthy controls at baseline. Post-intervention, the MI-BCI group showed increased ALFF in the contralesional SMN and decreased ALFF/ReHo in the DMN. My results match with previous findings on alterations of brain activity and connectivity in the DMN and the brain re-normalization hypothesis.

Alterations of brain activity and connectivity in the DMN were widely reported in stroke patients with impaired cognitive function (Ding et al., 2014; Liu et al., 2014; Park et al., 2014; Tuladhar et al., 2013; Wang et al., 2019). Stroke patients had significantly lower FC in the key DMN regions, namely precuneus and posterior cingulate gyrus compared to healthy controls (Ding et al., 2014; Tuladhar et al., 2013; Wang et al., 2019). Reduced ALFF and ReHo in the DMN were reported in stroke patients with early impairment in consciousness (Tsai et al., 2014). My results showed higher ALFF and ReHo in the DMN in stroke patients at baseline compared to healthy controls. The difference might be due to different function impairments (cognitive impairment vs. motor function impairment) and different stroke stages (acute/subacute vs. chronic). A possible explanation for higher brain activity and connectivity in the DMN is the compensatory effect for motor function. More resources were required to achieve normal motor function due to the ipsilesional SMN decline, resulting in higher DMN activity in patients than healthy controls as compensation for declined SMN function (Pan et al., 2017).

More importantly, re-normalization of the brain activity and connectivity were observed post-intervention. The higher ALFF and ReHo in the precuneus and posterior cingulate gyrus at baseline reduced post-intervention in the MI-BCI group, which refers to re-normalization of the local activity and connectivity. Brain re-normalization in previous studies focused on alterations in FC. Increased FC after BCI rehabilitation therapy in the SMN and DMN where FC was lower at baseline was reported, which also hints at re-normalization of brain connectivity (Park et al., 2014; Tsuchimoto et al., 2019; Wang et al., 2019).

2.4.3 Differential Mechanisms of MI-BCI and MI-BCI+tDCS

The efficacy of MI-BCI on improving motor function in stroke rehabilitation has been widely reported (Ang et al., 2009; Ang and Guan, 2015; Foong et al., 2020; Pichiorri et al., 2015; Ramos-Murguialday et al., 2019; Teo and Chew, 2014). Studies on tDCS also illustrated the beneficial effects of non-invasive cortical stimulation on stroke rehabilitation (Allman et al., 2016; Elsner et al., 2018; Kashiwagi et al., 2018; A. Liu et al., 2018; Madhavan et al., 2011; Nitsche & Paulus, 2001; Zaghi et al., 2010). However, the combination of MI-BCI and tDCS in this study did not further improve the motor function than MI-BCI therapy without tDCS. Both MI-BCI and MI-BCI-tDCS groups gained significant motor function improvement with no group differences reported regarding FMA scores. But the differential patterns of brain activity and connectivity post intervention and association between brain activity and connectivity with FMA in two groups underscored differential mechanisms underlying MI-BCI and tDCS. MI-BCI group showed increased ALFF at contralesional SMN and reduced ALFF/ReHo at DMN post intervention while no significant neuroimaging findings were observed in MI-BCI+tDCS group. Furthermore, contradictory correlations were found between FC changes and clinical outcome changes in MI-BCI group and MI-

BCI+tDCS group. The results indicated that MI-BCI and tDCS had potentially divergent ways of modulating functional brain activity. MI-BCI system enables stroke patients to move the impaired limb driven by a robotic arm via neural signals from the motor imagery of the arm and provides multisensory feedback to patients to enhance motor learning and recovery (Ang et al., 2014, 2009). tDCS modulates activity in both the motor and visual cortices and directly influences the excitability of the spinal cord (Elsner et al., 2018; Nitsche & Paulus, 2001). Generally, anodal stimulation increases cortical excitability, while cathodal stimulation decreases it. I suspect that the inhibition effect of cathodal might prevent or reverse the brain activity/connectivity changes in the MI-BCI+tDCS group, leading to insignificant results compared to MI-BCI only group and contradictory correlation with FMA scores. Consistent with our findings, another study reported that white matter integrity in the ipsilesional corticospinal tract and bilateral corpus callosum was increased but sensorimotor cerebral blood flow (CBF) was decreased, while in the MI-BCI group contradictory results or insignificant results were reported (Hong et al., 2017). Quantitative electroencephalographic (Q-EEG) features which changed significantly during these interventions were also mutually exclusive for MI-BCI and MI-BCI+tDCS group. The relative theta power was observed to be the signature monitoring biomarker for BCI intervention whereas the tDCS group was characterized by a change in brain symmetry index, indicating distinct mechanisms of neuronal repair of the two approaches (Mane et al., 2019). The detailed explanation of changes in the brain requires further understanding of both MI-BCI and tDCS mechanisms. The results suggest that a combined rehabilitation strategy should be designed considering not only the improvement of clinical outcomes but also changes in the brain.

2.4.4 Limitations

This is a pilot study of stroke rehabilitation involving complex multimodal design of neuroimaging, MI-BCI and tDCS, which is limited by the small sample size. Due to the limited sample, I was not able to control for stroke severity and lesion type or location in my analysis. Also, the possible inter-variability in conventional occupational therapy was not taken into account. Future research with large sample size should incorporate these potential important factors to evaluate the long-term rehabilitation effect. Another limitation is the lack of a tDCS-only group which would help to understand the mechanism of tDCS to facilitate the development of stroke rehabilitation strategies. Although the tDCS stimulation parameters applied in this study follow the standard protocol, it would be to study how stimulation parameters such as sites and placement of electrodes could impact the efficiency. Furthermore, while the current study focused on subcortical chronic stroke patients, it is crucial to design effective rehabilitations for stroke patients in acute or subacute phase moving forward.

2.5 Summary

In conclusion, stroke patients showed lower ALFF/FC at SMN and higher ALFF/ReHo at DMN at baseline. Reorganization of ALFF/ReHo were observed at SMN and DMN post intervention in MI-BCI group while MI-BCI+tDCS group showed no significant changes. Divergent association between intra SMN-DMN FC changes and FMA changes were observed in MI-BCI group and MI-BCI+tDCS group. The results validated the efficacy of both MI-BCI approach and MI-BCI+tDCS approaches while illustrating possible differential mechanisms between the two approaches.

Statistical analysis was utilized in this study and presented the group-level difference between stroke patients and healthy controls as well as differences pre and post

intervention. However, the study is limited by the small sample size. To further investigate the contextual information of neuroimaging data using more advanced techniques, new datasets with larger sample size were utilized in the following studies.

Chapter 3 Structural and diffusion MRI based schizophrenia classification using 2D pre-trained and 3D naive Convolutional Neural Networks

3.1. Introduction

Schizophrenia is a potentially severe and chronic mental disorder that imposes great burdens on patients, their families, and the society. Early and accurate diagnosis of schizophrenia could facilitate treatment planning and improve the outcome of the illness. Yet, the diagnosis of schizophrenia is typically based on clinical interview and corroboration of clinical data, which is challenging due to the complex and heterogeneous symptom presentations which can vary with the course of the illness especially at early onset (Del Barrio, 2016; Fanous et al., 2012; Kennedy et al., 2014). Therefore, it is important to establish an objective approach for accurate diagnosis which determines appropriate subsequent treatment.

Structural magnetic resonance imaging (sMRI) and diffusion MRI (dMRI) have been used to detect brain structural and microstructural abnormalities in patients with schizophrenia (Gong et al., 2019; Mitelman, 2019; Ott et al., 2019; Power et al., 2016; Shenton et al., 2001). Accumulating sMRI evidence suggests widespread grey matter reductions especially in frontal, temporal, thalamic, and striatal regions (Fornito et al., 2009; Haijma et al., 2013; Koelkebeck et al., 2019; Kuo and Pogue-Geile, 2019), cortical thinning in frontal, temporal, cingulate, and insular regions (Takayanagi et al., 2020; Van Erp et al., 2018; Yan et al., 2019), and enlargement of ventricles (Gaser et al., 2004; Kuo and Pogue-Geile, 2019; Fenglian Zheng et al., 2019) in schizophrenia patients compared to healthy controls. In parallel, dMRI or diffusion tensor imaging studies reported lower fractional anisotropy (FA) and higher mean diffusivity (MD) in

multiple white matter tracts implicating frontal-striatal-thalamic circuits and the cingulum in schizophrenia and its prodrome (Di Biase et al., 2020; Kelly et al., 2018; Wang et al., 2016a; X. Wang et al., 2019). However, the heterogeneity in both the effect sizes and the regional distribution of the brain alterations reported across studies have prevented the application of group-level findings to individual-level diagnosis (Arbabshirani et al., 2017; Di Biase et al., 2020; Kelly et al., 2018). Given the high-dimensional multimodal neuroimaging and clinical data, there is an increasing need to develop automatic and standardized multimodal probes for accurate and objective classification of schizophrenia.

Machine learning approaches have begun to demonstrate its potential in complementing the clinical diagnosis of psychiatric disorders using neuroimaging data (Arbabshirani et al., 2017; Rashid and Calhoun, 2020). Previous work on computer-aided classification of schizophrenia patients and healthy controls mainly focused on handcrafted feature-based machine learning approach, which requires feature extraction and reduction before classification. The most common features in previous studies are cortical thickness and voxel-based morphometry (via sMRI) (Chin et al., 2018; Nieuwenhuis et al., 2012; Salvador et al., 2017; Winterburn et al., 2019) and white matter microstructure such as FA (via dMRI) (Ardekani et al., 2011; Liang et al., 2019; Mikolas et al., 2018). Traditional classifiers like support vector machine (SVM), random forest, and logistic regression are the most widely used methods (Arbabshirani et al., 2017; Filippis et al., 2019; Winterburn et al., 2019). However, the subtle, mixed, and widespread brain anatomical changes in schizophrenia limit the performance of handcrafted machine learning approaches. Pre-selected features might not be efficient and generalizable across different cohorts with differing duration of illness, causing the accuracy to vary across datasets, features, and hyperparameter settings. Handcrafted

feature-based machine learning also has difficulty in uncovering new features to facilitate biological inferences (Arbabshirani et al., 2017; Rashid and Calhoun, 2020; Winterburn et al., 2019).

Convolutional Neural Network (CNN) has recently become a promising approach for medical image classification such as brain tumor, lung nodule, and Alzheimer's disease (Iizuka et al., 2019; Khvostikov et al., 2018; Lin et al., 2018; Liu and Kang, 2017). As a data-driven deep learning method, CNN is capable of automatic feature learning which mitigates the subjectivity and variability in pre-selecting relevant features. This is especially important for psychiatric disorders like schizophrenia which has subtle, complex, and widely distributed brain alterations (Lee et al., 2017). Deep model architecture with nonlinear layers also allows efficient mapping of complicated data patterns (Arbabshirani et al., 2017; Lee et al., 2017). Nevertheless, limited studies have applied CNN on structural neuroimaging data to differentiate patients with schizophrenia patients from healthy controls. A recent study applied a sequential 3D CNN model on sMRI data for classification and achieved an area under the receiver operating characteristic curve (ROC-AUC) of 0.96, but independent testing performance degraded significantly (Oh et al., 2020). Complicated 3D CNN architectures have not been investigated. Studies using transfer learning approaches that utilize powerful pre-trained 2D CNN networks to extract features from deep layers are also lacking. Of note, multimodal feature extraction from different neuroimaging modalities is critical for understanding the neural substrates underlying schizophrenia from complementary perspectives, potentially leading to higher classification performance (Lei et al., 2020; Lerman-Sinkoff et al., 2019; Salvador et al., 2019). The automatic feature learning capability of CNN enables more prominent

integration of multimodal inputs, yet, multi-channel 2D and 3D CNN have not been employed and evaluated for schizophrenia discrimination.

CNN models have demonstrated remarkable performance on image classification tasks, but they are often criticized as a “black box” as the learning process and predictions are not interpretable (Pinaya et al., 2019). Gradient-based methods and up-convolutional net have been proposed to visualize 2D CNN representations and provide visual explanations for decision making (Mahendran and Vedaldi, 2015; Selvaraju et al., 2017; Simonyan et al., 2014; Springenberg et al., 2015; Zeiler and Fergus, 2014; Zhang and Zhu, 2018; Zhou et al., 2016). As a state-of-the-art approach, gradient class activation map could localize the discriminative image regions from any CNN-based network without requiring architectural changes or re-training and it could be extended to 3D CNN (Selvaraju et al., 2017; C. Yang et al., 2018). Identifying the critical regions for classification could not only validate the underlying rationale of decision-making to enable clinical adoption but also facilitate biological inferences to improve the understanding of schizophrenia.

To fill these gaps, I developed naïve 3D CNN models trained from scratch and deep feature approach using pre-trained 2D CNN networks to identify patients with schizophrenia using 3D sMRI and dMRI data. A multi-channel input approach was utilized to integrate representations from different feature maps and modalities. I implemented a state-of-the-art handcrafted feature-based machine learning approach with SVM as a benchmark. I hypothesize that both 2D and 3D CNN models would outperform handcrafted feature-based machine learning and multimodal neuroimaging-based models integrating both structural and diffusion MRI would accomplish superior performance than single modality-based models. Furthermore, I determined the

discriminative brain regions for classification based on the models with the best performance using the gradient class activation map approach.

3.2. Methods

3.2.1 Participants

Two independent MRI datasets of schizophrenia and controls were used in this study which were comparable for age and gender for both groups (Table 3.1). The Northwestern University Schizophrenia Data and Software Tool (NUSDAST) is a repository of schizophrenia neuroimaging data collected from over 450 schizophrenia patients and healthy controls, which is publicly available on SchizConnect platform (Kogan et al., 2016; Wang et al., 2013). Overall, 141schizophrenia patients and 134 healthy controls from this public dataset were included after quality control.

A similar dataset with both structural MRI and diffusion MRI from the Institute of Mental Health (IMH), Singapore, was included as an independent dataset (Ho et al., 2017a, 2017b). In this dataset, 148 schizophrenia and 76 healthy controls were included after quality control.

Table 3. 1 Subject demographics of the two datasets.

	NUSDAST		IMH	
	SZ	HC	SZ	HC
Subject Number	141	134	148	76
Age (Years),	35.1	32.9	32.7	31.3
Mean (SD)	(12.8)	(14.0)	(9.0)	(9.8)
Sex (Male/Female)	90/51	72/62	102/46	47/29
Modality	sMRI		sMRI & dMRI	

Abbreviations: SZ - Schizophrenia Patients, HC - Healthy Controls, SD - standard deviation.

3.2.2 Image acquisition

For the NUSDAST dataset, all MRI scans were collected using the same 1.5 T Vision scanner platform (Siemens Medical Systems). Acquisition of all scans was performed at the Mallinckrodt Institute of Radiology at Washington University School of Medicine, where scanner stability (e.g., frequency, receiver gain, transmitter voltage, SNR) and artifacts were regularly monitored from 1998 to 2006 (Wang et al., 2013). 3D Turbo Flash images were acquired with following parameters: axial slice thickness = 1 mm, 180 slices, in-plane resolution = $1 \times 1 \text{ mm}^2$, repetition time = 20 ms, echo time = 5.4 ms, flip angle = 7° , and matrix size = 256×256 pixels.

For the IMH dataset, all MRI scans were performed using the same 3-Tesla whole-body scanner MRI (Philips Achieva, Best, The Netherlands) with an 8-channel SENSE (Sensitivity Encoding) head coil at the National Neuroscience Institute, Singapore, from 2006 to 2013 (Ho et al., 2017a, 2017b). T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) images were acquired with following parameters: axial slice thickness = 0.9 mm, 180 slices, in-plane resolution = $0.9 \times 0.9 \text{ mm}^2$, repetition time = 7200 ms, echo time = 3.3 ms, flip angle = 8° , and matrix size = 256×256 pixels. Diffusion MRI data were acquired with the following parameters: axial slice thickness = 3 mm, 42 slices, in-plane resolution = $0.9 \times 0.9 \text{ mm}^2$, repetition time = 3.725 s, echo time = 56 ms, flip angle = 90° , acquisition matrix size = 112×109 pixels, reconstruction matrix = 256×256 pixels. 15 diffusion-weighted images ($b = 800 \text{ sec/mm}^2$) of non-parallel directions and 1 baseline image ($b = 0 \text{ sec/mm}^2$) were obtained. Three runs of such DW-MRI images were acquired in the same session and were concatenated for processing.

3.2.3 Image processing

Processing of the structural MRI data was performed using Computational Anatomy Toolbox in Statistical Parametric Mapping 12 (SPM12) for voxel-wise estimation of grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) compartment (Kurth et al., 2015) following a previous work in my group (Ng et al., 2016). Images with motion artifacts were excluded after visual quality control. Subject-level probability maps were obtained from T1-weighted images with the following steps: (i) skull stripping; (ii) linear (FLIRT) and nonlinear (FNIRT) registration to the Montreal Neurological Institute (MNI) 152 standard space (Jesper L R Andersson et al., 2007); (iii) segmentation of the brain into GM, WM, and CSF compartments with 1.5 mm isotropic resolution ; (iv) modulation by multiplying voxel values with the linear and nonlinear component of the Jacobian determinant. The diffusion MRI data were preprocessed using FSL (<http://www.fmrib.ox.ac.uk/fsl>) with the following steps following a previous work in my group (Ho et al., 2017a): (i) head movements and eddy current distortion correction with reference to the first $b=0$ volume via affine registration of the diffusion-weighted images; (ii) diffusion gradients rotation to improve consistency with the motion parameters; (iii) visual inspection of signal dropout, artefacts, and additional motion (subjects with $> 3\text{mm}$ of motion displacement during the scan were excluded); (iv) tensor fitting to diffusion data at each voxel to create fractional anisotropy (FA) and mean diffusivity (MD) maps; (v) nonlinear registration to FMRIB58_FA standard space with FNIRT. For computational efficiency, all the resulting feature maps (GM, WM, CSF, FA, and MD) in the standard space were down-sampled from $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ ($121 \times 145 \times 121$) to $3 \times 3 \times 3 \text{ mm}^3$ ($61 \times 121 \times 61$).

3.2.4 Study design

I employed three approaches to classify schizophrenia patients and healthy controls (see detailed study design in Figure 3.1). To compare with the state-of-the-art handcrafted feature-based machine learning approach, I implemented linear and nonlinear SVM classifiers as the benchmark. To utilize powerful pre-trained 2D CNN networks, I applied deep feature approach based on feature maps extracted from pre-trained networks in a 2D manner. To exploit the 3D contextual information and investigate the effect of model structure, I developed naïve 3D CNN models trained from scratch with different architectures and depths.

GM, WM, and CSF probability maps were used as inputs for structural MRI models trained on the NUSDAST dataset. Nested 5-fold cross-validation was used to select hyperparameters and obtain testing results for all the models. To test the generalizability of trained models, sMRI models trained on the NUSDAST dataset were further tested on the independent IMH dataset with ensemble approach.

One step further, I developed multimodal models using GM, WM, CSF, FA, and MD maps as inputs for all three approaches above. I performed cross-validation on the IMH dataset and compared the classification performance with single-modality models.

Lastly, I evaluated the interpretability of the derived 3D CNN models with the best performance with reference to previous literature. Gradient class activation map approach was employed to identify brain regions whose GM, WM, CSF or white matter microstructure contributed significantly to the classification of schizophrenia patients.

More details of each step are as follows.

Figure 3. 1 Study Design.

I employed three approaches to classify schizophrenia patients and healthy controls. I implemented linear and nonlinear SVM classifiers as the benchmark methods. I applied deep feature approach which classified feature maps extracted from pre-trained networks to utilize the powerful pre-trained networks. Naïve 3D CNN models trained from scratch with different architecture and depths were developed to exploit 3D contextual information. GM, WM, and CSF probability maps were used as inputs for structural MRI models trained on the NUSDAST dataset. Nested 5-fold cross-validation was used to select hyperparameters and obtain testing results for all the models. To test the generalizability, sMRI models trained the NUSDAST dataset were further tested on the independent IMH dataset with ensemble approach. I also developed multimodal models using GM, WM, CSF, FA, and MD maps as inputs and evaluated on the IMH dataset using cross-validation. Lastly, I used gradient class activation map approach to interpret 3D CNN models with the best performance to identify brain regions whose GM, WM, CSF, or white matter microstructure contributed significantly to the classification of schizophrenia patients.

3.2.4.1 Handcrafted feature-based machine learning

I employed voxel-based morphometry as handcrafted features and SVM as classifiers to implement a benchmark method. GM, WM, and CSF probability maps extracted from sMRI as well as FA and MD maps extracted from dMRI were employed as features and flattened as feature vectors. Feature reduction was completed by principal

components analysis (PCA) with 99% variance explained for each input map. Linear SVM and nonlinear SVM with the Radial Basis Function (RBF) kernel were trained and tested.

3.2.4.2 Deep feature based on pre-trained 2D CNN

To investigate the impact of model architecture, I employed six state-of-the-art CNN models pre-trained on Imagenet dataset: VGG16 (Simonyan and Zisserman, 2015), Xception (Chollet, 2017), Resnet101 (He et al., 2016), Densenet121 (Huang et al., 2017), Inception_v3 (Szegedy et al., 2015), and Inception_resnet_v2 (Szegedy et al., 2017). Each 2D slice of the 3D maps was used as input to pre-trained networks and the deep feature map taken from the last convolutional layer was used as the resulting extracted features. To fully utilize the contextual information of 3D images, the feature maps from each 2D slice for each of the three views (axial, coronal, and sagittal) were combined and flattened as a large feature vector at the individual level. Feature reduction was performed with PCA with 99% variance explained for each input map and classification was completed with linear SVM.

3.2.4.3 Naïve 3D CNN models

Typical CNN models consist of convolutional layers, pooling layers, and fully connected layers in sequential and use backpropagation to learn multi-level features (Lee et al., 2017). The convolutional layer computes the output of neurons that are connected to local regions in the input, each computing a dot product between their weights and a small region they are connected to in the input volume. The pooling layer performs a down-sampling operation along the spatial dimensions. The fully connected layer connects each neuron to all the numbers in the previous volume and computes the class probabilities. Note that in 3D CNN networks, the convolutions and pooling operate in a cubic manner with 3D feature volumes instead of 2D feature maps, which

fully utilized the 3D contextual information in brain structural imaging. Furthermore, advanced architectures interconnect the layers and form modules with more complicated topologies, such as inception module and residual module (He et al., 2016; Szegedy et al., 2015). In this study, the following three types of 3D CNN model architectures with different depths were implemented and evaluated.

3.2.4.3.1 Sequential models

Sequential models followed the typical CNN architecture with convolutional layers, pooling layers, and fully connected layers in sequential. The convolutional kernel and pooling kernel were set with dimension 3x3x3 as selected using grid search. GM, WM, and CSF probability maps extracted from sMRI as well as FA and MD maps extracted from dMRI were employed as independent input maps connecting to different network branches. The resulted feature maps from each branch were flattened and connected to a fully connected layer with 128 neurons. Output was obtained by sigmoid function.

Three sequential models with different numbers of layers were trained and tested. As shown in Figure 3.2A, Sequential_1 has the structure of one convolutional layer (Conv), one maxpooling layer (Maxpooling), and one fully connected layer (FC), presented as Conv+Maxpooling+FC; Sequential_2 has structure 2(Conv+Maxpooling)+FC, representing two levels of convolutional layer and maxpooling layer connecting to a fully connected layer; Sequential_3 has structure 3(Conv+Maxpooling)+FC, representing 3 levels of convolutional layer and maxpooling layer connecting to a fully connected layer. The deeper the network, the smaller the feature volumes become.

3.2.4.3.2 Inception models

Inspired by the GoogLeNet (Szegedy et al., 2015), 3D inception module was utilized in inception models (Figure 3.2B and 3.2C). The inception module divides the network into multiple branches with different convolutional kernels, allowing operating convolutions with different kernels on the same level. The inception module could not only improve the performance of the network but also could control overfitting and reduce computational expenses.

3.2.4.3.3 Inception_resnet Models

Inspired by the residual module (He et al. 2016), Inception_resnet_model combined inception architecture and residual module to utilize the information from previous layers (Figure 3.2D). Inception_resnet_1 has the same arterial structure as Inception_1 with an extra connection which adds the output from the previous layer and output from the inception module together. Similarly, Inception_resnet_2 has two extra connections adding outputs from different layers together.

Figure 3. 2 Architectures of the naïve 3D CNN models.

A) Three sequential models with different numbers of layers were trained and tested. Sequential_1 model contains 1 convolutional layer (Conv), 1 maxpooling layer

(Maxpooling) and 1 fully connected layer (FC); Sequential_2 model has two levels of convolutional layer and maxpooling layer connected to one final fully connected layer; Sequential_3 has structure 3(Conv+Maxpooling)+FC, representing 3 levels of convolutional layer and maxpooling layer connecting to fully connected layer. **B)** 3D inception module was utilized in inception models. The inception module divides the network into multiple branches with different convolutional kernels. **C)** Inception_1 contains 1 convolutional layer and 1 maxpooling layer followed by an 3D inception module, the fully connected layer is replaced by a convolutional layer and sigmoid function. Inception_2 contains 2 inception modules. **D)** Inception_resnet models employed the same stream structure as inception models. An extra connection adds the output from the previous layer and output from the inception module together. Inception_resnet_1 has one inception module while inception_resnet_2 has two inception modules.

3.2.4.5 Nested cross-validation and ensemble approach

To avoid overfitting, I used nested cross-validation consisting of an inner loop and an outer loop. The outer loop split data into 5 folds and each round used 4 folds for training and the remaining for testing. The inner loop further split the training data from the outer loop into 5 folds and used cross-validation to select hyperparameters for 3D CNN models (optimizer, kernel size, kernel number) and nonlinear SVM (kernel type, kernel coefficient, regularization term) (Supplementary Table 3.1). Testing results were obtained through outer 5-fold cross-validation which averages the test error over multiple train–test splits. The testing results for naïve 3D CNN were reported as the average of 10 repeats to reduce randomness generated from the training process. Furthermore, a random seed was appointed for data split of nested cross-validation to ensure training and testing data are the same among different approaches and different repeats to reduce randomness.

After the nested cross-validation on the NUSDAST dataset, I took the ensemble approach to evaluate the classification performance on the independent testing IMH dataset. Specifically, 5-fold cross-validation trained 5 optimized models in each fold for handcrafted feature-based machine learning and deep feature based on pre-trained 2D CNN networks. Independent testing results on the IMH dataset were determined by majority voting among 5 predictions from the 5 models trained for each method. For naïve 3D CNN, I selected 5 models from one repeat of 5-fold cross-validation with the highest accuracy out of 10 repeats and the independent testing results on the IMH dataset were determined by majority voting among 5 selected models.

3.2.4.6 Interpretation

To interpret the 3D CNN models and classification decision process, I adopted gradient class activation map approach on both single and multi-modality models with the best performance to localize the brain regions contributed significantly to the classification of schizophrenia patients. The discriminative regions were determined by calculating the backpropagated class signal at the last rectified convolutional layer of each input branch and thus heat maps were generated separately for GM, WM, CSF, FA, and MD for each individual. Subsequently, one sample T-test (familywise error corrected at $p < 0.01$) identified the critical regions for classification at the group-level.

3.3. Results

3.3.1 Nested cross-validation results on the NUSDAST dataset with sMRI models

Accuracy, sensitivity, specificity, and ROC-AUC from nested cross-validation (mean and standard deviation) were reported for sMRI models trained on the NUSDAST dataset (Table 3.2). In general, both 2D and 3D CNN models outperformed handcrafted feature-based machine learning approaches. Nonlinear SVM the RBF kernel with

achieved an averaged accuracy of 70.22% and ROC-AUC of 0.78. Deep feature based on pre-trained inception_v3 outperformed nonlinear SVM with an accuracy of 72.41% and ROC-AUC of 0.82. Naïve 3D CNN models trained from scratch further exceeded the performance of deep feature based on pre-trained 2D CNN networks with an accuracy of 79.27% and ROC-AUC of 0.81.

The classification performance of different models was further visualized in Figure 3.3A and 3.4A. Figure 3.3A directly compares the accuracy of different models in bar charts. Both 2D and 3D CNN models obtained higher accuracy than handcrafted feature-based machine learning. Naïve 3D CNN model Inception_resnet_1 achieved the highest accuracy. Figure 3.4A further demonstrates model performance regarding sensitivity and specificity with prediction probability of being patients plotted. Random predictions for both controls and patients have a distribution peak at around 0.5 while predictions generated by models have a distribution peak towards 0 for controls and 1 for patients. In concordance with accuracies and ROC-AUC, handcrafted feature-based machine learning performed slightly better than random predictions. Deep feature based on pre-trained 2D CNN outperformed handcrafted feature-based machine learning. Naïve 3D CNN models clearly separated patients from controls with prediction distribution peaks apart from each other.

Replication of the same cross-validation process was performed on the sMRI data of the IMH dataset and demonstrated similar observations (Supplementary Table 3.3 and Supplementary Figure 3.1).

Table 3. 2 Single modal (sMRI) cross-validation results on the NUSDAST dataset.

		ACC	SP	SE	ROC-AUC
HANDCRAFTED FEATURE- BASED MACHINE LEARNING	Linear SVM	69.85% (+/- 4.02%)	67.98% (+/- 4.70%)	71.63% (+/- 3.93%)	0.78 (+/- 0.04)
	Nonlinear SVM (RBF kernel)	70.22% (+/- 5.28%)	75.41% (+/- 3.56%)	65.25% (+/- 7.95%)	0.78 (+/- 0.05)
DEEP FEATURE BASED ON PRE-TRAINED 2D CNN	VGG16	68.05% (+/- 5.22%)	63.53% (+/- 9.81%)	72.29% (+/- 5.89%)	0.75 (+/- 0.04)
	Xception	66.59% (+/- 7.92%)	69.43% (+/- 7.81%)	63.84% (+/- 10.87%)	0.73 (+/- 0.07)
	Resnet50	70.59% (+/- 6.83%)	69.52% (+/- 9.59%)	71.55% (+/- 10.72%)	0.78 (+/- 0.04)
	Densenet121	69.07% (+/- 3.21%)	67.95% (+/- 7.84%)	70.12% (+/- 8.21%)	0.79 (+/- 0.05)
	Inception_V3	72.41% (+/- 4.70%)	70.94% (+/- 8.45%)	73.74% (+/- 5.86%)	0.82 (+/- 0.05)
	Inception_resn et_V2	72.40% (+/- 3.82%)	70.88% (+/- 4.38%)	73.77% (+/- 9.17%)	0.79 (+/- 0.06)
NAÏVE 3D CNN MODELS	Sequential_1	77.78% (+/- 3.56%)	80.32% (+/- 6.98%)	75.35% (+/- 8.08%)	0.82 (+/- 0.04)
	Sequential_2	76.50% (+/- 3.52%)	75.91% (+/- 7.12%)	77.07% (+/- 2.58%)	0.79 (+/- 0.05)
	Sequential_3	73.91% (+/- 2.17%)	73.13% (+/- 7.13%)	74.57% (+/- 4.48%)	0.77 (+/- 0.04)
	Inception_1	77.71% (+/- 4.05%)	76.90% (+/- 6.62%)	78.42% (+/- 5.36%)	0.81 (+/- 0.04)
	Inception_2	76.24% (+/- 3.52%)	78.08% (+/- 4.47%)	74.42% (+/- 7.40%)	0.79 (+/- 0.05)
	Inception_res net_1	79.27% (+/- 3.92%)	80.44% (+/- 5.96%)	78.15% (+/- 4.12%)	0.81 (+/- 0.05)
	Inception_resn et_2	78.76% (+/- 3.70%)	81.54% (+/- 5.12%)	76.10% (+/- 4.55%)	0.81 (+/- 0.05)

Abbreviations: ACC – accuracy, SP – specificity, SE – sensitivity, ROC-AUC - area under the receiver operating characteristic curve.

A. Cross-validation results on the NUSDAST dataset (sMRI models)

B. Independent testing results on the IMH dataset (sMRI models)

C. Cross-validation results on the IMH dataset (sMRI + dMRI models)

Figure 3. 3 Classification Accuracy in cross-validation and independent testing across all models.

Row A represents cross-validation results on the NUSDAST dataset on sMRI models. Some deep feature models performed better than handcrafted feature-based machine learning. Naïve 3D CNN models achieved higher accuracy than both handcrafted feature-based machine learning and deep feature based on pre-trained 2D CNN. **Row B** represents independent testing results on the IMH dataset on sMRI models trained with the NUSDAST dataset. Most naïve 3D CNN models achieved relatively high accuracy except Sequential_2 model. Row C represents cross-validation results on the IMH dataset on sMRI+dMRI models. Naïve 3D CNN models achieved higher accuracy

than both handcrafted feature-based machine learning and deep feature based on pre-trained 2D CNN. In overall, 3D Inception_resnet_2 model achieved the highest accuracy across all tasks.

3.3.2 Independent testing results on the IMH dataset with sMRI models

To further test the generalizability of my models, accuracy, sensitivity, specificity, and ROC-AUC on the independent testing IMH dataset were reported for sMRI models trained on the NUSDAST dataset (Table 3.3 and Figure 3.3B). Naïve 3D CNN inception_resnet_1 model achieved the highest accuracy of 70.98% and ROC-AUC of 0.75. Handcrafted feature-based machine learning had inferior performance with low accuracy. Deep feature based on pre-trained 2D CNN and naïve 3D CNN models with sequential architecture achieved higher accuracy but sensitivity and specificity were greatly imbalanced. Meanwhile, 3D CNN models with more complex architecture obtained higher accuracy as well as more balanced sensitivity and specificity.

Prediction distributions correspond well with accuracy/sensitivity/specificity. Handcrafted feature-based machine learning approaches and deep feature based on pre-trained 2D CNN barely differed from random predictions. Sequential models categorized most subjects into one class and thus resulted in highly imbalanced specificity and sensitivity. Naïve 3D CNN inception models and inception_resnet models satisfactorily separated patients from controls with prediction distribution peaks apart from each other and thus obtained better classification results with more balanced sensitivity and specificity.

I performed testing on the NUSDAST dataset based on models trained with the IMH dataset; similar conclusions were reached (Supplementary Table 3.4 and Supplementary Figure 3.1).

Table 3. 3 Single modal (sMRI) independent testing results on the IMH dataset.

		ACC	SP	SE	ROC-AUC
HANDCRAFTED FEATURE-BASED MACHINE LEARNING	Linear SVM	54.02%	85.53%	37.84%	0.72
	Nonlinear SVM (RBF kernel)	42.41%	97.37%	14.19%	0.73
DEEP FEATURE BASED ON PRE-TRAINED 2D CNN	VGG16	66.52%	59.21%	70.27%	0.71
	Xception	65.62%	36.84%	80.41%	0.70
	Resnet50	64.73%	69.74%	62.16%	0.73
	Densenet121	70.09%	42.11%	84.46%	0.73
	Inception_V3	67.86%	36.84%	83.78%	0.71
	Inception_resnet_V2	65.18%	48.68%	73.65%	0.70
NAÏVE 3D CNN MODELS	Sequential_1	62.95%	75.00%	56.76%	0.73
	Sequential_2	54.46%	93.42%	34.46%	0.72
	Sequential_3	70.09%	46.05%	82.43%	0.72
	Inception_1	68.30%	68.42%	68.24%	0.74
	Inception_2	66.96%	65.79%	67.57%	0.71
	Inception_resnet_1	70.98%	63.16%	75.00%	0.75
	Inception_resnet_2	66.96%	72.37%	64.19%	0.61

Figure 3. 4 Prediction probability distribution of schizophrenia and controls in cross-validation and independent testing across all approaches.

Random predictions for both controls (blue) and patients (orange) have a distribution peak at around 0.5 (first column). Y-axis represents the predicted probability of being patient from 0 to 1. Prediction probability distributions are presented in the following order: handcrafted feature-based machine learning are in the green box, deep feature based on pre-trained 2D CNN are in the red box, and naïve 3D CNN models are in the purple box. **Row A** represents cross-validation results on the NUSDAST dataset on sMRI models. Predictions generated by the proposed models demonstrated higher than randomness accuracy, which had wider gaps between the predicted probability distributions of controls and patients. Naïve 3D CNN models performed the best with clear separation of patients and controls. **Row B** represents independent testing results on the IMH dataset on sMRI models trained with the NUSDAST dataset. Handcrafted feature-based machine learning approaches and deep feature based on pre-trained 2D CNN barely differ from random predictions. Most naïve 3D CNN models obtained relatively higher performance, but sequential models categorize all subjects into one class. Inception models and Inception_resnet models obtained better classification results with more balanced specificity and sensitivity. **Row C** represents cross-validation results on the IMH dataset on sMRI+dMRI models. Handcrafted feature-based machine learning and deep feature based on pre-trained 2D CNN performed better than random predictions. Naïve 3D CNN models demonstrated better performance with wider gaps between the prediction of patients and controls.

3.3.3 Nested cross-validation results on the IMH dataset with sMRI+dMRI models

To evaluate whether the integration of multimodal images could further improve classification results, I built up models using all three approaches with a combination of sMRI and dMRI maps. Accuracy, sensitivity, specificity and ROC-AUC trained on the IMH dataset were reported for sMRI+dMRI models (Table 3.4 and Figure 3.3C). Overall, multimodal sMRI+dMRI models outperformed single-modal sMRI models. Comparing with cross-validation results on sMRI models (Supplementary Table 3.3), multimodal sMRI+dMRI models achieved superior performance for all three approaches, especially on specificity. Multimodal inception_resnet_1 model obtained the highest accuracy of 81.02%, ROC-AUC of 0.84 and 5.31% improvement on specificity comparing with the sMRI inception_resnet_1 model. The corresponding visualization of prediction distributions is included in Figure 3.4C. Multimodal 3D CNN models showed superior ability to differentiate patients from controls with prediction distribution peaks apart from each other.

Table 3. 4 Multimodal (sMRI and dMRI) cross-validation results on the IMH dataset.

		ACC	SP	SE	ROC-AUC
HANDCRAFTED FEATURE- BASED MACHINE LEARNING	Linear SVM	76.37% (+/- 3.96%)	52.50% (+/- 13.27%)	88.51% (+/- 5.88%)	0.82 (+/- 0.02)
	Nonlinear SVM (RBF kernel)	74.58% (+/- 6.36%)	74.92% (+/- 5.27%)	74.32% (+/- 11.74%)	0.81 (+/- 0.04)
DEEP FEATURE BASED ON PRE-TRAINED 2D CNN	VGG16	76.85% (+/- 6.36%)	55.25% (+/-12.92%)	87.86% (+/- 5.87%)	0.82 (+/- 0.05)
	Xception	72.45% (+/- 8.56%)	46.08% (+/- 11.22%)	85.91% (+/- 9.75%)	0.77 (+/- 0.07)
	Resnet50	74.18% (+/- 5.80%)	52.50% (+/- 5.82%)	85.20% (+/- 11.23%)	0.81 (+/- 0.03)

	Densenet121	77.26% (+/- 3.93%)	55.08% (+/- 11.93%)	88.51% (+/- 7.54%)	0.84 (+/- 0.06)
	Inception_V3	74.19% (+/- 5.57%)	48.75% (+/- 9.29%)	87.22% (+/- 4.32%)	0.81 (+/- 0.04)
	Inception_resnet_V2	70.54% (+/- 3.51%)	46.00% (+/- 5.33%)	83.10% (+/- 5.70%)	0.77 (+/- 0.03)
NAÏVE 3D CNN MODELS	Sequential_1	78.07% (+/- 3.64%)	53.87% (+/- 19.14%)	90.46% (+/- 7.74%)	0.81 (+/- 0.06)
	Sequential_2	76.61% (+/- 3.72%)	49.85% (+/- 19.84%)	90.20% (+/- 8.13%)	0.79 (+/- 0.06)
	Sequential_3	74.81% (+/- 4.94%)	50.91% (+/- 22.99%)	87.10% (+/- 9.61%)	0.75 (+/- 0.08)
	Inception_1	80.28% (+/- 2.24%)	64.39% (+/- 13.52%)	88.41% (+/- 6.91%)	0.84 (+/- 0.02)
	Inception_2	76.78% (+/- 3.06%)	57.67% (+/- 20.43%)	86.64% (+/- 11.31%)	0.79 (+/- 0.05)
	Inception_resnet_1	81.02% (+/- 2.52%)	70.42% (+/- 12.00%)	86.44% (+/- 6.45%)	0.84 (+/- 0.03)
	Inception_resnet_2	79.43% (+/- 2.46%)	63.73% (+/- 18.18%)	87.39% (+/- 8.74%)	0.84 (+/- 0.03)

3.3.4 Interpretation of the trained CNN models

To examine the interpretability of my models, I applied gradient class activation map approach on multi-channel and multimodal inception_resnet_1 models which had the highest classification accuracy on the NUSDAST dataset and IMH dataset to localize the discriminative regions for classification. Individual-level heatmap (Figure 3.5, left) and group-level statistical maps (Figure 3.5, right) were generated for each input channel (GM, WM, CSF, FA, and MD).

Overall, the brain regions within which GM, WM, CSF, or white matter microstructure contributed significantly to the classification of schizophrenia patients resembled previous literature in schizophrenia (Figure 3.5, Supplementary Table 3.5 and 3.6). Specifically, grey matter volume in the bilateral insula, orbital prefrontal

cortex, putamen, caudate, amygdala, thalamus, and cerebellum lobule VI are critical features for classification. In addition, the WM volume of widespread deep WM regions and corpus callosum as well as the CSF of the third ventricle and fourth ventricle were identified. Using dMRI, the FA in frontotemporal, interhemispheric, and cortico-striatal-thalamic white matter tracts, including corpus callosum, fornix, corona radiata, and thalamic radiation and the MD in the lateral ventricle, third ventricle, and fourth ventricle were reported from group-level discrimination maps.

Figure 3. 5 Gradient class activation mapping for schizophrenia classification.

The left panel shows heat maps generated by gradient class activation map of one representative subject at the convolutional layer in each network branch of different modalities respectively. Hot colors represent more significant contribution to

classification results. The right panel represents T maps (familywise error corrected at $p < 0.01$) generated from group-level statistical analysis with heat maps of all subjects in each modality. Bright colors represent a higher chance that these regions contribute more to classification results at a group-level. The region names in grey matter and FA are listed in Supplementary Table 3.5 and 3.6.

3.4. Discussion

This study investigated the performance of both 2D and 3D CNN on the classification of schizophrenia patients based on multimodal structural brain imaging. Deep feature based on pre-trained 2D CNN and naïve 3D CNN models trained from scratch were compared with handcrafted feature-based machine learning. Naïve 3D CNN models achieved superior performance in terms of both cross-validation and generalizability on an independent testing dataset. I also demonstrated, for the first time, that multimodal neuroimaging-based CNN models integrating both structural and diffusion MRI accomplished superior performance than single modality-based models. Furthermore, the 3D CNN models were interpreted with gradient class activation map to identify brain regions critical for classification. I localized insula, orbital prefrontal cortex, striatum, thalamus, cerebellum lobule VI in grey matter volume, cortico-subcortical fiber tracts in FA, and enlarged ventricles in CSF and MD, which were consistent with previous literature and supported the salience network/striatum dysfunction hypothesis in schizophrenia.

3.4.1 CNN performed better than handcrafted feature-based machine learning

The classification performance in previous studies varies due to different subject selection criteria, preprocessing protocols, and model implementation (Arbabshirani et al., 2017; Winterburn et al., 2019). I implemented the benchmark handcrafted feature-

based machine learning and CNN models on the same data for a fair comparison among different approaches. In my cross-validation results, deep feature approach based on pre-trained 2D inception_v3 outperformed nonlinear SVM with a gap of 9.05% in accuracy. Naïve 3D inception_resnet_1 model trained from scratch outperformed deep feature approach with 6.87% improvement in accuracy. Comparing to other diseases such as Alzheimer’s disease accompanied by distinct and specific atrophy patterns, the neuroanatomical alterations in schizophrenia tend to be subtle, variable, and widely distributed (Kelly et al., 2018; Van Erp et al., 2018). The superior performance of CNN models reported here further demonstrated its powerful capability of anatomical contextual information extraction and feature learning, which is critical for schizophrenia classification. The independent testing results indicated higher generalizability of 3D CNN models compared to handcrafted feature-based machine learning, which is critical to real-world applications. Feature extraction in handcrafted feature-based machine learning might be affected by heterogeneity in clinical and demographic factors such as disease duration, medications, age, and hence pose restrictions on applying trained models to new data (Arbabshirani et al., 2017). My approach demonstrated the potential of 3D CNN as efficient deep learning models for classifying schizophrenia with unseen data.

3.4.2 3D naïve CNN performed better than deep feature based on pre-trained 2D CNN

My results showed that naïve 3D CNN trained from scratch outperformed deep feature approach based on pre-trained 2D CNN in terms of both cross-validation and independent testing results. Previous studies compared 2D and 3D CNN models as well as models trained from scratch and transfer learning in other classification tasks (Kermany et al., 2018; Litjens et al., 2017; Y. Yang et al., 2018; Yu et al., 2019; Zhu et

al., 2019). Transfer learning including both fine-tune and deep feature approaches have been proven premium in many 2D image classification tasks, especially when compared with new models trained from scratch with limited sample size (Kermany et al., 2018; Y. Yang et al., 2018; Yu et al., 2019). Deep feature approach outperformed the fine-tune approach in a task of tumor classification based on MRI patches (Zhu et al. 2019). Moreover, 3D CNN models trained from scratch performed better than 2D models trained from scratch in the classification of pulmonary nodules (Dou et al., 2017; Liu and Kang, 2017).

To date, there is no consensus regarding the performance comparison between transfer learning approaches based on 2D CNN and 3D CNN models trained from scratch. My results suggest that compared to 2D networks, 3D networks are more suitable for 3D MRI data-based classification. Convolution and pooling in 3D CNN models were operated in a cubic manner using 3D kernels, which are naturally suitable for volumetric medical image processing. Thus, 3D CNN networks are more proficient in processing 3D spatial and contextual information than 2D networks, resulting in more efficient feature representations across levels, which is critical for schizophrenia identification.

3.4.3 Multimodal inputs and complex topologies improved classification accuracy

Multimodal imaging-based models integrating sMRI and dMRI data outperformed single-modal models with only sMRI data for all the three approaches. Notably, the integration of multimodal information greatly improved classification specificity, which is very important for classification with imbalanced classes. Multimodal features provide information from different perspectives allowing models to understand the neural substrates associated with schizophrenia with complementary information from

various modalities. Previous studies illustrated the benefits of combining sMRI and dMRI as well as fMRI for the classification of schizophrenia using handcrafted feature-based machine learning (Isobe et al., 2016; Lei et al., 2020; Saarinen et al., 2020; Salvador et al., 2019), suggesting possible future research with incorporation of additional neuroimaging modalities.

Comparing different 3D CNN architectures trained from scratch, models with complex topologies such as inception module and residual module improved the classification accuracy further. The inception module divides the network into multiple branches with different convolutional kernels, allowing operating convolutions with different kernels on the same level (Szegedy et al., 2015). The residual module allows information incorporation with previous layers (He et al., 2016). The inception module and residual module enhanced the feature learning process of CNN and upgraded the performance of developed models. A previous study examining the classification of lung nodules using CT also found that the inception module outperformed sequential models (Liu and Kang, 2017), but the residual module did not enhance the CNN models' performance which might be due to the small scaling factor used in that study. Another factor might be the training sample size. A previous study with a rather large sample size achieved good cross-validation performance with sequential models (Oh et al., 2020). Future work is needed to train the proposed multimodal 3D CNN models with complex topologies based on a larger sample, which is expected to achieve even higher accuracy and generalizability.

An interesting observation is that models with deeper architecture did not improve accuracy. Sequential_1 which has the least layers achieved the highest accuracy among three sequential models. Inception_1 and inception_resnet_1 outperformed inception_2 and inception_resnet_2 which have deeper architectures.

Kang et al. (2017) had the same observation and concluded that using 3D CNN to classify lung nodules using CT did not need a very deep network (Liu and Kang, 2017). My speculation is that preprocessing steps like down-sampling and registration to standard template caused spatial or finer information loss, which might affect the efficient feature representations at very deep layers and therefore lead to lower performance of models with deeper architecture. Future investigations using high-resolution 3D neuroimaging data in native space is needed to evaluate models with deeper architecture.

3.4.4 Gradient class activation map identified critical regions for classification

Explanation of the classification process verifies the countability of the model and also leads to biological interference (Guidotti et al., 2018). Using gradient class activation map approach, I identified grey matter volume in the insula, striatum, thalamus, FA in cortico-subcortical fibers, and enlarged ventricles as crucial brain structural features for discriminating schizophrenia patients from controls, which are in agreement with earlier findings in schizophrenia.

Converging evidence have shown widespread grey matter reduction and cortical thickness thinning in frontal, temporal lobes, and subcortical regions including striatum and hippocampus (Bora et al., 2011; Haukvik et al., 2018; Koelkebeck et al., 2019; Mitelman, 2019; Pergola et al., 2015; Van Erp et al., 2018; Fenglian Zheng et al., 2019). Specifically, my results resembled previous meta-analysis findings that schizophrenia is featured with gray matter reduction at bilateral insula, medial frontal cortex, and the thalamus (Bora et al., 2011). Insula is the critical component of the salience network which is responsible for switching between default mode network and central execution network (Sridharan et al., 2008). Abnormalities in the frontal lobe (especially insula,

orbital prefrontal cortex, and anterior cingulate cortex), striatum, and thalamus suggested impairment in the cortico-striatal-thalamic loop circuits, which serve as a discrete regulatory loop circuit for salience network. Cerebellum lobule VI found in my results corresponds to the cerebellar contribution to the salience network (Habas et al., 2009). Together with my findings here, it supports salience network dysfunction hypothesis which impairs cognitive control, behavior and emotion, thereby leading to symptoms of schizophrenia (Fornito et al., 2012; Miyata, 2019; Palaniyappan et al., 2013; Palaniyappan and Liddle, 2012; Peters et al., 2016; Van Den Heuvel and Fornito, 2014).

In parallel, widespread FA was reported in dMRI meta-analysis studies with regional specificity at frontotemporal, interhemispheric and corticothalamic regions forming the cortico-striatal-thalamic loop circuits, which is in line with my findings from the FA maps and salience network dysfunction hypothesis (Cookey et al., 2014; Di Biase et al., 2020; Kelly et al., 2018). I also identified ventricles as significant regions from CSF and MD maps, which are in line with previous reports of ventricle enlargement (Gaser et al., 2004; Kempton et al., 2010; Kuo and Pogue-Geile, 2019; Wright et al., 2000). The findings of my study suggest that the developed 3D CNN model has the potential to identify crucial neuroanatomical features for classification of psychiatric illnesses such as schizophrenia from healthy controls and better understanding of the neural basis of schizophrenia.

3.4.5 Limitations

One limitation of this study is that the sample size is relatively modest especially for 3D CNN network training, which might result in less efficient feature extraction and lower generalizability. Registration error and down-sampling may ignore some subtle anatomical differences and low-level contextual features that could be important for

classification. The 2D CNN transfer learning approach adopted here did not contain any manipulation of the produced feature maps. Further research on deep feature fusion across dimensions and scales might improve the performance of pre-trained 2D CNN models. Future work in native brain space with data augmentation is needed to account for inter-subject anatomical variability and data quality variation across sites to improve generalizability.

3.5 Summary

To classify patients with schizophrenia and healthy controls using 3D brain MR images, I developed multimodal 3D CNN models with different architectures and utilized deep feature approach based on 2D pre-trained CNN. My study demonstrated the superiority of using 3D CNN models and multimodal deep learning features extracted from sMRI and dMRI data over approaches using handcrafted feature-based method and single neuroimaging modality. Based on the learned 3D CNN models, I further localized the crucial regions for classification which consisted of grey matter volume in insula, orbital prefrontal cortex, striatum, thalamus, FA in cortico-subcortical fiber tracts, and enlarged ventricles. These findings were in agreement with previous literature and supported the salience network/striatum dysfunction hypothesis in schizophrenia. This study highlighted the potential of CNN for automatic and efficient feature extraction from 3D brain structural imaging data and multimodal imaging information integration, providing an interpretable framework for objective imaging-based assays for individual-level classification in psychiatric disorders.

Despite that the 3D CNN models developed in this study achieved better performance than handcrafted feature-based machine learning and deep feature approach, the models remain shallow limited by the small training sample size and high training cost. To

further utilize the contextual information in neuroimaging via very deep networks which were pre-trained on natural images, new methods on decomposing 3D images into 2+1D were proposed in the following study.

Chapter 4 Applying Pre-trained 2D Networks to 3D Neuroimaging for Classification of Schizophrenia Patients and Controls

4.1. Introduction

Deep learning approaches such as Convolutional Neural Network (CNN) has been successfully applied on medical images for the classification of brain tumor (Nadeem et al., 2020), lung nodule (Kang et al., 2017), Alzheimer’s disease (M. Liu et al., 2018; Pan et al., 2020) and so on. CNN is capable of automatic feature learning and hence removes the subjectivity in feature selection for machine learning, which is particularly important for psychiatric disorders such as schizophrenia that have complex and widely distributed brain alterations (Arbabshirani et al., 2017). The deep model architecture and nonlinear layers of CNN also allow investigating the complicated data patterns of images (Lee et al., 2017). Nevertheless, the application of deep learning to classify psychiatric disorders is restricted due to the lack of representative slices and small sample size. There are no specific slices indicating differences between patients and healthy controls, which limits the training of 2D CNN models with slices. Moreover, boundary slices containing little brain regions are similar for both patients and healthy controls but have different labels and hence leading to the disconvergence of 2D CNN models trained with whole-brain slices. Applications of powerful pre-trained 2D CNN models to medical images are limited to specific 2D slices or regions of interest (Abidin et al., 2018; Qin et al., 2020a), causing a lack of applications for psychiatric disorder classification. Recent works on whole-brain MRI images have utilized 3D CNN models for classifying schizophrenia patients and healthy controls (Hu et al., 2020)(Oh et al., 2020). Yet, challenged by the high demand of computational costs and training sample

size, the architecture of 3D CNN models utilized remains shallow and therefore may not be able to extract the complicated data patterns.

To exploit the powerful 2D deep CNN pre-trained on ImageNet, I propose a framework that decomposes 3D neuroimages to 2+1D processing for the classification of schizophrenia patients and healthy controls. Specifically, 3D MRI images are decomposed to 2D slices with regard to neighboring voxel positions to resemble the characteristics of natural images. Firstly, feature maps are extracted from 2D slices of MRI metrics via a pre-trained 2D CNN network from three views (axial, coronal, and sagittal) and maxpooled according to decomposition positions. The extracted 2D feature maps of all slices are used to train an 1D network along the third dimension unprocessed by the 2D CNN network. Secondly, global pooling along the third dimension reduces the number of slices and channels to remove redundant information based on sparsely distributed activation patterns in the feature maps. Thirdly, channelwise convolution and slicewise convolution aggregate the contextual information in the unprocessed 1D dimension. Multi-view and multi-metric information are incorporated for the final prediction. The proposed approach overperforms handcrafted feature-based machine learning, 2D CNN models as well as 3D CNN models with better cross-validation results on publicly available Northwestern University Schizophrenia Dataset and independent testing results on a private dataset.

4.2. Related studies

Review papers (Arbabshirani et al., 2017) and (Winterburn et al., 2019) summarized previous studies for classifying schizophrenia patients and healthy controls using handcrafted feature-based machine learning. Voxel-based morphometry and cortical thickness are the most commonly used features extracted from structural MRI. Features

with high dimensionality are often processed with Principle Component Analysis (PCA) or knowledge-based ROI selection for dimensionality reduction before classification. The most widely used classifier is SVM. The performance of handcrafted feature-based machine learning varies among different datasets across studies and more importantly, the feature extraction and selection prior to classification might be non-reliable and non-generalizable when challenged by confounders such as disease duration, race, medication effect, and so on. Besides numerous work on handcrafted feature-based machine learning, there are also some recent works utilizing 3D CNN models trained from scratch on whole-brain MRI images (Hu et al., 2020) (Oh et al., 2020). Yet, the 3D CNN models utilized remain shallow and rather simple architectures due to the high computational costs and the requirement of a large sample size to train a model.

Pre-trained 2D CNN has been applied to multiple types of medical images such as digital mammograms (Huynh et al., 2016), X-ray (Rajpurkar et al., 2017), histological image (Mazo et al., 2018), computer tomography (Kim and MacKinnon, 2018), and MRI (Dawud et al., 2019) for various disease classification tasks. Due to the lack of available powerful networks pre-trained on medical images, most studies utilized models pre-trained with ImageNet (Morid et al., 2020). Finetune method was utilized with relatively large datasets that have more than 1000 images and the models were re-trained with input data. Deep feature method was utilized for relatively small datasets and deep features were extracted from the frozen pre-trained networks then classified with fully-connected layers or conventional classifiers such as SVM and logistic regression (LR) (Cheplygina et al., 2019; Morid et al., 2020). A few studies performed extra feature selection via pooling layers (Song et al., 2019; Zhu et al., 2019), or statistical methods (Qin et al., 2020b) to reduce the high dimensionality of extracted features. Most studies reported superior or comparable performance comparing to

handcrafted feature-based machine learning. Yet most of the studies were slice or ROI-based, in which specific slices or ROIs were selected to re-train the 2D networks or to extract features from 2D networks, limiting the application of such methods to psychiatric disorders which has no representative slices.

4.3. Methodology

The proposed framework is presented in detail in this section. The selected pre-trained 2D CNN model and feature map extraction procedure with image decomposition and feature maxpooling are introduced, followed by introduction to global pooling in slice and channel dimensions. Then the classification network consisting of channelwise and slicewise convolution is introduced. Lastly, multi-metric and multi-view fusion are introduced. The overall flowchart is presented in Figure 4.1.

Figure 4. 1 Framework of the proposed method.

Step (A) decomposed 3D MRI images into 2D slices regarding neighboring positions, extracted feature maps from Inception_resnet_v2 pre-trained on ImageNet dataset, and performed maxpooling on feature maps to retain the max values with regard to decomposition coordinates. Slice pooling and channel pooling in step (B) removed the redundant information via global pooling on the slice and channel dimension with information distribution over all training samples. Step (C) trained a 1D CNN model to

perform channelwise and slicewise convolution to further remove the redundant information on slice and channel dimension and integrate the information on the unprocessed view dimension. Predict fusion in step (C) merges information from multi brain metrics and multi views for final prediction.

4.3.1 Image decomposition, feature extraction and feature maxpooling

The 3D MRI volumes are decomposed into 2D slices for feature extraction via pre-trained networks. To stimulate the characteristics of natural images for effective and accurate feature extraction, the decomposition involves not only slice separation, but also downsampling according to neighboring voxel locations. Each 3D MRI image of size $121 \times 145 \times 121$ is downsampled into eight volumes of size $61 \times 73 \times 61$ with regard to voxel locations and then further separated as slices from axial, coronal and sagittal views. The downsampled images share similar contextual information of MRI images and have sharpened boundaries that resemble the attributes of natural images so that they better fit the 2D network trained by natural images.

Inception_resnet V2 is the pre-trained model adopted in this study for feature extraction. Inception_resnet V2 is one of the most powerful deep learning models for image classification tasks (Szegedy et al., 2017). It utilizes inception blocks which allows multi-level feature extraction at the same time and residual connections which addresses the degradation problem for training very deep networks. The architecture of Inception_resnet V2 is shown in Figure 4.1A.

Passing a slice through the pre-trained Inception_resnet V2 model in a forward manner, I get a feature map at the last convolutional layer. For eight downsampled volumes, I obtained eight sets of extracted feature maps $F^k(n, w, h, ch)$, $k = 1, 2, \dots, 8$. Maxpooling is performed across eight sets of feature maps as in equation (1) to retain the maximum values since the downsampled volumes share similar information with

close voxel coordinates in the original volume and maxpooling makes the retained feature insensitive to spatial locations.

$$F(n, w, h, ch) = \max_k \{F^k(n, w, h, ch)\} \quad (1)$$

where $F(n, w, h, ch)$ represents the set of feature maps that have maximum values pooled among eight sets of feature maps $F^k(n, w, h, ch)$ with element-wise values, n represents the slice index, $n \in [1, N]$, $N = 61$ for axial and sagittal views, $N = 73$ for coronal view, w, h, ch represent the width, height, channel indices of the feature maps respectively, $w \in [1, W]$, $h \in [1, H]$, $ch \in [1, CH]$, $W = 3$, $H = 3$, $CH = 1536$.

All 3D MRI images are converted into feature maps $F(n, w, h, ch)$ after image decomposition, feature extraction from the pre-trained model and maxpooling. Now I will further process them along the third dimension (view axis n) and channel dimension (channel axis ch) based on learning the 3D MRI training images in following sections.

4.3.2 Remove redundant information via global pooling in the slice and channel dimensions

For obtained feature maps at the last convolutional layer of the pre-trained network, the number of width and height tend to be small while the number of channels tends to be large. In my case, Inception_resnet V2 extract feature maps with dimension $3 \times 3 \times 1536$ at the last convolutional layer, where the number of width and height is 3 while the number of channels is 1536. The number of slices is also large as there was no pooling operation performed on the view axis. Information is sparsely distributed in extracted feature maps. Therefore, it is critical to remove the redundant information in the slice and channel dimension.

I propose to perform global pooling in slice dimension via equation (2). The values are summed up along width, height and channel dimension to obtain a representative value for each slice. The rectified linear units (ReLU) activation is utilized in the pre-trained network and therefore higher values in extracted feature maps correspond to higher responses to structures that are more important for classification. Slices from different positions of the 3D image cover different parts of the brain. Some slices may contain mostly background which results in small values in extracted feature maps. The redundant information is removed by discarding corresponding feature map extracted by such slices. Furthermore, I sum up the values over all training data to avoid overfitting to specific individuals. I found J desired indices of slice n' via equation (2) where $J = N/2$. The feature map is represented by $F(n', w, h, ch)$ with updated slice indices.

$$n' = \underset{n}{\operatorname{argmax}} \{ \sum_t^T \sum_{w=1}^W \sum_{h=1}^H \sum_{ch=1}^{CH} F_t(n, w, h, ch) \} \quad (2)$$

where $F_t(n, w, h, ch)$ represents the pooled feature maps obtained from equation (1) for subject t with element-wise values. W, H, CH represent the width, height, and channel, respectively. T represents the number of subjects (samples) in training data.

Global pooling in channel dimension is proposed via equation (3). The feature maps are summed along width and height dimension to form feature cubes for each channel in each slice. The feature cubes with small values which contain less information were discarded. I found K desired indices of channel ch' via equation (3) where $K = CH/4$. The feature map is represented by $F(n', w, h, ch')$ with updated channel indices.

$$ch' = \underset{ch}{\operatorname{argmax}} \{ \sum_t^T \sum_{w=1}^W \sum_{h=1}^H F_t(n', w, h, ch) \} \quad (3)$$

where $F_t(n', w, h, ch)$ represents the updated feature maps obtained from equation (2) for each subject t with element-wise values. W, H represent the width and height, respectively. T represents the number of subjects (samples) in training data.

4.3.3 Channelwise & slicewise convolution and multi-brain metric & multi-view fusion

To integrate the information on the view axis which was not processed by the pre-trained 2D CNN model and to further remove the redundant information in the channel and slice dimension, two types of convolution are proposed. Following equation (4), channelwise convolution performs $(P, 1, 1)$ convolution in slice, width and height dimension, and the number of channels is updated according to layers. With a small number of nodes chosen at the bottom layer, the dimensionality of channels is greatly reduced and hence the redundant information is removed. The convolutional kernel $(P, 1, 1)$ extracts contextual information from the slice dimension without interrupting the other two dimensions that have been well-processed by 2D networks.

$$F^l(n', ch'') = \sigma \left(\sum_{ch'=0}^{K-1} \sum_{p=-\frac{P-1}{2}}^{\frac{P-1}{2}} h(p, ch', ch'') F^{l-1}(n' + p, ch') + b(ch'') \right) \quad (4)$$

where F^l and F^{l-1} represents the feature map in the l -th layer and the previous layer. For symbolic simplicity, I omit indices w and h of $F(n', w, h, ch')$. $F^l(n', ch'')$ and $F^{l-1}(n' + p, ch')$ represent their element-wise value with slice and channel dimension coordinates. $h(\cdot)$ represents the weights of convolutional kernel connecting F^l and F^{l-1} , $b(\cdot)$ represents the bias term, $\sigma(\cdot)$ represents the nonlinear activation function, i.e., the ReLU activation function, ($\sigma(a) = \max(0, a)$), K represents the total number of channels in the input feature map, P represents the size of the convolutional kernel.

Equation (5) demonstrates slicewise convolution which performs (1,1,1) convolution in width, height and channel dimension while updating the number of slices by changing the number of nodes. The number of slices is gradually reduced in different layers and becomes comparable to width and height which were processed by the deep pre-trained network.

$$F^l(n'') = \sigma(\sum_{n'=0}^{J-1} h(n', n'') F^{l-1}(n') + b(n'')) \quad (5)$$

where F^l and F^{l-1} represents the feature map in the l -th layer and the previous layer. For symbolic simplicity, I omit indices w, h and ch'' of $F(n', w, h, ch'')$. $F^l(n'')$ and $F^{l-1}(n')$ represent their element-wise value with slice dimension coordinates. $h(\cdot)$ represents the weights of convolutional kernel connecting F^l and F^{l-1} , $b(\cdot)$ represents the bias term, $\sigma(\cdot)$ represents the nonlinear activation function ReLu, J represents the total number of slices in the $(l - 1)$ -th layer.

The input 3D images include three brain metrics: gray matter, white matter, and cerebrospinal fluid maps. Three brain metrics provide information from different perspectives of the brain structures. The 2D slices were decomposed from three views: axial, coronal, and sagittal. Therefore, the final prediction is determined by the majority vote of multi-brain metric and multi-view results.

4.4. Experimental settings and results

4.4.1 Experimental settings

4.4.1.1. Dataset

The same datasets are used for this study and the previous study in Chapter 3. The Northwestern University Schizophrenia Data and Software Tool (NUSDAST) is a repository of schizophrenia neuroimaging data collected from over 450 schizophrenia

patients and healthy controls, which is publicly available on SchizConnect platform (Kogan et al., 2016; Wang et al., 2013). Overall, 141schizophrenia patients and 134 healthy controls from this public dataset were included after quality control. A similar dataset from the Institute of Mental Health (IMH), Singapore, was included as an independent dataset (Ho et al., 2017a, 2017b). In this dataset, 148 schizophrenia and 76 healthy controls were included after quality control. Detailed scanning protocols can be found in Chapter 3.

Table 4. 1 Subject demographics of the datasets.

	NUSDAST		IMH	
	SZ	HC	SZ	HC
Subject number	141	134	148	76
Age(years)	35.1	32.9	32.7	31.3
mean (SD)	(12.8)	(14.0)	(9.0)	(9.8)
Sex (M/F)	90/51	72/62	102/46	47/29

Abbreviations: SZ - Schizophrenia Patients, HC - Healthy Controls, SD - standard deviation.

4.4.1.2. Preprocessing

Processing of the structural MRI data was performed using Computational Anatomy Toolbox in Statistical Parametric Mapping 12 (SPM12) for voxel-wise estimation of grey matter, white matter, and cerebrospinal fluid compartment (Kurth et al., 2015). Images with motion artifacts were excluded after visual quality control. Subject-level probability maps were obtained with the following steps: (i) skull stripping; (ii) linear (FLIRT) and nonlinear (FNIRT) registration to the Montreal Neurological Institute (MNI) 152 standard space (J L R Andersson et al., 2007); (iii) segmentation of the brain into gray matter, white matter, and cerebrospinal fluid compartments with 1.5 mm

isotropic resolution ; (iv) modulation by multiplying voxel values with the linear and nonlinear components of the Jacobian determinant.

4.4.1.3. Channelwise and slicewise convolutional neural network architecture

The feature map obtained after image decomposition, feature extraction and feature maxpooling in step A (Fig. 1) has dimension $N \times W \times H \times CH$, where $N = 61$ for axial and sagittal views, $N = 73$ for coronal view, $W = 3, H = 3, CH = 1536$. After global pooling in slice and channel dimension, the feature map has dimension $K \times W \times H \times J$, where $J = N/2, K = CH/4$.

Table 4. 2 Channelwise and slicewise convolutional neural network architecture.

Layer	Feature map dimension	Kernel size	Num. of nodes
C1	$J \times W \times H \times K$	(3,1,1)	32
S1	$J \times W \times H \times 32$	(1,1,1)	$J/2$
C2	$J/2 \times W \times H \times 32$	(3,1,1)	32
S2	$J/2 \times W \times H \times 32$	(1,1,1)	$J/4$
C3	$J/4 \times W \times H \times 32$	(3,1,1)	64
S3	$J/4 \times W \times H \times 64$	(1,1,1)	$J/8$
C4	$J/8 \times W \times H \times 64$	(1,1,1)	128
FC	$128WH(J/8)$	-	2

To further remove redundant information and integrate the information in slice dimension, I trained an 1D CNN model with channelwise convolution and slicewise convolution. The architecture is illustrated in Fig. 1C and input feature map dimension, kernel size, number of nodes in each layer is listed in Table 4.2. Channelwise convolution performs (3,1,1) convolution with an increasing number of nodes to extract deep features while slicewise convolution reduces the dimensionality of slice dimension by (1,1,1) convolutions with reducing number of nodes. The fully-

connected (FC) layer takes a vectorized input from the previous layer and generates two outputs as classification results. Binary_crossentropy loss and Stochastic gradient descent (SGD) optimizer were used for model training.

4.4.1.4. Performance evaluation

The performance is quantitatively determined via accuracy, sensitivity, specificity and area under the receiver operating characteristic curve (ROC-AUC). 5-fold cross-validation was utilized for multiple runs of training and performance evaluation, which averaged the test error over multiple train–test splits. Results were reported based on the average of ten repeats of 5-fold cross-validation to reduce randomness caused by the system. A random seed was assigned for data splitting to ensure that the same data were used for training and testing in each round. Independent testing results were obtained from the models achieved the highest cross-validation accuracy.

4.4.2 Compare with handcrafted feature-based machine learning

According to the literature, voxel-based morphometry is one of the most widely utilized handcrafted feature and SVM is the most widely applied classifier. To compare with the state of art approach using handcrafted feature-based machine learning, I used the grey matter, white matter, and cerebrospinal fluid probability maps extracted by cat12

Figure 4.2 Accuracy and ROC-AUC curve comparisons with previous methods.

toolkit and trained both linear and nonlinear SVM for classification. The classification results are presented in Figure 4. 2 and Table 4.3. Linear SVM achieved cross-validation accuracy 69.81%. Both linear and nonlinear SVM are not applicable for independent testing.

4.4.3 Compare with transfer learning approach with direct SVM

2D CNN models trained from scratch were not available due to the lack of representative slices in schizophrenia and disconvergence caused by confusing labels when using whole-brain data.

Deep feature approach utilizes features extracted from pre-trained CNN networks and performs classification with conventional classifiers such as SVM and LR, which provides a practical way for applying pre-trained 2D CNN models for the classification of schizophrenia patients and healthy controls using 3D MRI data. To compare with the benchmark deep feature approach, I implemented an SVM classifier to classify deep features. The feature maps extracted from pre-trained inception_resnet_v2 for each 2D slice for each of the three views (axial, coronal, and sagittal) and each of the three brain metrics (grey matter, white matter, and cerebrospinal fluid) were combined and flattened as a large feature vector at the individual level. Linear SVM was trained to classify the feature vectors and achieved accuracy 68.35%, which is ~16% lower comparing to my approach (Figure 4.2 and Table 4.3). Deep feature approach achieved high independent testing accuracy, but the sensitivity (85.14%) and specificity (44.74%) are greatly imbalanced.

4.4.4 Compare with 3D CNN models trained from scratch

3D CNN models employ 3D convolutional kernels to fully utilize the contextual information of 3D images. However, the development of 3D CNN was limited to simple

architecture and small image size due to the high computational cost. There are also no available pre-trained 3D CNN models. In my previous work, I proposed 3D Naïve CNN with different architectures trained from scratch (Hu et al., 2020). The model with the best performance employs the inception module and residual connection. Multi-channel inputs including grey matter, white matter, and cerebrospinal fluid probability maps are used to provide additional information for classification. The performance of the 3D Naïve CNN with the best performance is listed in Table 4.3. The 3D Naïve CNN consists of 19 layers while my approach utilized a 571-layer pre-trained network and an 8-layer network trained from scratch. My approach not only achieved ~5% improvement on accuracy than 3D Naïve CNN but also has fewer parameters and significantly lower computational cost.

Table 4. 3 Comparison with previous methods.

Method	Cross-validation results			Independent testing results		
	Accuracy	Specificity	Sensitivity	Accuracy	Specificity	Sensitivity
Linear SVM	69.81%	65.61%	73.77%	-	-	-
Nonlinear SVM	66.50%	68.58%	64.51%	-	-	-
Deep feature + direct SVM	68.35%	63.45%	73.05%	71.43%	44.74%	85.14%
3D CNN trained from scratch	79.27%	80.44%	78.15%	70.98%	63.16%	75.00%
Proposed approach	84.30%	84.54%	84.09%	70.09%	65.79%	72.30%

4.5. Discussion

I presented an efficient framework that processes 3D neuroimaging data by 2+1D network for the classification of schizophrenia patients and healthy controls. My approach utilizes the whole brain images instead of specific slices for classification which addresses the issue of no representative slice in schizophrenia and other psychiatric disorders. I proposed image decomposition and feature map maxpooling to

resemble the characteristics of natural images for fully-utilization of models pre-trained on the ImageNet dataset. Global pooling in slice and channel dimension removed the redundant information without interrupting the feature map spatial architecture. Channelwise and slicewise convolution further aggregate the contextual information in the third dimension unprocessed by the 2D network. Prediction fusion integrated multi-view and multi-metric information for the final prediction.

The classification results in previous studies vary due to different data selection and exclusion criteria, preprocessing protocols, and model implementation procedure (Arbabshirani et al., 2017; Rashid and Calhoun, 2020). Therefore, comparisons among handcrafted feature-based machine learning, 2D CNN models using deep feature approach, 3D CNN models trained from scratch and my 2+1D approach were illustrated on the same dataset in this study for a fair comparison. The proposed approach greatly outperformed handcrafted feature-based machine learning with a ~15% accuracy gap and 0.16 roc-auc value when compared to linear SVM trained with grey matter, white matter, and cerebrospinal fluid probability maps. Handcrafted feature-based machine learning approaches that extract features prior to the classification might not be sufficiently discriminative, especially for schizophrenia which has subtle, mixed and widespread brain anatomical changes (Rashid and Calhoun, 2020; Winterburn et al., 2019). On the other hand, CNN automatically extract features from the contextual information which mitigates the subjectivity and variability in selecting relevant features. Deep 2D CNN models trained from scratch were not available due to the lack of representative slices in schizophrenia and disconvergence caused by confusing labels when using whole-brain data. Therefore, I implemented a deep feature approach combined with direct SVM as the benchmark for approaches utilizing 2D CNN models. Deep feature approach takes advantage of networks pre-trained on large datasets and

enables the feature extraction for small datasets (Morid et al., 2020). Yet, the high dimensionality of the unprocessed view axis dimension and channel dimension limits the performance of deep feature approach. The proposed approach efficiently removes the redundant information and integrates the information in the unprocessed view dimension via three steps, achieving $\sim 16\%$ improvement on accuracy than the deep feature+SVM approach.

3D CNN models operate convolutions and pooling in a cubic manner with 3D feature volumes instead of 2D feature maps to fully utilize the contextual information of 3D images. However, the high computational cost and requirement of a large sample size for training prevent the development of very deep 3D CNN models and applications to datasets with a small sample size. My previous work trained a 19-layer 3D CNN model with inception modules and residual connections and resulted in 729,058 parameters (Hu et al., 2021, 2020). Another recent work trained an 8-layer sequential 3D CNN models with 873 subjects and has 1,246,434 trainable parameters (Oh et al., 2020). The training expenses increase exponentially when 3D CNN models get deeper and employs advanced architectures. The sample size required to train the model also increases greatly. Therefore, the current shallow 3D CNN models may not be able to fully extract the complicated data patterns. The proposed approach utilizes a very deep pre-trained 2D CNN model which has 571 layers to extract the feature maps from decomposed 2D slices and uncover the contextual information from the deep layers. As a result, my approach achieved higher accuracy than the 3D CNN models with fewer parameters and significantly lower computational cost. The framework highlights the possibility of utilizing very deep 2D networks on datasets with a small sample size and utilizing deep 2D networks with low computational cost.

I performed ablation analysis step by step to verify the usefulness of each step in the proposed framework, including image decomposition and feature maxpooling, global pooling in slice and channel dimension, slicewise convolution, convolutional network, multi-metric & multi-view fusion. Results presented in Table IV indicate that every step contributed significantly as all methods with an ablation have decreased accuracy and imbalanced specificity and sensitivity. Results without image decomposition and feature map maxpooling were obtained using 2D slices directly split from the 3D volumes without downsampling according to neighboring voxel locations and therefore no feature map maxpooling was performed. The ~9% accuracy gap comparing to the original approach verified the assumption that downsampling according to neighbor voxel positions sharpened the boundaries of MRI images and resembled the characteristics of natural images, leading to better fitting in 2D CNN models trained with the ImageNet dataset. Results without global pooling in slice and channel dimension has a ~ 4% accuracy gap and much higher computational cost as much more parameters were needed to train the 1D CNN model. The convolutional network plays the most important role as reflected by the ~13% accuracy gap. The ablation results were obtained by replacing the convolutional network with a linear SVM for classification. The results highlight the importance of engaging information in the view axis dimension and removing redundant information. The convolutional network enables the model to be trained in an end-to-end manner with steady performance. The ablation study on the slicewise convolution was performed by replacing the slicewise convolutional layers with local maxpooling layers. The reduced accuracy indicates the usefulness of using slicewise convolution to aggregate contextual information along the slice dimension unprocessed by the 2D networks. The improvement with multi-metric and multi-view fusion is also compelling (~11% gap in

accuracy), highlighting the critical role of multi-view processing of 3D images while classifying them in a 2D framework.

Despite the promising results, there are a few limitations of this study. The sample size is rather small for network training involving 3D convolutional layer, which might limit the performance of the model and result in low generalizability. The networks explored in this study are pre-trained on a natural image dataset Imagenet which is very different from medical images. Future work may explore networks pre-trained on medical images which share more similarity with MRI images.

Table 4. 4 Results for ablation study.

Method	Accuracy	Specificity	Sensitivity
No convolutional network	71.25%	74.62%	68.10%
No multi-metric & multi-view fusion	72.84%	66.80%	78.56%
No image decomposition and feature map maxpooling	75.44%	75.90%	75.00%
No global pooling in slice and channel dimension	79.84%	80.84%	78.86%
No slicewise convolution	80.31%	80.30%	80.29%
My approach	84.30%	84.54%	84.09%

Despite the promising results, there are a few limitations of this study. The sample size is rather small for network training involving 3D convolutional layer, which might limit the performance of the model and result in low generalizability. The networks explored in this study are pre-trained on a natural image dataset Imagenet which is very different from medical images. Future work may explore networks pre-trained on medical images which share more similarity with MRI images

4.6. Summary

I proposed an efficient framework for 3D neuroimaging classification with a deep 2D network pre-trained by huge natural image dataset ImageNet plus a 1D network trained by a small number of neuroimages, which addresses the challenging classification problem of psychiatric disorders that have no representative slice and limited number of training samples. The framework decomposed 3D neuroimaging data into 2+1D and proposed new pooling and convolution strategies to remove redundant information and integrate deep contextual information of the data. With promising results obtained, this study highlights the possibility of utilizing pre-trained deep 2D CNN for 3D neuroimaging classification and lays the foundation for computer-aid diagnosis of psychiatric disorders utilizing deep learning approaches.

Chapter 5 Conclusions and Future Work

5.1 Conclusions

Neuropsychiatric disorders are the leading causes of disability and mortality. Multimodal neuroimaging data plays an essential role on investigating the functional and structural brain changes. This thesis performed three studies with multimodal neuroimaging data and different analytic approaches to examine the brain alteration in stroke patients and construct frameworks for computer-aided diagnosis of schizophrenia.

The first study examined the brain functional activity and connectivity changes in patients post stroke and rehabilitation effect of MI-BCI and tDCS with functional MRI data using multiple statistical analysis approaches. In overall, stroke patients showed lower ALFF/FC at SMN and higher ALFF/ReHo at DMN at baseline. Reorganization of ALFF/ReHo were observed at SMN and DMN post intervention in MI-BCI group while MI-BCI+tDCS group showed no significant changes. Divergent association between intra SMN-DMN FC changes and FMA changes were observed in MI-BCI group and MI-BCI+tDCS group. My results validated the efficacy of both MI-BCI approach and MI-BCI+tDCS approaches while illustrating possible differential mechanisms between the two approaches.

The second study constructed 3D convolutional neural networks trained from scratch for classification of schizophrenia patients and healthy controls with structural MRI and diffusion MRI data. My study demonstrated the superiority of using 3D CNN models and multimodal deep learning features extracted from sMRI and dMRI data over approaches using handcrafted feature-based method and single neuroimaging modality. Based on the learned 3D CNN models, I further localized the crucial regions

for classification which consisted of grey matter volume in insula, orbital prefrontal cortex, striatum, thalamus, FA in cortico-subcortical fiber tracts, and enlarged ventricles. These findings were in agreement with previous literature and supported the salience network/striatum dysfunction hypothesis in schizophrenia.

The third study proposed an efficient framework for 3D neuroimaging classification with pre-trained 2D networks which addresses the classification problem of neuropsychiatric disorders which have no visible alterations on specific slices. The framework consists of image decomposition, feature extraction, feature maxpooling, global pooling in slice and channel dimension, channelwise convolution and slice-wise convolution. With promising results obtained, this study highlights the possibility of utilizing pre-trained deep 2D CNN for 3D neuroimaging classification and lays the foundation for computer-aid diagnosis of psychiatric disorders utilizing deep learning approaches.

Together, these studies illustrated multiple advanced analytic methods for multimodal neuroimaging data. Statistical analysis examined group-level brain functional activity and connectivity changes and associations with behavioural changes. Machine learning approaches including naïve 3D CNN and pre-trained 2D CNN build models for individual-level classification and prediction. The proposed framework lays the foundation for objective imaging-based assays for individual-level classification in neuropsychiatric disorders.

5.2 Future Directions

The proposed framework for both naïve 3D CNN and pre-trained 2D CNN could be extended to applications of various neuropsychiatric disorders such as depression, bipolar disease, and seizures. Establishing an objective approach for accurate

classification of such disorders could enforce early and accurate diagnosis and thus determine appropriate subsequent treatment. Furthermore, the models built with cross-sectional data could be extended to application of longitudinal data and thus support not only the diagnosis but also prognosis of neuropsychiatric disorders. Here I introduce two proposed future directions.

5.2.1. Prediction of clinical high-risk state for psychosis

To enforce early detection and treatment of psychoses in prodromal stage, an operationalized criteria, Clinical High-Risk (CHR) for psychosis, has been developed to identify subjects at enhanced “imminent development of a first-episode psychotic disorder” (Yung et al., 2005). The criteria apply to young patients who seek for help with prodromal symptoms. Meta-analysis suggest that about one third of the CHR patients will develop psychosis within five years while one third will have a clinical remission within two years (Fusar-Poli et al., 2012; Schultze-Lutter et al., 2015; Simon et al., 2013). Particularly, about 73% patients who transit to psychosis will develop schizophrenic psychoses (Fusar-Poli et al., 2013). Therefore, estimating the risk of developing psychosis at individual level offers great potential for enhancing clinical decision making and improving preventive interventions. However, there is a lack of risk prediction model adopted in clinical practice (Studerus et al., 2017). The complex disorders with large phenomenological, pathophysiological and etiological heterogeneity (Keshavan et al., 2011) and heterogeneous subgroups within CHR patients together with rather small sample sizes imposed great restrictions in developing predictive models with sufficient validity and clinical utility. Limited studies have incorporated machine learning models and neuroimaging data for predicting psychosis (Koutsouleris et al., 2015; Nieman et al., 2014). A recent study and its follow-up combining clinical data and neuroimaging data developed multimodal machine

learning approaches for predicting functional outcomes in CHP patients and achieved promising results (a balanced accuracy of 85.5%) for predicting psychosis when combining algorithmic and human predictions (Koutsouleris et al., 2020, 2018). Yet, there still exist a gap for applying more advanced machine learning techniques such as convolutional neural networks and utilizing pre-trained psychiatric disorder classification models.

Here, I propose two study schemes for predicting CHR converter and non-converter with convolutional neural networks on neuroimaging data. The first scheme utilizes 3D CNN models pre-trained with schizophrenia patients and healthy control data in study 2. Studies reported ventricular enlargement, reduction of cortical grey matter, and change in white matter are linked in prodromal youth who develop psychosis (Chung et al., 2017; Nägele et al., 2020). To utilize the overlapping brain alterations in schizophrenia patients and CHR patients who converted to psychosis, the 3D CNN model could be utilized for classifying converters and non-converters. The model could be utilized as a feature extractor to extract features from multimodal neuroimaging data for further processing and classifying. The second scheme utilizes the framework in study 3 which apply 2D pre-trained networks on 3D neuroimaging data. Considering the small sample size of CHR data in general, the framework in study 3 allows classifying converters and non-converters with powerful pre-trained models which might extract more ambiguous information from neuroimaging data.

5.2.2. Prediction of Alzheimer's disease

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders and is the leading cause of dementia in elderly (Association, 2016). There are currently estimated to be over 50 million people worldwide living with dementia. With rapid

growing of aged population, the number of people with dementia is expected to be more than 152 million by 2050, presenting a tremendous challenge to healthcare system globally (Fleming et al., 2020). Furthermore, so far there is no treatment available to prevent or slow down the pathological damage of AD on the brain. Therefore, early detection and intervention is a critical demand at the moment.

The hallmarks of AD include increased level of hyperphosphorylated tau and amyloid precursor protein (Harrington, 2012). MRI revealed the brain atrophy in hippocampus and entorhinal cortex (Du et al., 2004; Vasavada et al., 2015) and such brain abnormalities observed on MRI have been recommended for the consideration of AD diagnostic criteria (McKhann et al., 2011). Mild cognitive impairment (MCI) is the prodromal form of AD and is characterized by neurocognitive dysfunction, but not to the extent of dementia, and minor difficulties in functional ability (Sanford, 2017). Individuals with MCI are more likely to develop dementia. It is believed that early intervention at MCI or pre-clinical stage will slow down the progression of AD (X. Liu et al., 2018). Yet it remains a difficult to predict whether or when patients with MCI will progress to AD dementia at baseline due to the heterogeneous symptoms and brain alterations along the gradual progression. Classification among AD patients, patients with MCI and healthy controls have been investigated by previous studies with various machine learning techniques including conventional classifiers such as support vector machine (Fan et al., 2008; Salvatore et al., 2015), logistic regression (Casanova et al., 2011) and deep learning approaches such as convolutional neural network (Bae et al., 2020; Basaia et al., 2019), deep belief network (Ortiz et al., 2016) and so on.

Here I propose to design a multimodal regression model to provide accurate risk prediction of AD progression combining multimodal neuroimaging data and clinical cognitive measurements. Study 2 provided the 3D CNN framework study 3 provided

the 2D CNN framework. I aim to build a prognostic model upon the extracted features from 3D or 2D CNN to predict progression of MCI subjects in a time-to-event analysis setting and thus provide accurate prediction of AD prognosis.

Bibliography

- Abidin, A.Z., Deng, B., DSouza, A.M., Nagarajan, M.B., Coan, P., Wismüller, A., 2018. Deep transfer learning for characterizing chondrocyte patterns in phase contrast X-Ray computed tomography images of the human patellar cartilage. *Comput. Biol. Med.* 95, 24–33. <https://doi.org/10.1016/j.compbimed.2018.01.008>
- Addington, J., Heinssen, R., 2012. Prediction and prevention of psychosis in youth at clinical high risk. *Annu. Rev. Clin. Psychol.* 8, 269–289. <https://doi.org/10.1146/annurev-clinpsy-032511-143146>
- Allman, C., Amadi, U., Winkler, A.M., Wilkins, L., Filippini, N., Kischka, U., Stagg, C.J., Johansen-Berg, H., 2016. Ipsilesional anodal tDCS enhances the functional benefits of rehabilitation in patients after stroke. *Sci. Transl. Med.* 8, 1–21. <https://doi.org/10.1126/scitranslmed.aad5651>
- Andersson, Jesper L R, Jenkinson, M., Smith, S., 2007. Non-linear registration aka Spatial normalisation FMRIB Technial Report TR07JA2. FMRIB Anal. Gr. Univ. Oxford.
- Andersson, J L R, Jenkinson, M., Smith, S., 2007. Non-linear registration aka spatial normalisation. *FMRIB Tech. Rep. TRO7JA2* 22, 22.
- Ang, K.K., Chin, Z.Y., Wang, C., Guan, C., Zhang, H., 2012. Filter bank common spatial pattern algorithm on BCI competition IV datasets 2a and 2b. *Front. Neurosci.* 6, 39. <https://doi.org/10.3389/fnins.2012.00039>
- Ang, K.K., Guan, C., 2015. Brain-computer interface for neurorehabilitation of upper limb after stroke. *Proc. IEEE* 103, 944–953. <https://doi.org/10.1109/JPROC.2015.2415800>
- Ang, K.K., Guan, C., Chua, K.S.G., Ang, B.T., Kuah, C., Wang, C., Phua, K.S., Chin, Z.Y., Zhang, H., 2009. A clinical study of motor imagery-based brain-computer interface for upper limb robotic rehabilitation. *Proc. 31st Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. Eng. Futur. Biomed. EMBC 2009* 5981–5984. <https://doi.org/10.1109/IEMBS.2009.5335381>
- Ang, K.K., Guan, C., Phua, K.S., Wang, C., Zhou, L., Tang, K.Y., Ephraim Joseph, G.J., Keong Kuah, C.W., Geok Chua, K.S., 2014. Brain-computer interface-based robotic end effector system for wrist and hand rehabilitation: Results of a three-armed randomized controlled trial for chronic stroke. *Front. Neuroeng.* 7, 1–9. <https://doi.org/10.3389/fneng.2014.00030>
- Arbabshirani, M.R., Plis, S., Sui, J., Calhoun, V.D., 2017. Single subject prediction of brain disorders in neuroimaging: Promises and pitfalls. *Neuroimage* 145, 137–165. <https://doi.org/10.1016/j.neuroimage.2016.02.079>
- Arciniegas, D.B., Kaufer, D.I., Bachmann, D.L., Silver, J.M., Campbell, J.J., Coffey, C.E., Hart, J., McAllister, T.W., Restak, R.M., 2006. Core curriculum for training in behavioral neurology & neuropsychiatry. *J. Neuropsychiatry Clin. Neurosci.* 18, 6–13. <https://doi.org/10.1176/jnp.18.1.6>
- Ardekani, B.A., Tabesh, A., Sevy, S., Robinson, D.G., Bilder, R.M., Szeszko, P.R., 2011. Diffusion tensor imaging reliably differentiates patients with schizophrenia

- from healthy volunteers. *Hum. Brain Mapp.* 32, 1–9. <https://doi.org/10.1002/hbm.20995>
- Arzy, S., Danziger, S., 2014. The science of neuropsychiatry: Past, present, and future. *J. Neuropsychiatry Clin. Neurosci.* 26, 392–395. <https://doi.org/10.1176/appi.neuropsych.13120371>
- Association, A., 2016. 2016 Alzheimer's disease facts and figures. *Alzheimer's Dement.* 12, 459–509.
- Bae, J. Bin, Lee, S., Jung, W., Park, S., Kim, W., Oh, H., Han, J.W., Kim, G.E., Kim, J.S., Kim, J.H., Kim, K.W., 2020. Identification of Alzheimer's disease using a convolutional neural network model based on T1-weighted magnetic resonance imaging. *Sci. Rep.* 10, 22252. <https://doi.org/10.1038/s41598-020-79243-9>
- Basaia, S., Agosta, F., Wagner, L., Canu, E., Magnani, G., Santangelo, R., Filippi, M., 2019. Automated classification of Alzheimer's disease and mild cognitive impairment using a single MRI and deep neural networks. *NeuroImage. Clin.* 21, 101645. <https://doi.org/10.1016/j.nicl.2018.101645>
- Biswal, B., Zerrin Yetkin, F., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magn. Reson. Med.* 34, 537–541. <https://doi.org/10.1002/mrm.1910340409>
- Bockbrader, M.A., Francisco, G., Lee, R., Olson, J., Solinsky, R., Boninger, M.L., 2018. Brain Computer Interfaces in Rehabilitation Medicine. *PM R.* <https://doi.org/10.1016/j.pmrj.2018.05.028>
- Bora, E., Fornito, A., Radua, J., Walterfang, M., Seal, M., Wood, S.J., Yücel, M., Velakoulis, D., Pantelis, C., 2011. Neuroanatomical abnormalities in schizophrenia: A multimodal voxelwise meta-analysis and meta-regression analysis. *Schizophr. Res.* 127, 46–57. <https://doi.org/10.1016/j.schres.2010.12.020>
- Braun, N., Kranczioch, C., Liepert, J., Dettmers, C., Zich, C., Büsching, I., Debener, S., 2017. Motor Imagery Impairment in Postacute Stroke Patients. *Neural Plast.* 2017, 4653256. <https://doi.org/10.1155/2017/4653256>
- Brett, M., Anton, J.L., Valabregue, R., Poline, J.B., 2002. Region of interest analysis using an SPM toolbox, in: *NeuroImage. Sendai, Japan*, p. 497. [https://doi.org/http://dx.doi.org/10.1016/S1053-8119\(02\)90010-8](https://doi.org/http://dx.doi.org/10.1016/S1053-8119(02)90010-8)
- Brown, K.E., Neva, J.L., Feldman, S.J., Staines, W.R., Boyd, L.A., 2018. Sensorimotor integration in chronic stroke: Baseline differences and response to sensory training. *Restor. Neurol. Neurosci.* 36, 245–259. <https://doi.org/10.3233/RNN-170790>
- Buch, E., Weber, C., Cohen, L.G., Braun, C., Dimyan, M.A., Ard, T., Mellinger, J., Caria, A., Soekadar, S., Fourkas, A., Birbaumer, N., 2008. Think to move: A neuromagnetic brain-computer interface (BCI) system for chronic stroke. *Stroke* 39, 910–917. <https://doi.org/10.1161/STROKEAHA.107.505313>
- Buckner, R.L., Krienen, F.M., Castellanos, A., Diaz, J.C., Thomas Yeo, B.T., 2011. The organization of the human cerebellum estimated by intrinsic functional connectivity. *J. Neurophysiol.* 106, 2322–2345.

<https://doi.org/10.1152/jn.00339.2011>

- Bueteifisch, C.M., 2015. Role of the contralesional hemisphere in post-stroke recovery of upper extremity motor function. *Front. Neurol.* 6, 1–10. <https://doi.org/10.3389/fneur.2015.00214>
- Bundy, D.T., Souders, L., Baranyai, K., Leonard, L., Schalk, G., Coker, R., Moran, D.W., Huskey, T., Leuthardt, E.C., 2017. Contralesional Brain-Computer Interface Control of a Powered Exoskeleton for Motor Recovery in Chronic Stroke Survivors. *Stroke* 48, 1908–1915. <https://doi.org/10.1161/STROKEAHA.116.016304>
- Büteifisch, C.M., Netz, J., Weßling, M., Seitz, R.J., Hömberg, V., 2003. Remote changes in cortical excitability after stroke. *Brain* 126, 470–481. <https://doi.org/10.1093/brain/awg044>
- Butler, A.J., Shuster, M., O’Hara, E., Hurley, K., Middlebrooks, D., Guilkey, K., 2013. A meta-analysis of the efficacy of anodal transcranial direct current stimulation for upper limb motor recovery in stroke survivors. *J. Hand Ther.* 26, 162–171. <https://doi.org/10.1016/j.jht.2012.07.002>
- Casanova, R., Wagner, B., Whitlow, C.T., Williamson, J.D., Shumaker, S.A., Maldjian, J.A., Espeland, M.A., 2011. High dimensional classification of structural MRI Alzheimer’s disease data based on large scale regularization. *Front. Neuroinform.* 5, 22.
- Chen, J., Sun, D., Shi, Y., Jin, W., Wang, Y., Xi, Q., Ren, C., 2019. Dynamic alterations in spontaneous neural activity in multiple brain networks in subacute stroke patients: A resting-state fMRI study. *Front. Neurosci.* 13, 1–10. <https://doi.org/10.3389/fnins.2018.00994>
- Cheng, H.-J., Ng, K. K., Qian, X., Ji, F., Lu, Z., Teo, W. P., ... Zhou, J.H., 2021. Task-related brain functional network reconfigurations relate to motor recovery in chronic subcortical stroke. *Sci. Rep.*
- Cheplygina, V., de Bruijne, M., Pluim, J.P.W., 2019. Not-so-supervised: A survey of semi-supervised, multi-instance, and transfer learning in medical image analysis. *Med. Image Anal.* 54, 280–296. <https://doi.org/10.1016/j.media.2019.03.009>
- Chesney, E., Goodwin, G.M., Fazel, S., 2014. Risks of all-cause and suicide mortality in mental disorders: A meta-review. *World Psychiatry* 13, 153–160. <https://doi.org/10.1002/wps.20128>
- Chin, R., You, A.X., Meng, F., Zhou, J., Sim, K., 2018. Recognition of Schizophrenia with Regularized Support Vector Machine and Sequential Region of Interest Selection using Structural Magnetic Resonance Imaging. *Sci. Rep.* 8, 1–10. <https://doi.org/10.1038/s41598-018-32290-9>
- Chollet, F., 2017. Xception: Deep learning with depthwise separable convolutions. *Proc. - 30th IEEE Conf. Comput. Vis. Pattern Recognition, CVPR 2017* 2017-Janua, 1800–1807. <https://doi.org/10.1109/CVPR.2017.195>
- Chong, H.Y., Teoh, S.L., Wu, D.B.C., Kotirum, S., Chiou, C.F., Chaiyakunapruk, N., 2016. Global economic burden of schizophrenia: A systematic review. *Neuropsychiatr. Dis. Treat.* 12, 357–373. <https://doi.org/10.2147/NDT.S96649>

- Chong, J.S.X., Liu, S., Loke, Y.M., Hilal, S., Ikram, M.K., Xu, X., Tan, B.Y., Venketasubramanian, N., Chen, C.L.H., Zhou, J., 2017a. Influence of cerebrovascular disease on brain networks in prodromal and clinical Alzheimer's disease. *Brain* 140, 3012–3022. <https://doi.org/10.1093/brain/awx224>
- Chong, J.S.X., Ng, G.J.P., Lee, S.C., Zhou, J., 2017b. Salience network connectivity in the insula is associated with individual differences in interoceptive accuracy. *Brain Struct. Funct.* 222, 1635–1644.
- Chong, J.S.X., Ng, K.K., Tandir, J., Wang, C., Poh, J.-H., Lo, J.C., Chee, M.W.L., Zhou, J.H., 2019. Longitudinal changes in the cerebral cortex functional organization of healthy elderly. *J. Neurosci.* 39, 5534–5550.
- Chung, Y., Haut, K.M., He, G., van Erp, T.G.M., McEwen, S., Addington, J., Bearden, C.E., Cadenhead, K., Cornblatt, B., Mathalon, D.H., McGlashan, T., Perkins, D., Seidman, L.J., Tsuang, M., Walker, E., Woods, S.W., Cannon, T.D., 2017. Ventricular enlargement and progressive reduction of cortical gray matter are linked in prodromal youth who develop psychosis. *Schizophr. Res.* 189, 169–174. <https://doi.org/10.1016/j.schres.2017.02.014>
- Cookey, J., Bernier, D., Tibbo, P.G., 2014. White matter changes in early phase schizophrenia and cannabis use: An update and systematic review of diffusion tensor imaging studies. *Schizophr. Res.* 156, 137–142. <https://doi.org/10.1016/j.schres.2014.04.026>
- Cox, R.W., 1996. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Comput. Biomed. Res.* 29, 162–173. <https://doi.org/10.1006/cbmr.1996.0014>
- Daly, J.J., Wolpaw, J.R., 2008. Brain-computer interfaces in neurological rehabilitation. *Lancet Neurol.* 7, 1032–1043. [https://doi.org/10.1016/S1474-4422\(08\)70223-0](https://doi.org/10.1016/S1474-4422(08)70223-0)
- Dancause, N., Touvykine, B., Mansoori, B.K., 2015. Inhibition of the contralesional hemisphere after stroke: Reviewing a few of the building blocks with a focus on animal models, 1st ed, *Progress in Brain Research*. Elsevier B.V. <https://doi.org/10.1016/bs.pbr.2015.01.002>
- Dawud, A.M., Yurtkan, K., Oztoprak, H., 2019. Application of deep learning in neuroradiology: Brain haemorrhage classification using transfer learning. *Comput. Intell. Neurosci.* 2019. <https://doi.org/10.1155/2019/4629859>
- De Bruyn, N., Meyer, S., Kessner, S.S., Essers, B., Cheng, B., Thomalla, G., Peeters, A., Sunaert, S., Duprez, T., Thijs, V., Feys, H., Alaerts, K., Verheyden, G., 2018. Functional network connectivity is altered in patients with upper limb somatosensory impairments in the acute phase post stroke: A cross-sectional study. *PLoS One* 13, 1–18. <https://doi.org/10.1371/journal.pone.0205693>
- Del Barrio, V., 2016. Diagnostic and statistical manual of mental disorders, The Curated Reference Collection in Neuroscience and Biobehavioral Psychology. American Psychiatric Pub. <https://doi.org/10.1016/B978-0-12-809324-5.05530-9>
- Di Biase, M.A., Pantelis, C., Zalesky, A., 2020. White Matter Pathology in Schizophrenia, in: Kubicki, M., Shenton, M.E. (Eds.), *Neuroimaging in Schizophrenia*. Springer International Publishing, Cham, pp. 71–91. https://doi.org/10.1007/978-3-030-35206-6_4

- Di Lazzaro, V., Oliviero, A., Profice, P., Insola, A., Mazzone, P., Tonali, P., Rothwell, J.C., 1999. Direct demonstration of interhemispheric inhibition of the human motor cortex produced by transcranial magnetic stimulation. *Exp. Brain Res.* 124, 520–524. <https://doi.org/10.1007/s002210050648>
- Ding, X., Li, C.Y., Wang, Q.S., Du, F.Z., Ke, Z.W., Peng, F., Wang, J., Chen, L., 2014. Patterns in default-mode network connectivity for determining outcomes in cognitive function in acute stroke patients. *Neuroscience* 277, 637–646. <https://doi.org/10.1016/j.neuroscience.2014.07.060>
- Dodakian, L., Stewart, J.C., Cramer, S.C., 2014. Motor imagery during movement activates the brain more than movement alone after stroke: A pilot study. *J. Rehabil. Med.* 46, 843–848. <https://doi.org/10.2340/16501977-1844>
- Dodd, K.C., Nair, V.A., Prabhakaran, V., 2017. Role of the contralesional vs. Ipsilesional hemisphere in stroke recovery. *Front. Hum. Neurosci.* 11, 1–9. <https://doi.org/10.3389/fnhum.2017.00469>
- Dou, Q., Chen, H., Yu, L., Qin, J., Heng, P.A., 2017. Multilevel Contextual 3-D CNNs for False Positive Reduction in Pulmonary Nodule Detection. *IEEE Trans. Biomed. Eng.* 64, 1558–1567. <https://doi.org/10.1109/TBME.2016.2613502>
- Du, A.T., Schuff, N., Kramer, J.H., Ganzer, S., Zhu, X.P., Jagust, W.J., Miller, B.L., Reed, B.R., Mungas, D., Yaffe, K., Chui, H.C., Weiner, M.W., 2004. Higher atrophy rate of entorhinal cortex than hippocampus in AD. *Neurology* 62, 422–427. <https://doi.org/10.1212/01.wnl.0000106462.72282.90>
- El Hachoui, H., Visch-Brink, E.G., de Lau, L.M.L., van de Sandt-Koenderman, M.W.M.E., Nouwens, F., Koudstaal, P.J., Dippel, D.W.J., 2017. Screening tests for aphasia in patients with stroke: a systematic review. *J. Neurol.* 264, 211–220. <https://doi.org/10.1007/s00415-016-8170-8>
- Elsner, B., Kugler, J., Mehrholz, J., 2018. Transcranial direct current stimulation (tDCS) for upper limb rehabilitation after stroke: Future directions. *11 Medical and Health Sciences 1109 Neurosciences Alan Godfrey; Rodrigo Vitorio. J. Neuroeng. Rehabil.* 15, 106. <https://doi.org/10.1186/s12984-018-0459-7>
- Fan, Y., Batmanghelich, N., Clark, C.M., Davatzikos, C., Initiative, A.D.N., 2008. Spatial patterns of brain atrophy in MCI patients, identified via high-dimensional pattern classification, predict subsequent cognitive decline. *Neuroimage* 39, 1731–1743.
- Fanous, A.H., Amdur, R.L., O'Neill, F.A., Walsh, D., Kendler, K.S., 2012. Concordance between chart review and structured interview assessments of schizophrenic symptoms. *Compr. Psychiatry* 53, 275–279. <https://doi.org/10.1016/j.comppsy.2011.04.006>
- Feigin, V.L., Roth, G.A., Naghavi, M., Parmar, P., Krishnamurthi, R., Chugh, S., Mensah, G.A., Norrving, B., Shiue, I., Ng, M., Estep, K., Cercy, K., Murray, C.J.L., Forouzanfar, M.H., 2016. Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol.* 15, 913–924. [https://doi.org/10.1016/S1474-4422\(16\)30073-4](https://doi.org/10.1016/S1474-4422(16)30073-4)
- Feldman, H.M., Yeatman, J.D., Lee, E.S., Barde, L.H.F., Gaman-Bean, S., 2010.

- Diffusion tensor imaging: a review for pediatric researchers and clinicians. *J. Dev. Behav. Pediatr. JDBP* 31, 346.
- Ferbert, A., Priori, A., Rothwell, J.C., Day, B.L., Colebatch, J.G., Marsden, C.D., 1992. Interhemispheric inhibition of the human motor cortex. *J. Physiol.* 453, 525–546. <https://doi.org/10.1113/jphysiol.1992.sp019243>
- Ferro, J.M., Caeiro, L., Figueira, M.L., 2016. Neuropsychiatric sequelae of stroke. *Nat. Rev. Neurol.* 12, 269–280. <https://doi.org/10.1038/nrneurol.2016.46>
- Filippis, R. De, Carbone, E.A., Bruni, A., Pugliese, V., Segura-garcia, C., Fazio, P. De, 2019. Machine learning techniques in a structural and functional MRI diagnostic approach in schizophrenia : a systematic review. *Neuropsychiatr. Dis. Treat.* 15, 1605–1627.
- Fleming, R., Zeisel, J., Bennett, K., 2020. World Alzheimer Report 2020. Design, Dignity, Dementia: Dementia-related design and the built environment. Volume 1. *Alzheimer's Dis. Int.* 1, 96.
- Foong, R., Tang, N., Chew, E., Chua, K.S.G., Ang, K.K., Quek, C., Guan, C., Phua, K.S., Kuah, C.W.K., Deshmukh, V.A., Yam, L.H.L., Rajeswaran, D.K., 2020. Assessment of the Efficacy of EEG-Based MI-BCI with Visual Feedback and EEG Correlates of Mental Fatigue for Upper-Limb Stroke Rehabilitation. *IEEE Trans. Biomed. Eng.* 67, 786–795. <https://doi.org/10.1109/TBME.2019.2921198>
- Fornito, A., Yücel, M., Patti, J., Wood, S.J., Pantelis, C., 2009. Mapping grey matter reductions in schizophrenia: An anatomical likelihood estimation analysis of voxel-based morphometry studies. *Schizophr. Res.* 108, 104–113. <https://doi.org/10.1016/j.schres.2008.12.011>
- Fornito, A., Zalesky, A., Pantelis, C., Bullmore, E.T., 2012. Schizophrenia, neuroimaging and connectomics. *Neuroimage* 62, 2296–2314. <https://doi.org/10.1016/j.neuroimage.2011.12.090>
- Fugl-Meyer, A.R., Jääskö, L., Leyman, I., Olsson, S., 1975. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scand. J. Rehabil. Med.* 7, 13.
- Fuller, G., Manford, M., 2010. Subarachnoid haemorrhage, in: Fuller, G., Manford, M.B.T.-N. (Third E. (Eds.), *Neurology*. Churchill Livingstone, pp. 72–73. <https://doi.org/https://doi.org/10.1016/B978-0-7020-3224-0.00037-9>
- Fusar-Poli, P., Bechdolf, A., Taylor, M.J., Bonoldi, I., Carpenter, W.T., Yung, A.R., McGuire, P., 2013. At risk for schizophrenic or affective psychoses? A meta-analysis of DSM/ICD diagnostic outcomes in individuals at high clinical risk. *Schizophr. Bull.* 39, 923–932.
- Fusar-Poli, P., Bonoldi, I., Yung, A.R., Borgwardt, S., Kempton, M.J., Valmaggia, L., Barale, F., Caverzasi, E., McGuire, P., 2012. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Arch. Gen. Psychiatry* 69, 220–229.
- Gaser, C., Nenadic, I., Buchsbaum, B.R., Hazlett, E.A., Buchsbaum, M.S., 2004. Ventricular Enlargement in Schizophrenia Related to Volume Reduction of the Thalamus, Striatum, and Superior Temporal Cortex. *Am. J. Psychiatry* 161, 154–

156. <https://doi.org/10.1176/appi.ajp.161.1.154>
- Gerloff, C., Cohen, L.G., Floeter, M.K., Chen, R., Corwell, B., Hallett, M., 1998. Inhibitory influence of the ipsilateral motor cortex on responses to stimulation of the human cortex and pyramidal tract. *J. Physiol.* 510, 249–259. <https://doi.org/10.1111/j.1469-7793.1998.249bz.x>
- Goldsmith, S.K., Pellmar, T.C., Kleinman, A.M., Bunney, W.E., 2002. Committee on pathophysiology and prevention of adolescent and adult suicide, Board on Neuroscience and Behavioural Health, Institute of Medicine. Reducing Suicide A Natl. Imp.
- Golestani, A.M., Tymchuk, S., Demchuk, A., Goodyear, B.G., 2013. Longitudinal evaluation of resting-state fMRI after acute stroke with hemiparesis. *Neurorehabil. Neural Repair* 27, 153–163. <https://doi.org/10.1177/1545968312457827>
- Gong, B., Naveed, S., Hafeez, D.M., Afzal, K.I., Majeed, S., Abele, J., Nicolaou, S., Khosa, F., 2019. Neuroimaging in Psychiatric Disorders: A Bibliometric Analysis of the 100 Most Highly Cited Articles. *J. Neuroimaging* 29, 14–33. <https://doi.org/10.1111/jon.12570>
- Guidotti, R., Monreale, A., Ruggieri, S., Turini, F., Giannotti, F., Pedreschi, D., 2018. A survey of methods for explaining black box models. *ACM Comput. Surv.* 51. <https://doi.org/10.1145/3236009>
- Guilbert, J.J., 2003. The world health report 2002 - Reducing risks, promoting healthy life [2], Education for Health. World Health Organization. <https://doi.org/10.1080/1357628031000116808>
- Habas, C., Kamdar, N., Nguyen, D., Prater, K., Beckmann, C.F., Menon, V., Greicius, M.D., 2009. Distinct cerebellar contributions to intrinsic connectivity networks. *J. Neurosci.* 29, 8586–8594. <https://doi.org/10.1523/JNEUROSCI.1868-09.2009>
- Hachinski, V., 2018. The convergence of stroke and dementia. *Arq. Neuropsiquiatr.* 76, 849–852. <https://doi.org/10.1590/0004-282x20180148>
- Haijma, S. V., Van Haren, N., Cahn, W., Koolschijn, P.C.M.P., Hulshoff Pol, H.E., Kahn, R.S., 2013. Brain volumes in schizophrenia: A meta-analysis in over 18 000 subjects. *Schizophr. Bull.* 39, 1129–1138. <https://doi.org/10.1093/schbul/sbs118>
- Harrington, C.R., 2012. The molecular pathology of Alzheimer's disease. *Neuroimaging Clin.* 22, 11–22.
- Haukvik, U.K., Tamnes, C.K., Söderman, E., Agartz, I., 2018. Neuroimaging hippocampal subfields in schizophrenia and bipolar disorder: A systematic review and meta-analysis. *J. Psychiatr. Res.* 104, 217–226. <https://doi.org/10.1016/j.jpsychires.2018.08.012>
- He, K., Zhang, X., Ren, S., Sun, J., 2016. Deep residual learning for image recognition. *Proc. IEEE Comput. Soc. Conf. Comput. Vis. Pattern Recognit.* 2016-Decem, 770–778. <https://doi.org/10.1109/CVPR.2016.90>
- Ho, N. F., Iglesias, J.E., Sum, M.Y., Kuswanto, C.N., Sitoh, Y.Y., De Souza, J., Hong, Z., Fischl, B., Roffman, J.L., Zhou, J., Sim, K., Holt, D.J., 2017. Progression from selective to general involvement of hippocampal subfields in schizophrenia. *Mol. Psychiatry* 22, 142–152. <https://doi.org/10.1038/mp.2016.4>

- Ho, New Fei, Li, Z., Ji, F., Wang, M., Kuswanto, C.N., Sum, M.Y., Tng, H.Y., Sitoh, Y.Y., Sim, K., Zhou, J., 2017. Hemispheric lateralization abnormalities of the white matter microstructure in patients with schizophrenia and bipolar disorder. *J. Psychiatry Neurosci.* 42, 242–251. <https://doi.org/10.1503/jpn.160090>
- Hong, X., Lu, Z.K., Teh, I., Nasrallah, F.A., Teo, W.P., Ang, K.K., Phua, K.S., Guan, C., Chew, E., Chuang, K.H., 2017. Brain plasticity following MI-BCI training combined with tDCS in a randomized trial in chronic subcortical stroke subjects: A preliminary study. *Sci. Rep.* 7, 1–12. <https://doi.org/10.1038/s41598-017-08928-5>
- Hordacre, B., Moezzi, B., Ridding, M.C., 2018. Neuroplasticity and network connectivity of the motor cortex following stroke: A transcranial direct current stimulation study. *Hum. Brain Mapp.* 39, 3326–3339. <https://doi.org/10.1002/hbm.24079>
- Hu, M., Qian, X., Liu, S., Koh, A.J., Sim, K., Jiang, X., Guan, C., Zhou, J.H., 2021. Structural and diffusion MRI based schizophrenia classification using 2D pretrained and 3D naive Convolutional Neural Networks. *Schizophr. Res.*
- Hu, M., Sim, K., Zhou, J.H., Jiang, X., Guan, C., 2020. Brain MRI-based 3D Convolutional Neural Networks for Classification of Schizophrenia and Controls. *Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE Eng. Med. Biol. Soc. Annu. Int. Conf.* 2020, 1742–1745. <https://doi.org/10.1109/EMBC44109.2020.9176610>
- Huang, G., Liu, Z., Van Der Maaten, L., Weinberger, K.Q., 2017. Densely connected convolutional networks. *Proc. - 30th IEEE Conf. Comput. Vis. Pattern Recognition, CVPR 2017* 2017-Janua, 2261–2269. <https://doi.org/10.1109/CVPR.2017.243>
- Huynh, B.Q., Li, H., Giger, M.L., 2016. Digital mammographic tumor classification using transfer learning from deep convolutional neural networks. *J. Med. Imaging* 3, 034501. <https://doi.org/10.1117/1.jmi.3.3.034501>
- Iizuka, T., Fukasawa, M., Kameyama, M., 2019. Deep-learning-based imaging-classification identified cingulate island sign in dementia with Lewy bodies. *Sci. Rep.* 9, 1–9. <https://doi.org/10.1038/s41598-019-45415-5>
- Insel, T.R., 2009. Review series introduction Disruptive insights in psychiatry : transforming a clinical discipline. *J. Clin. Invest.* 119, 700–705. <https://doi.org/10.1172/JCI38832.700>
- Isobe, M., Miyata, J., Hazama, M., Fukuyama, H., Murai, T., Takahashi, H., 2016. Multimodal neuroimaging as a window into the pathological physiology of schizophrenia: Current trends and issues. *Neurosci. Res.* 102, 29–38. <https://doi.org/10.1016/j.neures.2015.07.009>
- James, S.L., Abate, D., Abate, K.H., Abay, S.M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R.S., Abebe, Z., Abera, S.F., Abil, O.Z., Abraha, H.N., Abu-Raddad, L.J., Abu-Rmeileh, N.M.E., Accrombessi, M.M.K., Acharya, D., Acharya, P., Ackerman, I.N., Adamu, A.A., Adebayo, O.M., Adekanmbi, V., Adetokunboh, O.O., Adib, M.G., Adsuar, J.C., Afanvi, K.A., Afarideh, M., Afshin, A., Agarwal, G., Agesa, K.M., Aggarwal, R., Aghayan, S.A., Agrawal, S., Ahmadi, A., Ahmadi, M., Ahmadi, H., Ahmed,

M.B., Aichour, A.N., Aichour, I., Aichour, M.T.E., Akinyemiju, T., Akseer, N., Al-Aly, Z., Al-Eyadhy, A., Al-Mekhlafi, H.M., Al-Raddadi, R.M., Alahdab, F., Alam, K., Alam, T., Alashi, A., Alavian, S.M., Alene, K.A., Alijanzadeh, M., Alizadeh-Navaei, R., Aljunid, S.M., Alkerwi, A., Alla, F., Allebeck, P., Alouani, M.M.L., Altirkawi, K., Alvis-Guzman, N., Amare, A.T., Aminde, L.N., Ammar, W., Amoako, Y.A., Anber, N.H., Andrei, C.L., Androudi, S., Animut, M.D., Anjomshoa, M., Ansha, M.G., Antonio, C.A.T., Anwari, P., Arabloo, J., Arauz, A., Aremu, O., Ariani, F., Armoon, B., Ärnlov, J., Arora, A., Artaman, A., Aryal, K.K., Asayesh, H., Asghar, R.J., Ataro, Z., Atre, S.R., Ausloos, M., Avila-Burgos, L., Avokpaho, E.F.G.A., Awasthi, A., Ayala Quintanilla, B.P., Ayer, R., Azzopardi, P.S., Babazadeh, A., Badali, H., Badawi, A., Bali, A.G., Ballesteros, K.E., Ballew, S.H., Banach, M., Banoub, J.A.M., Banstola, A., Barac, A., Barboza, M.A., Barker-Collo, S.L., Bärnighausen, T.W., Barrero, L.H., Baune, B.T., Bazargan-Hejazi, S., Bedi, N., Beghi, E., Behzadifar, Masoud, Behzadifar, Meysam, Béjot, Y., Belachew, A.B., Belay, Y.A., Bell, M.L., Bello, A.K., Bensenor, I.M., Bernabe, E., Bernstein, R.S., Beuran, M., Beyranvand, T., Bhala, N., Bhattarai, S., Bhaumik, S., Bhutta, Z.A., Biadgo, B., Bijani, A., Bikbov, B., Bilano, V., Bililign, N., Bin Sayeed, M.S., Bisanzio, D., Blacker, B.F., Blyth, F.M., Bou-Orm, I.R., Boufous, S., Bourne, R., Brady, O.J., Brainin, M., Brant, L.C., Brazinova, A., Breitborde, N.J.K., Brenner, H., Briant, P.S., Briggs, A.M., Briko, A.N., Britton, G., Brugha, T., Buchbinder, R., Busse, R., Butt, Z.A., Cahuana-Hurtado, L., Cano, J., Cárdenas, R., Carrero, J.J., Carter, A., Carvalho, F., Castañeda-Orjuela, C.A., Castillo Rivas, J., Castro, F., Catalá-López, F., Cercy, K.M., Cerin, E., Chaiah, Y., Chang, A.R., Chang, H.Y., Chang, J.C., Charlson, F.J., Chattopadhyay, A., Chattu, V.K., Chaturvedi, P., Chiang, P.P.C., Chin, K.L., Chitheer, A., Choi, J.Y.J., Chowdhury, R., Christensen, H., Christopher, D.J., Cicuttini, F.M., Ciobanu, L.G., Cirillo, M., Claro, R.M., Collado-Mateo, D., Cooper, C., Coresh, J., Cortesi, P.A., Cortinovis, M., Costa, M., Cousin, E., Criqui, M.H., Cromwell, E.A., Cross, M., Crump, J.A., Dadi, A.F., Dandona, L., Dandona, R., Dargan, P.I., Daryani, A., Das Gupta, Rajat, Das Neves, J., Dasa, T.T., Davey, G., Davis, A.C., Davitoiu, D.V., De Courten, B., De La Hoz, F.P., De Leo, D., De Neve, J.W., Degefa, M.G., Degenhardt, L., Deiparine, S., Dellavalle, R.P., Demoz, G.T., Deribe, K., Derveniz, N., Des Jarlais, D.C., Dessie, G.A., Dey, S., Dharmaratne, S.D., Dinberu, M.T., Dirac, M.A., Djalalinia, S., Doan, L., Dokova, K., Doku, D.T., Dorsey, E.R., Doyle, K.E., Driscoll, T.R., Dubey, M., Dubljanin, E., Duken, E.E., Duncan, B.B., Duraes, A.R., Ebrahimi, H., Ebrahimpour, S., Echko, M.M., Edvardsson, D., Effiong, A., Ehrlich, J.R., El Bcheraoui, C., El Sayed Zaki, M., El-Khatib, Z., Elkout, H., Elyazar, I.R.F., Enayati, A., Endries, A.Y., Er, B., Erskine, H.E., Eshrati, B., Eskandarieh, S., Esteghamati, A., Esteghamati, S., Fakhim, H., Fallah Omrani, V., Faramarzi, M., Fareed, M., Farhadi, F., Farid, T.A., Farinha, C.S.E., Farioli, A., Faro, A., Farvid, M.S., Farzadfar, F., Feigin, V.L., Fentahun, N., Fereshtehnejad, S.M., Fernandes, E., Fernandes, J.C., Ferrari, A.J., Feyissa, G.T., Filip, I., Fischer, F., Fitzmaurice, C., Foigt, N.A., Foreman, K.J., Fox, J., Frank, T.D., Fukumoto, T., Fullman, N., Fürst, T., Furtado, J.M., Futran, N.D., Gall, S., Ganji, M., Gankpe, F.G., Garcia-Basteiro, A.L., Gardner, W.M., Gebre, A.K., Gebremedhin, A.T., Gebremichael, T.G., Gelano, T.F., Geleijnse, J.M., Genova-Maleras, R., Geramo, Y.C.D., Gething, P.W., Gezae, K.E., Ghadiri, K., Ghasemi Falavarjani, K., Ghasemi-Kasman, M., Ghimire, M., Ghosh, R., Ghoshal, A.G., Giampaoli, S., Gill, P.S., Gill, T.K., Ginawi, I.A., Giussani, G., Gnedovskaya, E. V., Goldberg, E.M., Goli, S., Gómez-

Dantés, H., Gona, P.N., Gopalani, S.V., Gorman, T.M., Goulart, A.C., Goulart, B.N.G., Grada, A., Grams, M.E., Grosso, G., Gugnani, H.C., Guo, Y., Gupta, P.C., Gupta, Rahul, Gupta, Rajeev, Gupta, T., Gyawali, B., Haagsma, J.A., Hachinski, V., Hafezi-Nejad, N., Haghparast Bidgoli, H., Hagos, T.B., Hailu, G.B., Haj-Mirzaian, Arvin, Haj-Mirzaian, Arya, Hamadeh, R.R., Hamidi, S., Handal, A.J., Hankey, G.J., Hao, Y., Harb, H.L., Harikrishnan, S., Haro, J.M., Hasan, M., Hassankhani, H., Hassen, H.Y., Havmoeller, R., Hawley, C.N., Hay, R.J., Hay, S.I., Hedayatizadeh-Omran, A., Heibati, B., Hendrie, D., Henok, A., Herteliu, C., Heydarpour, S., Hibstu, D.T., Hoang, H.T., Hoek, H.W., Hoffman, H.J., Hole, M.K., Homaie Rad, E., Hoogar, P., Hosgood, H.D., Hosseini, S.M., Hosseinzadeh, M., Hostiuc, M., Hostiuc, S., Hotez, P.J., Hoy, D.G., Hsairi, M., Htet, A.S., Hu, G., Huang, J.J., Huynh, C.K., Iburg, K.M., Ikeda, C.T., Ileanu, B., Ilesanmi, O.S., Iqbal, U., Irvani, S.S.N., Irvine, C.M.S., Mohammed, Sheikh, Islam, S., Islami, F., Jacobsen, K.H., Jahangiry, L., Jahanmehr, N., Jain, S.K., Jakovljevic, M., Javanbakht, M., Jayatilleke, A.U., Jeemon, P., Jha, R.P., Jha, V., Ji, J.S., Johnson, C.O., Jonas, J.B., Jozwiak, J.J., Jungari, S.B., Jürisson, M., Kabir, Z., Kadel, R., Kahsay, A., Kalani, R., Kanchan, T., Karami, M., Karami Matin, B., Karch, A., Karema, C., Karimi, N., Karimi, S.M., Kasaeian, A., Kassa, D.H., Kassa, G.M., Kassa, T.D., Kassebaum, N.J., Katikireddi, S.V., Kawakami, N., Kazemi Karyani, A., Keighobadi, M.M., Keiyoro, P.N., Kemmer, L., Kemp, G.R., Kengne, A.P., Keren, A., Khader, Y.S., Khafaei, B., Khafaie, M.A., Khajavi, A., Khalil, I.A., Khan, E.A., Khan, M.S., Khan, M.A., Khang, Y.H., Khazaei, M., Khoja, A.T., Khosravi, A., Khosravi, M.H., Kiadaliri, A.A., Kiirithio, D.N., Kim, C. Il, Kim, D., Kim, P., Kim, Y.E., Kim, Y.J., Kimokoti, R.W., Kinfu, Y., Kisa, A., Kissimova-Skarbek, K., Kivimäki, M., Knudsen, A.K.S., Kocarnik, J.M., Kochhar, S., Kokubo, Y., Kolola, T., Kopec, J.A., Kosen, S., Kotsakis, G.A., Koul, P.A., Koyanagi, A., Kravchenko, M.A., Krishan, K., Krohn, K.J., Kuate Defo, B., Kucuk Bicer, B., Kumar, G.A., Kumar, M., Kyu, H.H., Lad, D.P., Lad, S.D., Lafranconi, A., Laloo, R., Lallukka, T., Lami, F.H., Lansingh, V.C., Latifi, A., Lau, K.M.M., Lazarus, J. V., Leasher, J.L., Ledesma, J.R., Lee, P.H., Leigh, J., Leung, J., Levi, M., Lewycka, S., Li, S., Li, Y., Liao, Y., Liben, M.L., Lim, L.L., Lim, S.S., Liu, S., Lodha, R., Looker, K.J., Lopez, A.D., Lorkowski, S., Lotufo, P.A., Low, N., Lozano, R., Lucas, T.C.D., Lucchesi, L.R., Lunevicius, R., Lyons, R.A., Ma, S., Macarayan, E.R.K., Mackay, M.T., Madotto, F., Magdy Abd El Razek, H., Magdy Abd El Razek, M., Maghavani, D.P., Mahotra, N.B., Mai, H.T., Majdan, M., Majdzadeh, R., Majeed, A., Malekzadeh, R., Malta, D.C., Mamun, A.A., Manda, A.L., Manguerra, H., Manhertz, T., Mansournia, M.A., Mantovani, L.G., Mapoma, C.C., Maravilla, J.C., Marcenes, W., Marks, A., Martins-Melo, F.R., Martopullo, I., März, W., Marzan, M.B., Mashamba-Thompson, T.P., Massenburg, B.B., Mathur, M.R., Matsushita, K., Maulik, P.K., Mazidi, M., McAlinden, C., McGrath, J.J., McKee, M., Mehndiratta, M.M., Mehrotra, R., Mehta, K.M., Mehta, V., Mejia-Rodriguez, F., Mekonen, T., Melese, A., Melku, M., Meltzer, M., Memiah, P.T.N., Memish, Z.A., Mendoza, W., Mengistu, D.T., Mengistu, G., Mensah, G.A., Mereta, S.T., Meretoja, A., Meretoja, T.J., Mestrovic, T., Mezerji, N.M.G., Miazgowski, B., Miazgowski, T., Millear, A.I., Miller, T.R., Miltz, B., Mini, G.K., Mirarefin, M., Mirrahimov, E.M., Misganaw, A.T., Mitchell, P.B., Mitiku, H., Moazen, B., Mohajer, B., Mohammad, K.A., Mohammadifard, N., Mohammadnia-Afrouzi, M., Mohammed, M.A., Mohammed, Shafiu, Mohebi, F., Moitra, M., Mokdad, A.H., Molokhia, M., Monasta, L., Moodley, Y., Moosazadeh, M., Moradi, G., Moradi-Lakeh, M.,

Moradinazar, M., Moraga, P., Morawska, L., Moreno Velásquez, I., Morgado-Da-Costa, J., Morrison, S.D., Moschos, M.M., Mousavi, S.M., Mruts, K.B., Muche, A.A., Muchie, K.F., Mueller, U.O., Muhammed, O.S., Mukhopadhyay, S., Muller, K., Mumford, J.E., Murhekar, M., Musa, J., Musa, K.I., Mustafa, G., Nabhan, A.F., Nagata, C., Naghavi, M., Naheed, A., Nahvijou, A., Naik, G., Naik, N., Najafi, F., Naldi, L., Nam, H.S., Nangia, V., Nansseu, J.R., Nascimento, B.R., Natarajan, G., Neamati, N., Negoi, I., Negoi, R.I., Neupane, S., Newton, C.R.J., Ngunjiri, J.W., Nguyen, A.Q., Nguyen, Ha Thu, Nguyen, H.L.T., Nguyen, Huong Thanh, Nguyen, L.H., Nguyen, M., Nguyen, N.B., Nguyen, S.H., Nichols, E., Ningrum, D.N.A., Nixon, M.R., Nolutshungu, N., Nomura, S., Norheim, O.F., Noroozi, M., Norrving, B., Noubiap, J.J., Nouri, H.R., Nourollahpour Shiadeh, M., Nowroozi, M.R., Nsoesie, E.O., Nyasulu, P.S., Odell, C.M., Ofori-Asenso, R., Ogbo, F.A., Oh, I.H., Oladimeji, O., Olagunju, A.T., Olagunju, T.O., Olivares, P.R., Olsen, H.E., Olusanya, B.O., Ong, K.L., Ong, S.K., Oren, E., Ortiz, A., Ota, E., Otstavnov, S.S., øverland, S., Owolabi, M.O., Mahesh, P.A., Pacella, R., Pakpour, A.H., Pana, A., Panda-Jonas, S., Parisi, A., Park, E.K., Parry, C.D.H., Patel, S., Pati, S., Patil, S.T., Patle, A., Patton, G.C., Paturi, V.R., Paulson, K.R., Pearce, N., Pereira, D.M., Perico, N., Pesudovs, K., Pham, H.Q., Phillips, M.R., Pigott, D.M., Pillay, J.D., Piradov, M.A., Pirsaeheb, M., Pishgar, F., Plana-Ripoll, O., Plass, D., Polinder, S., Popova, S., Postma, M.J., Pourshams, A., Poustchi, H., Prabhakaran, D., Prakash, S., Prakash, V., Purcell, C.A., Purwar, M.B., Qorbani, M., Quistberg, D.A., Radfar, A., Rafay, A., Rafiei, A., Rahim, F., Rahimi, K., Rahimi-Movaghar, A., Rahimi-Movaghar, V., Rahman, M., Ur Rahman, M.H., Rahman, M.A., Rahman, S.U., Rai, R.K., Rajati, F., Ram, U., Ranjan, P., Ranta, A., Rao, P.C., Rawaf, D.L., Rawaf, S., Reddy, K.S., Reiner, R.C., Reinig, N., Reitsma, M.B., Remuzzi, G., Renzaho, A.M.N., Resnikoff, S., Rezaei, S., Rezai, M.S., Ribeiro, A.L.P., Robinson, S.R., Roeber, L., Ronfani, L., Roshandel, G., Rostami, A., Roth, G.A., Roy, A., Rubagotti, E., Sachdev, P.S., Sadat, N., Saddik, B., Sadeghi, E., Saedi Moghaddam, S., Safari, H., Safari, Y., Safari-Faramani, R., Safdarian, M., Safi, S., Safiri, S., Sagar, R., Sahebkar, A., Sahraian, M.A., Sajadi, H.S., Salam, N., Salama, J.S., Salamati, P., Saleem, K., Saleem, Z., Salimi, Y., Salomon, J.A., Salvi, S.S., Salz, I., Samy, A.M., Sanabria, J., Sang, Y., Santomauro, D.F., Santos, I.S., Santos, J.V., Santric Milicevic, M.M., Sao Jose, B.P., Sardana, M., Sarker, A.R., Sarrafzadegan, N., Sartorius, B., Sarvi, S., Sathian, B., Satpathy, M., Sawant, A.R., Sawhney, M., Saxena, S., Saylan, M., Schaeffner, E., Schmidt, M.I., Schneider, I.J.C., Schöttker, B., Schwebel, D.C., Schwendicke, F., Scott, J.G., Sekerija, M., Sepanlou, S.G., Serván-Mori, E., Seyedmousavi, S., Shabaninejad, H., Shafieesabet, A., Shahbazi, M., Shaheen, A.A., Shaikh, M.A., Shams-Beyranvand, M., Shamsi, M., Shamsizadeh, M., Sharafi, H., Sharafi, K., Sharif, M., Sharif-Alhoseini, M., Sharma, M., Sharma, R., She, J., Sheikh, A., Shi, P., Shibuya, K., Shigematsu, M., Shiri, R., Shirkoochi, R., Shishani, K., Shiue, I., Shokraneh, F., Shoman, H., Shrim, M.G., Si, S., Siabani, S., Siddiqi, T.J., Sigfusdottir, I.D., Sigurvinsdottir, R., Silva, J.P., Silveira, D.G.A., Singam, N.S.V., Singh, J.A., Singh, N.P., Singh, V., Sinha, D.N., Skiadaresi, E., Slepak, E.L.N., Sliwa, K., Smith, D.L., Smith, M., Soares Filho, A.M., Sobaih, B.H., Sobhani, S., Sobngwi, E., Soneji, S.S., Soofi, M., Soosaraei, M., Sorensen, R.J.D., Soriano, J.B., Soyiri, I.N., Sposato, L.A., Sreeramareddy, C.T., Srinivasan, V., Stanaway, J.D., Stein, D.J., Steiner, C., Steiner, T.J., Stokes, M.A., Stovner, L.J., Subart, M.L., Sudaryanto, A., Sufiyan, M.B., Sunguya, B.F., Sur, P.J., Sutradhar, I., Sykes, B.L., Sylte, D.O., Tabarés-Seisdedos, R., Tadakamadla, S.K., Tadesse, B.T., Tandon,

- N., Tassew, S.G., Tavakkoli, M., Taveira, N., Taylor, H.R., Tehrani-Banihashemi, A., Tekalign, T.G., Tekelemedhin, S.W., Tekle, M.G., Temesgen, H., Temsah, M.H., Temsah, O., Terkawi, A.S., Teweldemedhin, M., Thankappan, K.R., Thomas, N., Tilahun, B., To, Q.G., Tonelli, M., Topor-Madry, R., Topouzis, F., Torre, A.E., Tortajada-Girbés, M., Touvier, M., Tovani-Palone, M.R., Towbin, J.A., Tran, B.X., Tran, K.B., Troeger, C.E., Truelsen, T.C., Tsilimbaris, M.K., Tsoi, D., Tudor Car, L., Tuzcu, E.M., Ukwaja, K.N., Ullah, I., Undurraga, E.A., Unutzer, J., Updike, R.L., Usman, M.S., Uthman, O.A., Vaduganathan, M., Vaezi, A., Valdez, P.R., Varughese, S., Vasankari, T.J., Venketasubramanian, N., Villafaina, S., Violante, F.S., Vladimirov, S.K., Vlassov, V., Vollset, S.E., Vosoughi, K., Vujcic, I.S., Wagneu, F.S., Waheed, Y., Waller, S.G., Wang, Y., Wang, Y.P., Weiderpass, E., Weintraub, R.G., Weiss, D.J., Weldegebreal, F., Weldegewergs, K.G., Werdecker, A., West, T.E., Whiteford, H.A., Widecka, J., Wijeratne, T., Wilner, L.B., Wilson, S., Winkler, A.S., Wiyeh, A.B., Wiysonge, C.S., Wolfe, C.D.A., Woolf, A.D., Wu, S., Wu, Y.C., Wyper, G.M.A., Xavier, D., Xu, G., Yadgir, S., Yadollahpour, A., Yahyazadeh Jabbari, S.H., Yamada, T., Yan, L.L., Yano, Y., Yaseri, M., Yasin, Y.J., Yeshaneh, A., Yimer, E.M., Yip, P., Yisma, E., Yonemoto, N., Yoon, S.J., Yotebieng, M., Younis, M.Z., Yousefifard, M., Yu, C., Zadnik, V., Zaidi, Z., Zaman, S. Bin, Zamani, M., Zare, Z., Zeleke, A.J., Zenebe, Z.M., Zhang, K., Zhao, Z., Zhou, M., Zodpey, S., Zucker, I., Vos, T., Murray, C.J.L., 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 Diseases and Injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 392, 1789–1858. [https://doi.org/10.1016/S0140-6736\(18\)32279-7](https://doi.org/10.1016/S0140-6736(18)32279-7)
- Kalaria, R.N., Akinyemi, R., Ihara, M., 2016. Stroke injury, cognitive impairment and vascular dementia. *Biochim. Biophys. Acta - Mol. Basis Dis.* 1862, 915–925. <https://doi.org/10.1016/j.bbadis.2016.01.015>
- Kang, G., Liu, K., Hou, B., Zhang, N., 2017. 3D multi-view convolutional neural networks for lung nodule classification. *PLoS One* 12, e0188290–e0188290. <https://doi.org/10.1371/journal.pone.0188290>
- Kase, C.S., Mohr, J.P., Caplan, L.R., 2004. Intracerebral Hemorrhage, in: Mohr, J.P., Choi, D.W., Grotta, J.C., Weir, B., Wolf, P.A.B.T.-S. (Fourth E. (Eds.), *Stroke: Pathophysiology, Diagnosis, and Management*. Churchill Livingstone, Philadelphia, pp. 327–376. <https://doi.org/10.1016/B0-44-306600-0/50017-1>
- Kashiwagi, F.T., El Dib, R., Gomaa, H., Gawish, N., Suzumura, E.A., Da Silva, T.R., Winckler, F.C., De Souza, J.T., Conforto, A.B., Luvizutto, G.J., Bazan, R., 2018. Noninvasive Brain Stimulation for Unilateral Spatial Neglect after Stroke: A Systematic Review and Meta-Analysis of Randomized and Nonrandomized Controlled Trials. *Neural Plast.* 2018. <https://doi.org/10.1155/2018/1638763>
- Kelly, S., Jahanshad, N., Zalesky, A., Kochunov, P., Agartz, I., Alloza, C., Andreassen, O.A., Arango, C., Banaj, N., Bouix, S., Bousman, C.A., Brouwer, R.M., Bruggemann, J., Bustillo, J., Cahn, W., Calhoun, V., Cannon, D., Carr, V., Catts, S., Chen, J., Chen, J.X., Chen, X., Chiapponi, C., Cho, K.K., Ciullo, V., Corvin, A.S., Crespo-Facorro, B., Cropley, V., De Rossi, P., Diaz-Caneja, C.M., Dickie, E.W., Ehrlich, S., Fan, F.M., Faskowitz, J., Fatouros-Bergman, H., Flyckt, L., Ford, J.M., Fouche, J.P., Fukunaga, M., Gill, M., Glahn, D.C., Gollub, R., Goudzwaard,

- E.D., Guo, H., Gur, R.E., Gur, R.C., Gurholt, T.P., Hashimoto, R., Hatton, S.N., Henskens, F.A., Hibar, D.P., Hickie, I.B., Hong, L.E., Horacek, J., Howells, F.M., Hulshoff Pol, H.E., Hyde, C.L., Isaev, D., Jablensky, A., Jansen, P.R., Janssen, J., Jönsson, E.G., Jung, L.A., Kahn, R.S., Kikinis, Z., Liu, K., Klauser, P., Knöchel, C., Kubicki, M., Lagopoulos, J., Langen, C., Lawrie, S., Lenroot, R.K., Lim, K.O., Lopez-Jaramillo, C., Lyall, A., Magnotta, V., Mandl, R.C.W., Mathalon, D.H., McCarley, R.W., McCarthy-Jones, S., McDonald, C., McEwen, S., McIntosh, A., Melicher, T., Mesholam-Gately, R.I., Michie, P.T., Mowry, B., Mueller, B.A., Newell, D.T., O'Donnell, P., Oertel-Knöchel, V., Oestreich, L., Paciga, S.A., Pantelis, C., Pasternak, O., Pearlson, G., Pellicano, G.R., Pereira, A., Pineda Zapata, J., Piras, F., Potkin, S.G., Preda, A., Rasser, P.E., Roalf, D.R., Roiz, R., Roos, A., Rotenberg, D., Satterthwaite, T.D., Savadjiev, P., Schall, U., Scott, R.J., Seal, M.L., Seidman, L.J., Shannon Weickert, C., Whelan, C.D., Shenton, M.E., Kwon, J.S., Spalletta, G., Spaniel, F., Sprooten, E., Stäblein, M., Stein, D.J., Sundram, S., Tan, Y., Tan, S., Tang, S., Temmingh, H.S., Westlye, L.T., Tønnesen, S., Tordesillas-Gutierrez, D., Doan, N.T., Vaidya, J., Van Haren, N.E.M., Vargas, C.D., Vecchio, D., Velakoulis, D., Voineskos, A., Voyvodic, J.Q., Wang, Z., Wan, P., Wei, D., Weickert, T.W., Whalley, H., White, T., Whitford, T.J., Wojcik, J.D., Xiang, H., Xie, Z., Yamamori, H., Yang, F., Yao, N., Zhang, G., Zhao, J., Van Erp, T.G.M., Turner, J., Thompson, P.M., Donohoe, G., 2018. Widespread white matter microstructural differences in schizophrenia across 4322 individuals: Results from the ENIGMA Schizophrenia DTI Working Group. *Mol. Psychiatry* 23, 1261–1269. <https://doi.org/10.1038/mp.2017.170>
- Kempton, M.J., Stahl, D., Williams, S.C.R., DeLisi, L.E., 2010. Progressive lateral ventricular enlargement in schizophrenia: A meta-analysis of longitudinal MRI studies. *Schizophr. Res.* 120, 54–62. <https://doi.org/10.1016/j.schres.2010.03.036>
- Kennedy, J.L., Altar, C.A., Taylor, D.L., Degtiar, I., Hornberger, J.C., 2014. The social and economic burden of treatment-resistant schizophrenia: A systematic literature review. *Int. Clin. Psychopharmacol.* 29, 63–76. <https://doi.org/10.1097/YIC.0b013e32836508e6>
- Kermany, D.S., Goldbaum, M., Cai, W., Valentim, C.C.S., Liang, H., Baxter, S.L., McKeown, A., Yang, G., Wu, X., Yan, F., Dong, Justin, Prasadha, M.K., Pei, J., Ting, M., Zhu, J., Li, C., Hewett, S., Dong, Jason, Ziyar, I., Shi, A., Zhang, R., Zheng, L., Hou, R., Shi, W., Fu, X., Duan, Y., Huu, V.A.N., Wen, C., Zhang, E.D., Zhang, C.L., Li, O., Wang, X., Singer, M.A., Sun, X., Xu, J., Tafreshi, A., Lewis, M.A., Xia, H., Zhang, K., 2018. Identifying Medical Diagnoses and Treatable Diseases by Image-Based Deep Learning. *Cell* 172, 1122–1131.e9. <https://doi.org/10.1016/j.cell.2018.02.010>
- Keshavan, M.S., Nasrallah, H.A., Tandon, R., 2011. Schizophrenia, “Just the Facts” 6. Moving ahead with the schizophrenia concept: from the elephant to the mouse. *Schizophr. Res.* 127, 3–13.
- Khvostikov, A., Aderghal, K., Benois-Pineau, J., Krylov, A., Catheline, G., 2018. 3D CNN-based classification using sMRI and MD-DTI images for Alzheimer disease studies.
- Kim, D.H., MacKinnon, T., 2018. Artificial intelligence in fracture detection: transfer learning from deep convolutional neural networks. *Clin. Radiol.* 73, 439–445. <https://doi.org/10.1016/j.crad.2017.11.015>

- Koelkebeck, K., Dannlowski, U., Ohrmann, P., Suslow, T., Murai, T., Bauer, J., Pedersen, A., Matsukawa, N., Son, S., Haidl, T., Miyata, J., 2019. Gray matter volume reductions in patients with schizophrenia: A replication study across two cultural backgrounds. *Psychiatry Res. - Neuroimaging* 292, 32–40. <https://doi.org/10.1016/j.psychres.2019.08.008>
- Kogan, A., Alpert, K., Ambite, J.L., Marcus, D.S., Wang, L., 2016. Northwestern University schizophrenia data sharing for SchizConnect: A longitudinal dataset for large-scale integration. *Neuroimage* 124, 1196–1201. <https://doi.org/10.1016/j.neuroimage.2015.06.030>
- Kooyman, I., Dean, K., Harvey, S., Walsh, E., 2007. Outcomes of public concern in schizophrenia. *Br. J. Psychiatry* 191, s29–s36. <https://doi.org/DOI:10.1192/bjp.191.50.s29>
- Koutsouleris, N., Dwyer, D.B., Degenhardt, F., Maj, C., Urquijo-Castro, M.F., Sanfelici, R., Popovic, D., Oeztuerk, O., Haas, S.S., Weiske, J., Ruef, A., Kambeitz-Illankovic, L., Antonucci, L.A., Neufang, S., Schmidt-Kraepelin, C., Ruhrmann, S., Penzel, N., Kambeitz, J., Haidl, T.K., Rosen, M., Chisholm, K., Riecher-Rössler, A., Egloff, L., Schmidt, A., Andreou, C., Hietala, J., Schirmer, T., Romer, G., Walger, P., Francini, M., Traber-Walker, N., Schimmelmann, B.G., Flückiger, R., Michel, C., Rössler, W., Borisov, O., Krawitz, P.M., Heekeren, K., Buechler, R., Pantelis, C., Falkai, P., Salokangas, R.K.R., Lencer, R., Bertolino, A., Borgwardt, S., Nothen, M., Brambilla, P., Wood, S.J., Upthegrove, R., Schultze-Lutter, F., Theodoridou, A., Meisenzahl, E., 2020. Multimodal Machine Learning Workflows for Prediction of Psychosis in Patients With Clinical High-Risk Syndromes and Recent-Onset Depression. *JAMA psychiatry*. <https://doi.org/10.1001/jamapsychiatry.2020.3604>
- Koutsouleris, N., Kambeitz-Illankovic, L., Ruhrmann, S., Rosen, M., Ruef, A., Dwyer, D.B., Paolini, M., Chisholm, K., Kambeitz, J., Haidl, T., Schmidt, A., Gillam, J., Schultze-Lutter, F., Falkai, P., Reiser, M., Riecher-Rössler, A., Upthegrove, R., Hietala, J., Salokangas, R.K.R., Pantelis, C., Meisenzahl, E., Wood, S.J., Beque, D., Brambilla, P., Borgwardt, S., 2018. Prediction Models of Functional Outcomes for Individuals in the Clinical High-Risk State for Psychosis or With Recent-Onset Depression: A Multimodal, Multisite Machine Learning Analysis. *JAMA psychiatry* 75, 1156–1172. <https://doi.org/10.1001/jamapsychiatry.2018.2165>
- Koutsouleris, N., Riecher-Rössler, A., Meisenzahl, E.M., Smieskova, R., Studerus, E., Kambeitz-Illankovic, L., von Saldern, S., Cabral, C., Reiser, M., Falkai, P., 2015. Detecting the psychosis prodrome across high-risk populations using neuroanatomical biomarkers. *Schizophr. Bull.* 41, 471–482.
- Kuo, S.S., Pogue-Geile, M.F., 2019. Variation in fourteen brain structure volumes in schizophrenia: A comprehensive meta-analysis of 246 studies. *Neurosci. Biobehav. Rev.* 98, 85–94. <https://doi.org/10.1016/j.neubiorev.2018.12.030>
- Kurth, F., Gaser, C., Luders, E., 2015. A 12-step user guide for analyzing voxel-wise gray matter asymmetries in statistical parametric mapping (SPM). *Nat. Protoc.* 10, 293–304. <https://doi.org/10.1038/nprot.2015.014>
- La, C., Nair, V.A., Mossahebi, P., Stamm, J., Birn, R., Meyerand, M.E., Prabhakaran, V., 2016. Recovery of slow-5 oscillations in a longitudinal study of ischemic

- stroke patients. *NeuroImage Clin.* 11, 398–407.
<https://doi.org/10.1016/j.nicl.2016.03.008>
- Lee, J.G., Jun, S., Cho, Y.W., Lee, H., Kim, G.B., Seo, J.B., Kim, N., 2017. Deep learning in medical imaging: General overview. *Korean J. Radiol.* 18, 570–584.
<https://doi.org/10.3348/kjr.2017.18.4.570>
- Lee, J.H., Kyeong, S., Kang, H., Kim, D.H., 2019. Structural and functional connectivity correlates with motor impairment in chronic supratentorial stroke: A multimodal magnetic resonance imaging study. *Neuroreport* 30, 526–531.
<https://doi.org/10.1097/WNR.0000000000001247>
- Lei, D., Pinaya, W.H.L., Young, J., van Amelsvoort, T., Marcelis, M., Donohoe, G., Mothersill, D.O., Corvin, A., Vieira, S., Huang, X., Lui, S., Scarpazza, C., Arango, C., Bullmore, E., Gong, Q., McGuire, P., Mechelli, A., 2020. Integrating machine learning and multimodal neuroimaging to detect schizophrenia at the level of the individual. *Hum. Brain Mapp.* 41, 1119–1135.
<https://doi.org/10.1002/hbm.24863>
- Lerman-Sinkoff, D.B., Kandala, S., Calhoun, V.D., Barch, D.M., Mamah, D.T., 2019. Transdiagnostic Multimodal Neuroimaging in Psychosis: Structural, Resting-State, and Task Magnetic Resonance Imaging Correlates of Cognitive Control. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 4, 870–880.
<https://doi.org/10.1016/j.bpsc.2019.05.004>
- Liang, S., Li, Y., Zhang, Z., Kong, X., Wang, Q., Deng, W., Li, X., Zhao, L., Li, M., Meng, Y., Huang, F., Ma, X., Li, X.M., Greenshaw, A.J., Shao, J., Li, T., 2019. Classification of first-episode schizophrenia using multimodal brain features: A combined structural and diffusion imaging study. *Schizophr. Bull.* 45, 591–599.
<https://doi.org/10.1093/schbul/sby091>
- Liberato, B., Krakauer, J.W., 2007. Ischemic Stroke: Mechanisms, Evaluation, and Treatment, First Edit. ed, *Neurology and Clinical Neuroscience*. Elsevier Inc.
<https://doi.org/10.1016/B978-0-323-03354-1.50046-8>
- Liepert, J., Hamzei, F., Weiller, C., 2000. Motor cortex disinhibition of the unaffected hemisphere after acute stroke. *Muscle and Nerve* 23, 1761–1763.
[https://doi.org/10.1002/1097-4598\(200011\)23:11<1761::AID-MUS14>3.0.CO;2-M](https://doi.org/10.1002/1097-4598(200011)23:11<1761::AID-MUS14>3.0.CO;2-M)
- Lin, W., Tong, T., Gao, Q., Guo, D., Du, X., Yang, Y., Guo, G., Xiao, M., Du, M., Qu, X., 2018. Convolutional neural networks-based MRI image analysis for the Alzheimer's disease prediction from mild cognitive impairment. *Front. Neurosci.* 12, 1–13. <https://doi.org/10.3389/fnins.2018.00777>
- Lindenberg, R., Renga, V., Zhu, L.L., Nair, D., Schlaug, G., 2010. Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. *Neurology* 75, 2176–2184. <https://doi.org/10.1212/WNL.0b013e318202013a>
- Litjens, G., Kooi, T., Bejnordi, B.E., Setio, A.A.A., Ciompi, F., Ghafoorian, M., van der Laak, J.A.W.M., van Ginneken, B., Sánchez, C.I., 2017. A survey on deep learning in medical image analysis. *Med. Image Anal.* 42, 60–88.
<https://doi.org/10.1016/j.media.2017.07.005>
- Liu, A., Vöröslakos, M., Kronberg, G., Henin, S., Krause, M.R., Huang, Y., Opitz, A.,

- Mehta, A., Pack, C.C., Krekelberg, B., Berényi, A., Parra, L.C., Melloni, L., Devinsky, O., Buzsáki, G., 2018. Immediate neurophysiological effects of transcranial electrical stimulation. *Nat. Commun.* 9. <https://doi.org/10.1038/s41467-018-07233-7>
- Liu, G., Dang, C., Peng, K., Xie, C., Chen, H., Xing, S., Chen, X., Zeng, J., 2015. Increased spontaneous neuronal activity in structurally damaged cortex is correlated with early motor recovery in patients with subcortical infarction. *Eur. J. Neurol.* 22, 1540–1547. <https://doi.org/10.1111/ene.12780>
- Liu, J., Qin, W., Wang, H., Zhang, J., Xue, R., Zhang, X., Yu, C., 2014. Altered spontaneous activity in the default-mode network and cognitive decline in chronic subcortical stroke. *J. Neurol. Sci.* 347, 193–198. <https://doi.org/10.1016/j.jns.2014.08.049>
- Liu, K., Kang, G., 2017. Multiview convolutional neural networks for lung nodule classification. *Int. J. Imaging Syst. Technol.* 27, 12–22. <https://doi.org/10.1002/ima.22206>
- Liu, M., Cheng, D., Yan, W., Initiative, A.D.N., 2018. Classification of Alzheimer's Disease by Combination of Convolutional and Recurrent Neural Networks Using FDG-PET Images. *Front. Neuroinform.* 12, 35. <https://doi.org/10.3389/fninf.2018.00035>
- Liu, X., Chen, K., Wu, T., Weidman, D., Lure, F., Li, J., 2018. Use of multimodality imaging and artificial intelligence for diagnosis and prognosis of early stages of Alzheimer's disease. *Transl. Res.* 194, 56–67. <https://doi.org/10.1016/j.trsl.2018.01.001>
- Logothetis, N.K., 2008. What we can do and what we cannot do with fMRI. *Nature* 453, 869–878.
- Lotze, M., Markert, J., Sauseng, P., Hoppe, J., Plewnia, C., Gerloff, C., 2006. The role of multiple contralesional motor areas for complex hand movements after internal capsular lesion. *J. Neurosci.* 26, 6096–6102. <https://doi.org/10.1523/JNEUROSCI.4564-05.2006>
- Loubinoux, I., Carel, C., Pariente, J., Dechaumont, S., Albucher, J.F., Marque, P., Manelfe, C., Chollet, F., 2003. Correlation between cerebral reorganization and motor recovery after subcortical infarcts. *Neuroimage* 20, 2166–2180. <https://doi.org/10.1016/j.neuroimage.2003.08.017>
- Lüdemann-Podubecká, J., Bösl, K., Nowak, D.A., 2016. Inhibition of the contralesional dorsal premotor cortex improves motor function of the affected hand following stroke. *Eur. J. Neurol.* 23, 823–830. <https://doi.org/10.1111/ene.12949>
- Lv, H., Wang, Z., Tong, E., Williams, L.M., Zaharchuk, G., Zeineh, M., Goldstein-Piekarski, A.N., Ball, T.M., Liao, C., Wintermark, M., 2018. Resting-state functional MRI: Everything that nonexperts have always wanted to know. *Am. J. Neuroradiol.* 39, 1390–1399. <https://doi.org/10.3174/ajnr.A5527>
- Madhavan, S., Weber, K.A., Stinear, J.W., 2011. Non-invasive brain stimulation enhances fine motor control of the hemiparetic ankle: Implications for rehabilitation. *Exp. Brain Res.* 209, 9–17. <https://doi.org/10.1007/s00221-010-2511-0>

- Mahendran, A., Vedaldi, A., 2015. Understanding deep image representations by inverting them, in: *Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition*. pp. 5188–5196.
- Mak, T.W., Saunders, M.E., Jett, B.D., 2014. *Primer to The Immune Response: Second Edition, Primer to The Immune Response: Second Edition*. Newnes. <https://doi.org/10.1016/C2009-0-62217-0>
- Mane, R., Chew, E., Phua, K.S., Ang, K.K., Robinson, N., Vinod, A.P., Guan, C., 2019. Prognostic and monitory EEG-biomarkers for BCI upper-limb stroke rehabilitation. *IEEE Trans. Neural Syst. Rehabil. Eng.* 27, 1654–1664. <https://doi.org/10.1109/TNSRE.2019.2924742>
- Manganotti, P., Acler, M., Zanette, G.P., Smania, N., Fiaschi, A., 2008. Motor cortical disinhibition during early and late recovery after stroke. *Neurorehabil. Neural Repair* 22, 396–403. <https://doi.org/10.1177/1545968307313505>
- Mansfield, A., Inness, E.L., Mcilroy, W.E., 2018. *Stroke. Handb. Clin. Neurol.* 159, 205–228. <https://doi.org/10.1016/B978-0-444-63916-5.00013-6>
- Marwaha, S., Johnson, S., 2004. Schizophrenia and employment: A review. *Soc. Psychiatry Psychiatr. Epidemiol.* 39, 337–349. <https://doi.org/10.1007/s00127-004-0762-4>
- Matsuura, A., Onoda, K., Oguro, H., Yamaguchi, S., 2015. Magnetic stimulation and movement-related cortical activity for acute stroke with hemiparesis. *Eur. J. Neurol.* 22, 1526–1532. <https://doi.org/10.1111/ene.12776>
- Mazo, C., Bernal, J., Trujillo, M., Alegre, E., 2018. Transfer learning for classification of cardiovascular tissues in histological images. *Comput. Methods Programs Biomed.* 165, 69–76. <https://doi.org/10.1016/j.cmpb.2018.08.006>
- McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack, C.R.J., Kawas, C.H., Klunk, W.E., Koroshetz, W.J., Manly, J.J., Mayeux, R., Mohs, R.C., Morris, J.C., Rossor, M.N., Scheltens, P., Carrillo, M.C., Thies, B., Weintraub, S., Phelps, C.H., 2011. The diagnosis of dementia due to Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. *Alzheimers. Dement.* 7, 263–269. <https://doi.org/10.1016/j.jalz.2011.03.005>
- Mikolas, P., Hlinka, J., Skoch, A., Pitra, Z., Frodl, T., Spaniel, F., Hajek, T., 2018. Machine learning classification of first-episode schizophrenia spectrum disorders and controls using whole brain white matter fractional anisotropy. *BMC Psychiatry* 18, 1–7. <https://doi.org/10.1186/s12888-018-1678-y>
- Mitelman, S.A., 2019. Transdiagnostic neuroimaging in psychiatry: A review. *Psychiatry Res.* 277, 23–38. <https://doi.org/10.1016/j.psychres.2019.01.026>
- Miyata, J., 2019. Toward integrated understanding of salience in psychosis. *Neurobiol. Dis.* 131, 104414. <https://doi.org/10.1016/j.nbd.2019.03.002>
- Miyoshi, K., Morimura, Y., Maeda, K., 2010. Neuropsychiatric disorders, *Neuropsychiatric Disorders*. <https://doi.org/10.1007/978-4-431-53871-4>
- Mori, S., Zhang, J., 2006. Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron* 51, 527–539.

- Morid, M.A., Borjali, A., Del Fiol, G., 2020. A scoping review of transfer learning research on medical image analysis using ImageNet. *Comput. Biol. Med.* 128, 104115. <https://doi.org/10.1016/j.compbiomed.2020.104115>
- Murray, C.J.L., Lopez, A.D., World Health Organization., World Bank., Harvard School of Public Health., 1996. *Global health statistics: a compendium of incidence, prevalence, and mortality estimates for over 200 conditions, Global burden of disease and injury series 2*. Harvard University Press.
- Nadeem, M.W., Ghamdi, M.A. Al, Hussain, M., Khan, M.A., Khan, K.M., Almotiri, S.H., Butt, S.A., 2020. Brain Tumor Analysis Empowered with Deep Learning: A Review, Taxonomy, and Future Challenges. *Brain Sci.* 10. <https://doi.org/10.3390/brainsci10020118>
- Nägele, F.L., Pasternak, O., Bitzan, L. V, Mußmann, M., Rauh, J., Kubicki, M., Leicht, G., Shenton, M.E., Lyall, A.E., Mülert, C., 2020. Cellular and extracellular white matter alterations indicate conversion to psychosis among individuals at clinical high-risk for psychosis. *World J. Biol. Psychiatry* 1–14.
- Ng, K.K., Lo, J.C., Lim, J.K.W., Chee, M.W.L., Zhou, J., 2016. Reduced functional segregation between the default mode network and the executive control network in healthy older adults: A longitudinal study. *Neuroimage* 133, 321–330. <https://doi.org/10.1016/j.neuroimage.2016.03.029>
- Nieman, D.H., Ruhrmann, S., Dragt, S., Soen, F., Van Tricht, M.J., Koelman, J.H.T.M., Bour, L.J., Velthorst, E., Becker, H.E., Weiser, M., 2014. Psychosis prediction: stratification of risk estimation with information-processing and premorbid functioning variables. *Schizophr. Bull.* 40, 1482–1490.
- Nieuwenhuis, M., van Haren, N.E.M., Hulshoff Pol, H.E., Cahn, W., Kahn, R.S., Schnack, H.G., 2012. Classification of schizophrenia patients and healthy controls from structural MRI scans in two large independent samples. *Neuroimage* 61, 606–612. <https://doi.org/10.1016/j.neuroimage.2012.03.079>
- Nitsche, M.A., Paulus, W., 2001. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology* 57, 1899–1901. <https://doi.org/10.1212/WNL.57.10.1899>
- Nitsche, M.A., Paulus, W., 2000. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J. Physiol.* 527, 633–639. <https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x>
- Nowak, D.A., Grefkes, C., Ameli, M., Fink, G.R., 2009. Interhemispheric competition after stroke: Brain stimulation to enhance recovery of function of the affected hand. *Neurorehabil. Neural Repair* 23, 641–656. <https://doi.org/10.1177/1545968309336661>
- Nowak, D.A., Grefkes, C., Dafotakis, M., Eickhoff, S., Küst, J., Karbe, H., Fink, G.R., 2008. Effects of low-frequency repetitive transcranial magnetic stimulation of the contralesional primary motor cortex on movement kinematics and neural activity in subcortical stroke. *Arch. Neurol.* 65, 741–747. <https://doi.org/10.1001/archneur.65.6.741>
- Ogawa, S., Lee, T., Nayak, A.S., Glynn, P., 1990. Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magn. Reson.*

Med. 14, 68–78.

- Oh, J., Oh, B.L., Lee, K.U., Chae, J.H., Yun, K., 2020. Identifying Schizophrenia Using Structural MRI With a Deep Learning Algorithm. *Front. Psychiatry* 11, 16. <https://doi.org/10.3389/fpsyt.2020.00016>
- Ono, T., Shindo, K., Kawashima, K., Ota, N., Ito, M., Ota, T., Mukaino, M., Fujiwara, T., Kimura, A., Liu, M., Ushiba, J., 2014. Brain-computer interface with somatosensory feedback improves functional recovery from severe hemiplegia due to chronic stroke. *Front. Neuroeng.* 7, 1–8. <https://doi.org/10.3389/fneng.2014.00019>
- Ortiz, A., Munilla, J., Gorriz, J.M., Ramirez, J., 2016. Ensembles of deep learning architectures for the early diagnosis of the Alzheimer's disease. *Int. J. Neural Syst.* 26, 1650025.
- Ott, C.V., Johnson, C.B., Macoveanu, J., Miskowiak, K., 2019. Structural changes in the hippocampus as a biomarker for cognitive improvements in neuropsychiatric disorders: A systematic review. *Eur. Neuropsychopharmacol.* 29, 319–329. <https://doi.org/10.1016/j.euroneuro.2019.01.105>
- Owen, M.J., Sawa, A., Mortensen, P.B., 2016. Schizophrenia. *Lancet* 388, 86–97. [https://doi.org/10.1016/S0140-6736\(15\)01121-6](https://doi.org/10.1016/S0140-6736(15)01121-6)
- Palaniyappan, L., Liddle, P.F., 2012. Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. *J. Psychiatry Neurosci.*
- Palaniyappan, L., Simmonite, M., White, T.P., Liddle, E.B., Liddle, P.F., 2013. Neural primacy of the salience processing system in schizophrenia. *Neuron* 79, 814–828.
- Pan, D., Zeng, A., Jia, L., Huang, Y., Frizzell, T., Song, X., 2020. Early Detection of Alzheimer's Disease Using Magnetic Resonance Imaging: A Novel Approach Combining Convolutional Neural Networks and Ensemble Learning. *Front. Neurosci.* 14, 259. <https://doi.org/10.3389/fnins.2020.00259>
- Pan, P., Zhang, Y., Liu, Y., Zhang, H., Guan, D., Xu, Y., 2017. Abnormalities of regional brain function in Parkinson's disease: A meta-analysis of resting state functional magnetic resonance imaging studies. *Sci. Rep.* 7, 1–10. <https://doi.org/10.1038/srep40469>
- Park, C.H., Chang, W.H., Ohn, S.H., Kim, S.T., Bang, O.Y., Pascual-Leone, A., Kim, Y.H., 2011. Longitudinal changes of resting-state functional connectivity during motor recovery after stroke. *Stroke* 42, 1357–1362. <https://doi.org/10.1161/STROKEAHA.110.596155>
- Park, J.Y., Kim, Y.H., Chang, W.H. yu., Park, C. hyun, Shin, Y. Il, Kim, S.T. a., Pascual-Leone, A., 2014. Significance of longitudinal changes in the default-mode network for cognitive recovery after stroke. *Eur. J. Neurosci.* 40, 2715–2722. <https://doi.org/10.1111/ejn.12640>
- Pergola, G., Selvaggi, P., Trizio, S., Bertolino, A., Blasi, G., 2015. The role of the thalamus in schizophrenia from a neuroimaging perspective. *Neurosci. Biobehav. Rev.* 54, 57–75. <https://doi.org/10.1016/j.neubiorev.2015.01.013>
- Peters, S.K., Dunlop, K., Downar, J., 2016. Cortico-striatal-thalamic loop circuits of the salience network: A central pathway in psychiatric disease and treatment. *Front.*

- Syst. Neurosci. 10, 1–23. <https://doi.org/10.3389/fnsys.2016.00104>
- Phanthunane, P., Vos, T., Whiteford, H., Bertram, M., Udomratn, P., 2010. Schizophrenia in Thailand: prevalence and burden of disease. *Popul. Health Metr.* 8, 24. <https://doi.org/10.1186/1478-7954-8-24>
- Pichiorri, F., Morone, G., Petti, M., Toppi, J., Pisotta, I., Molinari, M., Paolucci, S., Inghilleri, M., Astolfi, L., Cincotti, F., Mattia, D., 2015. Brain-computer interface boosts motor imagery practice during stroke recovery. *Ann. Neurol.* 77, 851–865. <https://doi.org/10.1002/ana.24390>
- Pinaya, W.H.L., Mechelli, A., Sato, J.R., 2019. Using deep autoencoders to identify abnormal brain structural patterns in neuropsychiatric disorders: A large-scale multi-sample study. *Hum. Brain Mapp.* 40, 944–954. <https://doi.org/10.1002/hbm.24423>
- Power, B.D., Nguyen, T., Hayhow, B., Looi, J.C.L., 2016. Neuroimaging in psychiatry: An update on neuroimaging in the clinical setting. *Australas. Psychiatry* 24, 157–163. <https://doi.org/10.1177/1039856215618525>
- Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Corrigendum to “Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion” [*NeuroImage* 59 (3) (2012) 2142–2154]. *Neuroimage* 63, 999. <https://doi.org/10.1016/j.neuroimage.2012.01.069>
- Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. *Neuroimage* 84, 320–341. <https://doi.org/10.1016/j.neuroimage.2013.08.048>
- Puig, J., Blasco, G., Alberich-Bayarri, A., Schlaug, G., Deco, G., Biarnes, C., Navas-Martí, M., Rivero, M., Gich, J., Figueras, J., Torres, C., Daunis-I-Estadella, P., Oramas-Requejo, C.L., Serena, J., Stinear, C.M., Kuceyeski, A., Soriano-Mas, C., Thomalla, G., Essig, M., Figley, C.R., Menon, B., Demchuk, A., Nael, K., Wintermark, M., Liebeskind, D.S., Pedraza, S., 2018. Resting-state functional connectivity magnetic resonance imaging and outcome after acute stroke. *Stroke* 49, 2353–2360. <https://doi.org/10.1161/STROKEAHA.118.021319>
- Pykett, I.L., Newhouse, J.H., Buonanno, F.S., Brady, T.J., Goldman, M.R., Kistler, J.P., Pohost, G.M., 1982. Principles of nuclear magnetic resonance imaging. *Radiology* 143, 157–168.
- Qin, P., Wu, K., Hu, Y., Zeng, J., Chai, X., 2020a. Diagnosis of Benign and Malignant Thyroid Nodules Using Combined Conventional Ultrasound and Ultrasound Elasticity Imaging. 24, 1028–1036.
- Qin, P., Wu, K., Hu, Y., Zeng, J., Chai, X., 2020b. Diagnosis of Benign and Malignant Thyroid Nodules Using Combined Conventional Ultrasound and Ultrasound Elasticity Imaging. *IEEE J. Biomed. Heal. informatics* 24, 1028–1036. <https://doi.org/10.1109/JBHI.2019.2950994>
- Radaic, A., Martins-de-Souza, D., 2020. The state of the art of nanopsychiatry for schizophrenia diagnostics and treatment. *Nanomedicine Nanotechnology, Biol. Med.* 28, 102222. <https://doi.org/10.1016/j.nano.2020.102222>

- Raghavan, P., 2015. Upper Limb Motor Impairment After Stroke. *Phys. Med. Rehabil. Clin. N. Am.* 26, 599–610. <https://doi.org/10.1016/j.pmr.2015.06.008>
- Rajpurkar, P., Irvin, J., Zhu, K., Yang, B., Mehta, H., Duan, T., Ding, D., Bagul, A., Ball, R.L., Langlotz, C., Shpanskaya, K., Lungren, M.P., Ng, A.Y., 2017. CheXNet: Radiologist-level pneumonia detection on chest X-rays with deep learning. *arXiv*.
- Ramos-Murguialday, A., Curado, M.R., Broetz, D., Yilmaz, Ö., Brasil, F.L., Liberati, G., Garcia-Cossio, E., Cho, W., Caria, A., Cohen, L.G., Birbaumer, N., 2019. Brain-Machine Interface in Chronic Stroke: Randomized Trial Long-Term Follow-up. *Neurorehabil. Neural Repair*. <https://doi.org/10.1177/1545968319827573>
- Rashid, B., Calhoun, V., 2020. Towards a brain-based predictive of mental illness. *Hum. Brain Mapp.* 1–68. <https://doi.org/10.1002/hbm.25013>
- Reidler, J.S., Zaghi, S., Fregni, F., 2011. Neurophysiological Effects of Transcranial Direct Current Stimulation, Neurofeedback and Neuromodulation Techniques and Applications. Elsevier Inc. <https://doi.org/10.1016/B978-0-12-382235-2.00012-3>
- Reynolds, C.F., Lewis, D.A., Detre, T., Schatzberg, A.F., Kupfer, D.J., 2009. The future of psychiatry as clinical neuroscience. *Acad. Med.* 84, 446–450. <https://doi.org/10.1097/ACM.0b013e31819a8052>
- Robinson, R.G., Jorge, R.E., 2016. Post-Stroke Depression: A Review. *Am. J. Psychiatry* 173, 221–231. <https://doi.org/10.1176/appi.ajp.2015.15030363>
- Rohde, A., Worrall, L., Godecke, E., O'Halloran, R., Farrell, A., Massey, M., 2018. Diagnosis of aphasia in stroke populations: A systematic review of language tests. *PLoS One* 13, e0194143. <https://doi.org/10.1371/journal.pone.0194143>
- Rohde, D., Gaynor, E., Large, M., Conway, O., Bennett, K., Williams, D.J., Callaly, E., Dolan, E., Hickey, A., 2019. Stroke survivor cognitive decline and psychological wellbeing of family caregivers five years post-stroke: a cross-sectional analysis. *Top. Stroke Rehabil.* 26, 180–186. <https://doi.org/10.1080/10749357.2019.1590972>
- Saarinen, A.I.L., Huhtaniska, S., Pudas, J., Björnholm, L., Jukuri, T., Tohka, J., Granö, N., Barnett, J.H., Kiviniemi, V., Veijola, J., Hintsanen, M., Lieslehto, J., 2020. Structural and functional alterations in the brain gray matter among first-degree relatives of schizophrenia patients: A multimodal meta-analysis of fMRI and VBM studies. *Schizophr. Res.* 216, 14–23. <https://doi.org/10.1016/j.schres.2019.12.023>
- Sacco, R.L., Kasner, S.E., Broderick, J.P., Caplan, L.R., Connors, J.J., Culebras, A., Elkind, M.S.V., George, M.G., Hamdan, A.D., Higashida, R.T., Hoh, B.L., Janis, L.S., Kase, C.S., Kleindorfer, D.O., Lee, J.M., Moseley, M.E., Peterson, E.D., Turan, T.N., Valderrama, A.L., Vinters, H. V., 2013. An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American heart association/American stroke association. *Stroke* 44, 2064–2089. <https://doi.org/10.1161/STR.0b013e318296aeca>
- Sachdev, P., Mohan, A., 2017. An International Curriculum for Neuropsychiatry and Behavioural Neurology. *Rev. Colomb. Psiquiatr.* 46, 18–27.

<https://doi.org/10.1016/j.rcp.2017.05.001>

- Saha, S., Chant, D., Welham, J., McGrath, J., 2005. A systematic review of the prevalence of schizophrenia. *PLoS Med.* 2, 0413–0433. <https://doi.org/10.1371/journal.pmed.0020141>
- Salvador, R., Canales-Rodríguez, E., Guerrero-Pedraza, A., Sarró, S., Tordesillas-Gutiérrez, D., Maristany, T., Crespo-Facorro, B., McKenna, P., Pomarol-Clotet, E., 2019. Multimodal Integration of Brain Images for MRI-Based Diagnosis in Schizophrenia. *Front. Neurosci.* 13, 1–9. <https://doi.org/10.3389/fnins.2019.01203>
- Salvador, R., Radua, J., Canales-Rodríguez, E.J., Solanes, A., Sarroa, S., Goikolea, J.M., Valiente, A., Montea, G.C., Natividad, M.D.C., Guerrero-Pedraza, A., Moro, N., Fernández-Corcuera, P., Amann, B.L., Maristany, T., Vieta, E., McKenna, P.J., Pomarol-Clote, E., 2017. Evaluation of machine learning algorithms and structural features for optimal MRI-based diagnostic prediction in psychosis. *PLoS One* 12, 1–24. <https://doi.org/10.1371/journal.pone.0175683>
- Salvatore, C., Cerasa, A., Battista, P., Gilardi, M.C., Quattrone, A., Castiglioni, I., 2015. Magnetic resonance imaging biomarkers for the early diagnosis of Alzheimer's disease: a machine learning approach. *Front. Neurosci.* 9, 307. <https://doi.org/10.3389/fnins.2015.00307>
- Sanford, A.M., 2017. Mild Cognitive Impairment. *Clin. Geriatr. Med.* 33, 325–337. <https://doi.org/10.1016/j.cger.2017.02.005>
- Saver, J.L., 2006. Time is brain - Quantified. *Stroke* 37, 263–266. <https://doi.org/10.1161/01.STR.0000196957.55928.ab>
- Schaechter, J.D., Perdue, K.L., 2008. Enhanced cortical activation in the contralesional hemisphere of chronic stroke patients in response to motor skill challenge. *Cereb. Cortex* 18, 638–647. <https://doi.org/10.1093/cercor/bhm096>
- Schultze-Lutter, F., Michel, C., Schmidt, S.J., Schimmelmann, B.G., Maric, N.P., Salokangas, R.K.R., Riecher-Rössler, A., Van der Gaag, M., Nordentoft, M., Raballo, A., 2015. EPA guidance on the early detection of clinical high risk states of psychoses. *Eur. Psychiatry* 30, 405–416.
- Selvaraju, R.R., Cogswell, M., Das, A., Vedantam, R., Parikh, D., Batra, D., 2017. Grad-CAM: Visual Explanations from Deep Networks via Gradient-Based Localization. *Proc. IEEE Int. Conf. Comput. Vis.* 2017-Octob, 618–626. <https://doi.org/10.1109/ICCV.2017.74>
- Sharma, N., Pomeroy, V.M., Baron, J.C., 2006. Motor imagery: A backdoor to the motor system after stroke? *Stroke* 37, 1941–1952. <https://doi.org/10.1161/01.STR.0000226902.43357.fc>
- Shenton, M.E., Dickey, C.C., Frumin, M., McCarley, R.W., 2001. A review of MRI findings in schizophrenia. *Schizophr. Res.* 49, 1–52. [https://doi.org/10.1016/S0920-9964\(01\)00163-3](https://doi.org/10.1016/S0920-9964(01)00163-3)
- Simon, A.E., Borgwardt, S., Riecher-Rössler, A., Velthorst, E., de Haan, L., Fusar-Poli, P., 2013. Moving beyond transition outcomes: meta-analysis of remission rates in individuals at high clinical risk for psychosis. *Psychiatry Res.* 209, 266–272.

- Simonyan, K., Vedaldi, A., Zisserman, A., 2014. Deep inside convolutional networks: Visualising image classification models and saliency maps. 2nd Int. Conf. Learn. Represent. ICLR 2014 - Work. Track Proc.
- Simonyan, K., Zisserman, A., 2015. Very deep convolutional networks for large-scale image recognition. 3rd Int. Conf. Learn. Represent. ICLR 2015 - Conf. Track Proc. 1–14.
- Song, J., Chai, Y.J., Masuoka, H., Park, S.W., Kim, S.J., Choi, J.Y., Kong, H.J., Lee, K.E., Lee, J., Kwak, N., Yi, K.H., Miyauchi, A., 2019. Ultrasound image analysis using deep learning algorithm for the diagnosis of thyroid nodules. *Medicine (Baltimore)*. 98, e15133. <https://doi.org/10.1097/MD.00000000000015133>
- Song, J., Young, B.M., Nigogosyan, Z., Walton, L.M., Nair, V.A., Grogan, S.W., Tyler, M.E., Farrar-Edwards, D., Caldera, K.E., Sattin, J.A., Williams, J.C., Prabhakaran, V., 2014. Characterizing relationships of DTI, fMRI, and motor recovery in stroke rehabilitation utilizing brain-computer interface technology. *Front. Neuroeng.* 7, 1–11. <https://doi.org/10.3389/fneng.2014.00031>
- Spencer, K.A., Brown, K.A., 2018. Dysarthria following Stroke. *Semin. Speech Lang.* 39, 15–24. <https://doi.org/10.1055/s-0037-1608852>
- Sporns, O., 2003. Graph theory methods for the analysis of neural connectivity patterns, in: *Neuroscience Databases*. Springer, pp. 171–185.
- Springenberg, J.T., Dosovitskiy, A., Brox, T., Riedmiller, M., 2015. Striving for simplicity: The all convolutional net. 3rd Int. Conf. Learn. Represent. ICLR 2015 - Work. Track Proc.
- Sridharan, D., Levitin, D.J., Menon, V., 2008. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc. Natl. Acad. Sci. U. S. A.* 105, 12569–12574. <https://doi.org/10.1073/pnas.0800005105>
- Studerus, E., Ramyeed, A., Riecher-Rössler, A., 2017. Prediction of transition to psychosis in patients with a clinical high risk for psychosis: a systematic review of methodology and reporting. *Psychol. Med.* 47, 1163–1178.
- Sun, L., Yin, D., Zhu, Y., Fan, M., Zang, L., Wu, Y., Jia, J., Bai, Y., Zhu, B., Hu, Y., 2013. Cortical reorganization after motor imagery training in chronic stroke patients with severe motor impairment: A longitudinal fMRI study. *Neuroradiology* 55, 913–925. <https://doi.org/10.1007/s00234-013-1188-z>
- Szegedy, C., Ioffe, S., Vanhoucke, V., Alemi, A.A., 2017. Inception-v4, inception-ResNet and the impact of residual connections on learning. 31st AAAI Conf. Artif. Intell. AAAI 2017 4278–4284.
- Szegedy, C., Liu, W., Jia, Y., Sermanet, P., Reed, S., Anguelov, D., Erhan, D., Vanhoucke, V., Rabinovich, A., 2015. Going deeper with convolutions, in: *Proceedings of the IEEE Computer Society Conference on Computer Vision and Pattern Recognition*. pp. 1–9. <https://doi.org/10.1109/CVPR.2015.7298594>
- Takayanagi, Y., Sasabayashi, D., Takahashi, T., Furuichi, A., Kido, M., Nishikawa, Y., Nakamura, M., Noguchi, K., Suzuki, M., 2020. Reduced Cortical Thickness in Schizophrenia and Schizotypal Disorder. *Schizophr. Bull.* 46, 387–394.

<https://doi.org/10.1093/schbul/sbz051>

- Takeuchi, N., Chuma, T., Matsuo, Y., Watanabe, I., Ikoma, K., 2005. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. *Stroke* 36, 2681–2686. <https://doi.org/10.1161/01.STR.0000189658.51972.34>
- Teo, W.P., Chew, E., 2014. Is motor-imagery brain-computer interface feasible in stroke rehabilitation? *PM R* 6, 723–728. <https://doi.org/10.1016/j.pmrj.2014.01.006>
- Touvykine, B., Mansoori, B.K., Jean-Charles, L., Deffeyes, J., Quessy, S., Dancause, N., 2016. The effect of lesion size on the organization of the ipsilesional and contralesional motor cortex. *Neurorehabil. Neural Repair* 30, 280–292. <https://doi.org/10.1177/1545968315585356>
- Tsai, Y.H., Yuan, R., Huang, Y.C., Yeh, M.Y., Lin, C.P., Biswal, B.B., 2014. Disruption of brain connectivity in acute stroke patients with early impairment in consciousness. *Front. Psychol.* 4, 1–10. <https://doi.org/10.3389/fpsyg.2013.00956>
- Tsuchimoto, S., Shindo, K., Hotta, F., Hanakawa, T., Liu, M., Ushiba, J., 2019. Sensorimotor Connectivity after Motor Exercise with Neurofeedback in Post-Stroke Patients with Hemiplegia. *Neuroscience* 416, 109–125. <https://doi.org/10.1016/j.neuroscience.2019.07.037>
- Tuladhar, A.M., Snaphaan, L., Shumskaya, E., Rijpkema, M., Fernandez, G., Norris, D.G., de Leeuw, F.E., 2013. Default Mode Network Connectivity in Stroke Patients. *PLoS One* 8. <https://doi.org/10.1371/journal.pone.0066556>
- van de Ven, V.G., Formisano, E., Prvulovic, D., Roeder, C.H., Linden, D.E.J., 2004. Functional connectivity as revealed by spatial independent component analysis of fMRI measurements during rest. *Hum. Brain Mapp.* 22, 165–178.
- Van Den Heuvel, M.P., Fornito, A., 2014. Brain networks in schizophrenia. *Neuropsychol. Rev.* 24, 32–48. <https://doi.org/10.1007/s11065-014-9248-7>
- Van Erp, T.G.M., Walton, E., Hibar, D.P., Schmaal, L., Jiang, W., Glahn, D.C., Pearlson, G.D., Yao, N., Fukunaga, M., Hashimoto, R., 2018. Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium. *Biol. Psychiatry* 84, 644–654.
- Van Geuns, R.-J.M., Wielopolski, P.A., de Bruin, H.G., Rensing, B.J., van Ooijen, P.M.A., Hulshoff, M., Oudkerk, M., de Feyter, P.J., 1999. Basic principles of magnetic resonance imaging. *Prog. Cardiovasc. Dis.* 42, 149–156.
- Vasavada, M.M., Wang, J., Eslinger, P.J., Gill, D.J., Sun, X., Karunanayaka, P., Yang, Q.X., 2015. Olfactory cortex degeneration in Alzheimer's disease and mild cognitive impairment. *J. Alzheimer's Dis.* 45, 947–958.
- Virani, S.S., Alonso, A., Benjamin, E.J., Bittencourt, M.S., Callaway, C.W., Carson, A.P., Chamberlain, A.M., Chang, A.R., Cheng, S., Delling, F.N., Djousse, L., Elkind, M.S.V., Ferguson, J.F., Fornage, M., Khan, S.S., Kissela, B.M., Knutson, K.L., Kwan, T.W., Lackland, D.T., Lewis, T.T., Lichtman, J.H., Longenecker, C.T., Loop, M.S., Lutsey, P.L., Martin, S.S., Matsushita, K., Moran, A.E.,

Mussolino, M.E., Perak, A.M., Rosamond, W.D., Roth, G.A., Sampson, U.K.A., Satou, G.M., Schroeder, E.B., Shah, S.H., Shay, C.M., Spartano, N.L., Stokes, A., Tirschwell, D.L., VanWagner, L.B., Tsao, C.W., Wong, S.S., Heard, D.G., 2020. Heart disease and stroke statistics—2020 update: A report from the American Heart Association, *Circulation*. <https://doi.org/10.1161/CIR.0000000000000757>

Vos, T., Barber, R.M., Bell, B., Bertozzi-Villa, A., Biryukov, S., Bolliger, I., Charlson, F., Davis, A., Degenhardt, L., Dicker, D., Duan, L., Erskine, H., Feigin, V.L., Ferrari, A.J., Fitzmaurice, C., Fleming, T., Graetz, N., Guinovart, C., Haagsma, J., Hansen, G.M., Hanson, S.W., Heuton, K.R., Higashi, H., Kassebaum, N., Kyu, H., Laurie, E., Liang, X., Lofgren, K., Lozano, R., MacIntyre, M.F., Moradi-Lakeh, M., Naghavi, M., Nguyen, G., Odell, S., Ortblad, K., Roberts, D.A., Roth, G.A., Sandar, L., Serina, P.T., Stanaway, J.D., Steiner, C., Thomas, B., Vollset, S.E., Whiteford, H., Wolock, T.M., Ye, P., Zhou, M., Ávila, M.A., Aasvang, G.M., Abbafati, C., Ozgoren, A.A., Abd-Allah, F., Aziz, M.I.A., Abera, S.F., Aboyans, V., Abraham, J.P., Abraham, B., Abubakar, I., Abu-Raddad, L.J., Abu-Rmeileh, N.M.E., Aburto, T.C., Achoki, T., Ackerman, I.N., Adelekan, A., Ademi, Z., Adou, A.K., Adsuar, J.C., Arnlov, J., Agardh, E.E., Al Khabouri, M.J., Alam, S.S., Alasfoor, D., Albittar, M.I., Alegretti, M.A., Aleman, A. V., Alemu, Z.A., Alfonso-Cristancho, R., Alhabib, S., Ali, R., Alla, F., Allebeck, P., Allen, P.J., AlMazroa, M.A., Alsharif, U., Alvarez, E., Alvis-Guzman, N., Ameli, O., Amini, H., Ammar, W., Anderson, B.O., Anderson, H.R., Antonio, C.A.T., Anwari, P., Apfel, H., Arsenijevic, V.S.A., Artaman, A., Asghar, R.J., Assadi, R., Atkins, L.S., Atkinson, C., Badawi, A., Bahit, M.C., Bakfalouni, T., Balakrishnan, K., Balalla, S., Banerjee, A., Barker-Collo, S.L., Barquera, S., Barregard, L., Barrero, L.H., Basu, S., Basu, A., Baxter, A., Beardsley, J., Bedi, N., Beghi, E., Bekele, T., Bell, M.L., Benjet, C., Bennett, D.A., Bensenor, I.M., Benzian, H., Bernabe, E., Beyene, T.J., Bhala, N., Bhalla, A., Bhutta, Z., Bienhoff, K., Bikbov, B., Abdulhak, A. Bin, Blore, J.D., Blyth, F.M., Bohensky, M.A., Basara, B.B., Borges, G., Bornstein, N.M., Bose, D., Boufous, S., Bourne, R.R., Boyers, L.N., Brainin, M., Brauer, M., Brayne, C.E.G., Brazinova, A., Breitborde, N.J.K., Brenner, H., Briggs, A.D.M., Brooks, P.M., Brown, J., Brugha, T.S., Buchbinder, R., Buckle, G.C., Bukhman, G., Bulloch, A.G., Burch, M., Burnett, R., Cardenas, R., Cabral, N.L., Campos-Nonato, I.R., Campuzano, J.C., Carapetis, J.R., Carpenter, D.O., Caso, V., Castaneda-Orjuela, C.A., Catala-Lopez, F., Chadha, V.K., Chang, J.C., Chen, H., Chen, W., Chiang, P.P., Chimed-Ochir, O., Chowdhury, R., Christensen, H., Christophi, C.A., Chugh, S.S., Cirillo, M., Coggeshall, M., Cohen, A., Colistro, V., Colquhoun, S.M., Contreras, A.G., Cooper, L.T., Cooper, C., Cooperrider, K., Coresh, J., Cortinovis, M., Criqui, M.H., Crump, J.A., Cuevas-Nasu, L., Dandona, R., Dandona, L., Dansereau, E., Dantes, H.G., Dargan, P.I., Davey, G., Davitoiu, D. V., Dayama, A., De La Cruz-Gongora, V., De La Vega, S.F., De Leo, D., Del Pozo-Cruz, B., Dellavalle, R.P., Deribe, K., Derrett, S., Des Jarlais, D.C., Dessalegn, M., DeVeber, G.A., Dharmaratne, S.D., Diaz-Torne, C., Ding, E.L., Dokova, K., Dorsey, E.R., Driscoll, T.R., Duber, H., Durrani, A.M., Edmond, K.M., Ellenbogen, R.G., Endres, M., Ermakov, S.P., Eshrati, B., Esteghamati, A., Estep, K., Fahimi, S., Farzadfar, F., Fay, D.F.J., Felson, D.T., Fereshtehnejad, S.M., Fernandes, J.G., Ferri, C.P., Flaxman, A., Foigt, N., Foreman, K.J., Fowkes, F.G.R., Franklin, R.C., Furst, T., Futran, N.D., Gabbe, B.J., Gankpe, F.G., Garcia-Guerra, F.A., Geleijnse, J.M., Gessner, B.D., Gibney, K.B., Gillum, R.F., Ginawi, I.A., Giroud, M., Giussani, G., Goenka, S., Goginashvili, K., Gona, P., De Cosio,

T.G., Gosselin, R.A., Gotay, C.C., Goto, A., Gouda, H.N., Guerrant, R.L., Gugnani, H.C., Gunnell, D., Gupta, Rajeev, Gupta, Rahul, Gutierrez, R.A., Hafezi-Nejad, N., Hagan, H., Halasa, Y., Hamadeh, R.R., Hamavid, H., Hammami, M., Hankey, G.J., Hao, Y., Harb, H.L., Haro, J.M., Havmoeller, R., Hay, R.J., Hay, S., Hedayati, M.T., Pi, I.B.H., Heydarpour, P., Hajar, M., Hoek, H.W., Hoffman, H.J., Hornberger, J.C., Hosgood, H.D., Hossain, M., Hotez, P.J., Hoy, D.G., Hsairi, M., Hu, H., Hu, G., Huang, J.J., Huang, C., Huiart, L., Hussein, A., Iannarone, M., Iburg, K.M., Innos, K., Inoue, M., Jacobsen, K.H., Jassal, S.K., Jeemon, P., Jensen, P.N., Jha, V., Jiang, G., Jiang, Y., Jonas, J.B., Joseph, J., Juel, K., Kan, H., Karch, A., Karimkhani, C., Karthikeyan, G., Katz, R., Kaul, A., Kawakami, N., Kazi, D.S., Kemp, A.H., Kengne, A.P., Khader, Y.S., Khalifa, S.E.A.H., Khan, E.A., Khan, G., Khang, Y.H., Khonelidze, I., Kieling, C., Kim, D., Kim, S., Kimokoti, R.W., Kinfu, Y., King, J.M., Kissela, B.M., Kivipelto, M., Knibbs, L., Knudsen, A.K., Kokubo, Y., Kosen, S., Kramer, A., Kravchenko, M., Krishnamurthi, R. V., Krishnaswami, S., Defo, B.K., Bicer, B.K., Kuipers, E.J., Kulkarni, V.S., Kumar, K., Kumar, G.A., Kwan, G.F., Lai, T., Lalloo, R., Lam, H., Lan, Q., Lansingh, V.C., Larson, H., Larsson, A., Lawrynowicz, A.E.B., Leasher, J.L., Lee, J.T., Leigh, J., Leung, R., Levi, M., Li, B., Li, Yichong, Li, Yongmei, Liang, J., Lim, S., Lin, H.H., Lind, M., Lindsay, M.P., Lipshultz, S.E., Liu, S., Lloyd, B.K., Ohno, S.L., Logroscino, G., Looker, K.J., Lopez, A.D., Lopez-Olmedo, N., Lortet-Tieulent, J., Lotufo, P.A., Low, N., Lucas, R.M., Lunevicius, R., Lyons, R.A., Ma, J., Ma, S., MacKay, M.T., Majdan, M., Malekzadeh, R., Mapoma, C.C., Marcenes, W., March, L.M., Margono, C., Marks, G.B., Marzan, M.B., Masci, J.R., Mason-Jones, A.J., Matzopoulos, R.G., Mayosi, B.M., Mazorodze, T.T., McGill, N.W., McGrath, J.J., McKee, M., McLain, A., McMahon, B.J., Meaney, P.A., Mehndiratta, M.M., Mejia-Rodriguez, F., Mekonnen, W., Melaku, Y.A., Meltzer, M., Memish, Z.A., Mensah, G., Meretoja, A., Mhimbira, F.A., Micha, R., Miller, T.R., Mills, E.J., Mitchell, P.B., Mock, C.N., Moffitt, T.E., Ibrahim, N.M., Mohammad, K.A., Mokdad, A.H., Mola, G.L., Monasta, L., Montico, M., Montine, T.J., Moore, A.R., Moran, A.E., Morawska, L., Mori, R., Moschandreass, J., Moturi, W.N., Moyer, M., Mozaffarian, D., Mueller, U.O., Mukaigawara, M., Murdoch, M.E., Murray, J., Murthy, K.S., Naghavi, P., Nahas, Z., Naheed, A., Naidoo, K.S., Naldi, L., Nand, D., Nangia, V., Narayan, K.M.V., Nash, D., Nejjari, C., Neupane, S.P., Newman, L.M., Newton, C.R., Ng, M., Ngalesoni, F.N., Nhung, N.T., Nisar, M.I., Nolte, S., Norheim, O.F., Norman, R.E., Norrving, B., Nyakarahuka, L., Oh, I.H., Ohkubo, T., Omer, S.B., Opio, J.N., Ortiz, A., Pandian, J.D., Pabello, C.I.A., Papachristou, C., Park, E.K., Parry, C.D., Caicedo, A.J.P., Patten, S.B., Paul, V.K., Pavlin, B.I., Pearce, N., Pedraza, L.S., Pellegrini, C.A., Pereira, D.M., Perez-Ruiz, F.P., Perico, N., Pervaiz, A., Pesudovs, K., Peterson, C.B., Petzold, M., Phillips, M.R., Phillips, D., Phillips, B., Piel, F.B., Plass, D., Poenaru, D., Polanczyk, G. V., Polinder, S., Pope, C.A., Popova, S., Poulton, R.G., Pourmalek, F., Prabhakaran, D., Prasad, N.M., Qato, D., Quistberg, D.A., Rafay, A., Rahimi, K., Rahimi-Movaghar, V., Rahman, S.U., Raju, M., Rakovac, I., Rana, S.M., Razavi, H., Refaat, A., Rehm, J., Remuzzi, G., Resnikoff, S., Ribeiro, A.L., Riccio, P.M., Richardson, L., Richardus, J.H., Riederer, A.M., Robinson, M., Roca, A., Rodriguez, A., Rojas-Rueda, D., Ronfani, L., Rothenbacher, D., Roy, N., Ruhago, G.M., Sabin, N., Sacco, R.L., Ksoreide, K., Saha, S., Sahathevan, R., Sahraian, M.A., Sampson, U., Sanabria, J.R., Sanchez-Riera, L., Santos, I.S., Satpathy, M., Saunders, J.E., Sawhney, M., Saylan, M.I., Scarborough, P., Schoettker, B., Schneider, I.J.C., Schwebel, D.C., Scott,

- J.G., Seedat, S., Sepanlou, S.G., Serdar, B., Servan-Mori, E.E., Shackelford, K., Shaheen, A., Shahraz, S., Levy, T.S., Shangguan, S., She, J., Sheikhbahaei, S., Shepard, D.S., Shi, P., Shibuya, K., Shinohara, Y., Shiri, R., Shishani, K., Shiue, I., Shrimme, M.G., Sigfusdottir, I.D., Silberberg, D.H., Simard, E.P., Sindi, S., Singh, J.A., Singh, L., Skirbekk, V., Sliwa, K., Soljak, M., Soneji, S., Soshnikov, S.S., Speyer, P., Sposato, L.A., Sreeramareddy, C.T., Stoeckl, H., Stathopoulou, V.K., Steckling, N., Stein, M.B., Stein, D.J., Steiner, T.J., Stewart, A., Stork, E., Stovner, L.J., Stroupoulis, K., Sturua, L., Sunguya, B.F., Swaroop, M., Sykes, B.L., Tabb, K.M., Takahashi, K., Tan, F., Tandon, N., Tanne, D., Tanner, M., Tavakkoli, M., Taylor, H.R., Te Ao, B.J., Temesgen, A.M., Have, M. Ten, Tenkorang, E.Y., Terkawi, A.S., Theadom, A.M., Thomas, E., Thorne-Lyman, A.L., Thrift, A.G., Tleyjeh, I.M., Tonelli, M., Topouzis, F., Towbin, J.A., Toyoshima, H., Traebert, J., Tran, B.X., Trasande, L., Trillini, M., Truelsen, T., Trujillo, U., Tsilimbaris, M., Tuzcu, E.M., Ukwaja, K.N., Undurraga, E.A., Uzun, S.B., Van Brakel, W.H., Van De Vijver, S., Dingenen, R. Van, Van Gool, C.H., Varakin, Y.Y., Vasankari, T.J., Vavilala, M.S., Veerman, L.J., Velasquez-Melendez, G., Venketasubramanian, N., Vijayakumar, L., Villalpando, S., Violante, F.S., Vlassov, V. V., Waller, S., Wallin, M.T., Wan, X., Wang, L., Wang, J., Wang, Y., Warouw, T.S., Weichenthal, S., Weiderpass, E., Weintraub, R.G., Werdecker, A., Wessells, K.R., Westerman, R., Wilkinson, J.D., Williams, H.C., Williams, T.N., Woldeyohannes, S.M., Wolfe, C.D.A., Wong, J.Q., Wong, H., Woolf, A.D., Wright, J.L., Wurtz, B., Xu, G., Yang, G., Yano, Y., Yenesew, M.A., Yentur, G.K., Yip, P., Yonemoto, N., Yoon, S.J., Younis, M., Yu, C., Kim, K.Y., Zaki, M.E.S., Zhang, Y., Zhao, Z., Zhao, Y., Zhu, J., Zonies, D., Zunt, J.R., Salomon, J.A., Murray, C.J.L., 2015. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 386, 743–800. [https://doi.org/10.1016/S0140-6736\(15\)60692-4](https://doi.org/10.1016/S0140-6736(15)60692-4)
- Wang, C., Ji, F., Hong, Z., Poh, J.S., Krishnan, R., Lee, J., Rekhi, G., Keefe, R.S.E., Adcock, R.A., Wood, S.J., Fornito, A., Pasternak, O., Chee, M.W.L., Zhou, J., 2016a. Disrupted salience network functional connectivity and white-matter microstructure in persons at risk for psychosis: Findings from the LYRIKS study. *Psychol. Med.* 46, 2771–2783. <https://doi.org/10.1017/S0033291716001410>
- Wang, C., Ong, J.L., Patanaik, A., Zhou, J., Chee, M.W.L., 2016b. Spontaneous eyelid closures link vigilance fluctuation with fMRI dynamic connectivity states. *Proc. Natl. Acad. Sci. U. S. A.* 113, 9653–9658. <https://doi.org/10.1073/pnas.1523980113>
- Wang, H., Sun, L., Jia, J., 2018. The plasticity of resting-state brain networks associated with motor imagery training in chronic stroke patients. *Ann. Phys. Rehabil. Med.* 61, e20. <https://doi.org/10.1016/j.rehab.2018.05.043>
- Wang, H., Xu, G., Wang, X., Sun, C., Zhu, B., Fan, M., Jia, J., Guo, X., Sun, L., 2019. The reorganization of resting-state brain networks associated with motor imagery training in chronic stroke patients. *IEEE Trans. Neural Syst. Rehabil. Eng.* 27, 2237–2245.
- Wang, J., Chen, H., Liang, H., Wang, W., Liang, Yi, Liang, Ying, Zhang, Y., 2019. Low-frequency fluctuations amplitude signals exhibit abnormalities of intrinsic brain activities and reflect cognitive impairment in leukoaraiosis patients. *Med.*

- Sci. Monit. 25, 5219–5228. <https://doi.org/10.12659/MSM.915528>
- Wang, L., Kogan, A., Cobia, D., Alpert, K., Kolasny, A., Miller, M.I., Marcus, D., 2013. Northwestern University Schizophrenia Data and Software Tool (NUSDAST). *Front. Neuroinform.* 7, 1–13. <https://doi.org/10.3389/fninf.2013.00025>
- Wang, X., Zhao, N., Shi, J., Wu, Y., Liu, J., Xiao, Q., Hu, J., 2019. Discussion on the Application of Multi-modal Magnetic Resonance Imaging Fusion in Schizophrenia. *J. Med. Syst.* 43. <https://doi.org/10.1007/s10916-019-1215-7>
- Winterburn, J.L., Voineskos, A.N., Devenyi, G.A., Plitman, E., de la Fuente-Sandoval, C., Bhagwat, N., Graff-Guerrero, A., Knight, J., Chakravarty, M.M., 2019. Can we accurately classify schizophrenia patients from healthy controls using magnetic resonance imaging and machine learning? A multi-method and multi-dataset study. *Schizophr. Res.* 214, 3–10. <https://doi.org/10.1016/j.schres.2017.11.038>
- Wright, I.C., Rabe-Hesketh, S., Woodruff, P.W.R., David, A.S., Murray, R.M., Bullmore, E.T., 2000. Meta-analysis of regional brain volumes in schizophrenia. *Am. J. Psychiatry* 157, 16–25. <https://doi.org/10.1176/ajp.157.1.16>
- Yan, C.G., Wang, X. Di, Zuo, X.N., Zang, Y.F., 2016. DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. *Neuroinformatics* 14, 339–351. <https://doi.org/10.1007/s12021-016-9299-4>
- Yan, J., Cui, Y., Li, Q., Tian, L., Liu, B., Jiang, T., Zhang, D., Yan, H., 2019. Cortical thinning and flattening in schizophrenia and their unaffected parents. *Neuropsychiatr. Dis. Treat.* 15, 935–946. <https://doi.org/10.2147/NDT.S195134>
- Yang, C., Rangarajan, A., Ranka, S., 2018. Visual Explanations From Deep 3D Convolutional Neural Networks for Alzheimer’s Disease Classification. *AMIA ... Annu. Symp. proceedings. AMIA Symp.* 2018, 1571–1580.
- Yang, Y., Yan, L.F., Zhang, X., Han, Y., Nan, H.Y., Hu, Y.C., Hu, B., Yan, S.L., Zhang, J., Cheng, D.L., Ge, X.W., Cui, G. Bin, Zhao, D., Wang, W., 2018. Glioma grading on conventional MR images: A deep learning study with transfer learning. *Front. Neurosci.* 12, 1–10. <https://doi.org/10.3389/fnins.2018.00804>
- Young, B.M., Nigogosyan, Z., Walton, L.M., Song, J., Nair, V.A., Grogan, S.W., Tyler, M.E., Edwards, D.F., Caldera, K., Sattin, J.A., Williams, J.C., Prabhakaran, V., 2014. Changes in functional brain organization and behavioral correlations after rehabilitative therapy using a brain-computer interface. *Front. Neuroeng.* 7, 1–15. <https://doi.org/10.3389/fneng.2014.00026>
- Young, B.M., Stamm, J.M., Song, J., Remsik, A.B., Nair, V.A., Tyler, M.E., Edwards, D.F., Caldera, K., Sattin, J.A., Williams, J.C., Prabhakaran, V., 2016. Brain-Computer interface training after stroke affects patterns of brain-behavior relationships in corticospinal motor fibers. *Front. Hum. Neurosci.* 10, 1–13. <https://doi.org/10.3389/fnhum.2016.00457>
- Yousaf, T., Dervenoulas, G., Politis, M., 2018. *Advances in MRI Methodology*, 1st ed, International Review of Neurobiology. Elsevier Inc. <https://doi.org/10.1016/bs.irn.2018.08.008>
- Yu, Z., Jiang, X., Zhou, F., Qin, J., Ni, D., Chen, S., Lei, B., Wang, T., 2019. Melanoma

- Recognition in Dermoscopy Images via Aggregated Deep Convolutional Features. *IEEE Trans. Biomed. Eng.* 66, 1006–1016. <https://doi.org/10.1109/TBME.2018.2866166>
- Yung, A.R., Yung, A.R., Pan Yuen, H., McGorry, P.D., Phillips, L.J., Kelly, D., Dell’olio, M., Francey, S.M., Cosgrave, E.M., Killackey, E., 2005. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. *Aust. New Zeal. J. Psychiatry* 39, 964–971.
- Zaghi, S., Acar, M., Hultgren, B., Boggio, P.S., Fregni, F., 2010. Noninvasive brain stimulation with low-intensity electrical currents: Putative mechanisms of action for direct and alternating current stimulation. *Neuroscientist* 16, 285–307. <https://doi.org/10.1177/1073858409336227>
- Zang, Y., Jiang, T., Lu, Y., He, Y., Tian, L., 2004. Regional homogeneity approach to fMRI data analysis. *Neuroimage* 22, 394–400. <https://doi.org/10.1016/j.neuroimage.2003.12.030>
- Zang, Y.F., Yong, H., Chao-Zhe, Z., Qing-Jiu, C., Man-Qiu, S., Meng, L., Li-Xia, T., Tian-Zi, J., Yu-Feng, W., 2007. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain Dev.* 29, 83–91. <https://doi.org/10.1016/j.braindev.2006.07.002>
- Zeiler, M.D., Fergus, R., 2014. Visualizing and understanding convolutional networks, in: *European Conference on Computer Vision*. Springer, pp. 818–833.
- Zhang, L., Zuo, X.-N., Ng, K.K., Chong, J.S.X., Shim, H.Y., Ong, M.Q.W., Loke, Y.M., Choo, B.L., Chong, E.J.Y., Wong, Z.X., 2020. Distinct BOLD variability changes in the default mode and salience networks in Alzheimer’s disease spectrum and associations with cognitive decline. *Sci. Rep.* 10, 1–12.
- Zhang, Q., Zhu, S.-C., 2018. Visual interpretability for deep learning: a survey. *Front. Inf. Technol. Electron. Eng.* 19, 27–39.
- Zhao, Z., Tang, C., Yin, D., Wu, J., Gong, J., Sun, L., Jia, J., Xu, D., Fan, M., 2018. Frequency-specific alterations of regional homogeneity in subcortical stroke patients with different outcomes in hand function. *Hum. Brain Mapp.* 39, 4373–4384. <https://doi.org/10.1002/hbm.24277>
- Zheng, Fenglian, Li, C., Zhang, D., Cui, D., Wang, Z., Qiu, J., 2019. Study on the sub-regions volume of hippocampus and amygdala in schizophrenia. *Quant. Imaging Med. Surg.* 9, 1025–1036. <https://doi.org/10.21037/qims.2019.05.21>
- Zheng, Fanfan, Yan, L., Zhong, B., Yang, Z., Xie, W., 2019. Progression of cognitive decline before and after incident stroke. *Neurology* 93, e20–e28. <https://doi.org/10.1212/WNL.00000000000007716>
- Zhou, B., Khosla, A., Lapedriza, A., Oliva, A., Torralba, A., 2016. Learning Deep Features for Discriminative Localization. *Proc. IEEE Comput. Soc. Conf. Comput. Vis. Pattern Recognit.* 2016-Decem, 2921–2929. <https://doi.org/10.1109/CVPR.2016.319>
- Zhu, J., Jin, Y., Wang, K., Zhou, Y., Feng, Y., Yu, M., Jin, X., 2015. Frequency-dependent changes in the regional amplitude and synchronization of resting-state functional MRI in stroke. *PLoS One* 10, 1–10.

<https://doi.org/10.1371/journal.pone.0123850>

- Zhu, Z., Albadawy, E., Saha, A., Zhang, J., Harowicz, M.R., Mazurowski, M.A., 2019. Deep learning for identifying radiogenomic associations in breast cancer. *Comput. Biol. Med.* 109, 85–90. <https://doi.org/10.1016/j.combiomed.2019.04.018>
- Zou, Q.-H., Zhu, C.-Z., Yang, Y., Zuo, X.-N., Long, X.-Y., Cao, Q.-J., Wang, Y.-F., Zang, Y.-F., 2008. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. *J. Neurosci. Methods* 172, 137–141.

Appendix

Appendix A: Supplementary Materials

Supplementary Table 2.1 ROIs in DMN and SMN

ROI names	X	Y	Z	ROI names	X	Y	Z
Left Hemisphere				Right Hemisphere			
'LH_SomMotA'	-14	-38	74	'RH_SomMotA'	4	-38	62
'LH_SomMotB_Cent'	-62	0	20	'RH_SomMotB_Cent'	64	2	18
'LH_SomMotB_S2'	-60	-6	6	'RH_SomMotB_S2'	62	-6	10
'LH_SomMotB_Ins'	-32	-24	4	'RH_SomMotB_Ins'	36	-24	2
'LH_SomMotB_Aud'	-54	-10	4	'RH_SomMotB_Aud'	56	-8	0
'LH_DefaultA_IPL'	-48	-76	34	'RH_DefaultA_Temp'	62	-8	-16
'LH_DefaultA_PFCd'	-18	28	42	'RH_DefaultA_IPL'	58	-64	30
'LH_DefaultA_PCC'	-2	-48	18	'RH_DefaultA_PFCd'	28	38	42
'LH_DefaultA_PFCm'	-2	46	-4	'RH_DefaultA_PCC'	8	-48	20
'LH_DefaultB_Temp'	-56	-38	-6	'RH_DefaultA_PFCm'	4	52	-6
'LH_DefaultB_IPL'	-58	-52	26	'RH_DefaultB_Temp'	64	-34	-2
'LH_DefaultB_PFCd'	-8	22	56	'RH_DefaultB_AntTemp'	52	8	-40
'LH_DefaultB_PFCl'	-42	12	52	'RH_DefaultB_PFCd'	8	22	62
'LH_DefaultB_PFCv'	-44	36	-12	'RH_DefaultB_PFCv'	52	30	-12
'LH_DefaultC_IPL'	-44	-72	24	'RH_DefaultC_IPL'	56	-68	20
'LH_DefaultC_Rsp'	-12	-60	12	'RH_DefaultC_Rsp'	14	-56	12
'LH_DefaultC_PHC'	-22	-38	-14	'RH_DefaultC_PHC'	24	-32	-22

Supplementary Figure 2.1 Incidence maps of lesion. The overlapping proportion of lesions from (a) the MI-BCI group, (b) the MI-BCI+tDCS group, and (c) all patients combined, overlaid on the FMRIB58_FA template. Colors denote frequency of occurrence.

Supplementary Table 2.2a ALFF Comparison at Baseline

Brain Regions	Hemisphere	Peak Coordinates	Cluster Size	Peak T Value
Patients > HC				
Precuneus/ Posterior cingulate gyrus	L	-10 -62 46	431	5.2418
Angular gyrus/ Inferior parietal lobule	R	44 -66 30	1812	5.1099
Middle temporal gyrus	L	-66 -36 -6	304	4.3894
Middle frontal gyrus/ Superior frontal gyrus/ Insula	R	44 6 18	2276	5.6201
Patients < HC				
Precentral gyrus/ Postcentral gyrus	L	-32 -8 48	726	-4.3356
Middle temporal pole	R	18 10 -32	389	-3.7417
Superior frontal gyrus, orbital part	R	22 34 -24	898	-4.3785
Superior temporal gyrus	L	-48 -36 20	510	-5.6178
Fusiform gyrus	R	34 -68 -12	300	-4.8585

Supplementary Table 2.2b ReHo Comparison at Baseline

Brain Regions	Hemisphere	Peak Coordinates	Cluste r Size	Peak T Value
Patients > HC				
Precuneus/ Posterior cingulate gyrus	L	-8 -48 26	652	5.1805
Cerebellum	R	14 -92 -26	309	4.6987
Cerebellum	L	-42 -64 -26	223	4.3796
Patients < HC				
Superior temporal gyrus/insula	L	-38 -32 10	921	-4.6678
Calcarine sulcus	R	24 -58 6	331	-4.1559

Supplementary Table 2.3a ALFF Interaction Effect

Brain Regions	Hemisphere	Peak Coordinates	Cluster Size	Peak Value	F
Supplementary motor area	R	-2 0 58	652	21.3561	
Precentral gyrus	R	24 -24 74	280	12.4052	
Middle frontal gyrus	R	14 36 58	735	14.9206	
Middle occipital gyrus	R	40 -74 24	371	22.9306	
Precuneus/ Angular gyrus	L&R	8 -50 52	3914	34.2711	
Inferior temporal gyrus	L	-44 -24 -30	345	20.5512	
Cerebellum	L	-16 -48 -48	269	30.7413	
Gyrus rectus	L	4 28 -22	265	12.623	

Supplementary Table 2.3b ALFF Intervention Effect

Brain Regions	Hemisphere	Peak Coordinates	Cluster Size	Peak T Value
MI-BCI Group				
Post > Pre				
Supplementary motor area/ Precentral gyrus	R	20 6 58	534	7.3404
Superior frontal gyrus	L	14 -2 -28	674	6.1248
Inferior temporal gyrus	L	-48 -12 -44	239	4.9617
Cerebellum	L	-24 -56 -50	183	10.1847
Post < Pre				
Precuneus/ Inferior parietal lobule	R&L	-2 -78 52	2889	-8.5867
Middle occipital gyrus	R	36 -72 30	185	-7.148
MI-BCI+tDCS Group				
None				

Supplementary Table 2.4a ReHo Interaction Effect

Brain Regions	Hemisphere	Peak Coordinates	Cluster Size	Peak F Value
Precuneus/ Posterior cingulate gyrus	R&L	8 -62 40	1199	33.061
Anterior cingulate gyrus	L	-4 42 2	306	15.5411

Supplementary Table 2.4b ReHo Intervention Effect

Brain Regions	Hemisphere	Peak Coordinates	Cluster Size	Peak Value	T
MI-BCI Group					
Post < Pre					
Precuneus/ cingulate gyrus	Posterior R&L	8 -64 26	590	-11.163	
MI-BCI+tDCS Group					
None					

Supplementary Table 4.1 Hyperparameters for nonlinear SVM and 3D CNN models.

	Nonlinear SVM Hyperparameters
Kernel type	'rbf' , 'poly', 'sigmoid'
Kernel coefficient	1, 10, 100 , 1000
Regularization term	0.1, 0.01, 0.001 , 0.0001
	3D CNN Hyperparameters
Convolutional kernel size	3x3x3 , 5x5x5, 7x7x7, 9x9x9
Maxpooling kernel size	2x2x2, 3x3x3
Kernel number	128 , 256, 512, 1024
Optimizer	SGD, Adam, Adadelta

Hyperparameters for nonlinear SVM include kernel type, kernel coefficient, and regularization term. Hyperparameters were selected as the final choices via grid-search were highlighted in bold. Hyperparameters for 3D CNN models include kernel size for convolutional layer and maxpooling layer, kernel number for fully connected layer, and optimizer. Hyperparameters were optimized by non-strict grid-search which did not exhaust all the combinations due to computational cost. The final choices were highlighted in bold.

Supplementary Table 4.2 Number of layer and parameters in naïve 3D CNN models.

	Number of layers	Number of trainable parameters
Sequential_1	5	2,266,050
Sequential_2	7	1,208,610
Sequential_3	9	89,410
Inception_1	18	648,418
Inception_2	30	689,698
Inception_resnet_1	22	652,642
Inception_resnet_2	35	693,922

Supplementary Table 4.3 Single modal (sMRI) cross-validation results on the IMH dataset.

		ACC	SP	SE	ROC-AUC
Handcrafted Feature-based Machine Learning	Linear SVM	74.60% (+/- 3.27%)	43.25% (+/- 9.78%)	90.62% (+/- 6.45%)	0.80 (+/- 0.05)
	Nonlinear SVM	75.48% (+/- 2.48%)	48.58% (+/- 9.26%)	89.24% (+/- 5.29%)	0.80 (+/- 0.05)
Deep Feature based on Pre-trained 2D CNN	VGG16	74.62% (+/- 5.48%)	54.00% (+/- 0.83%)	85.17% (+/- 4.50%)	0.81 (+/- 0.06)
	Xception	70.59% (+/- 5.63%)	44.50% (+/- 4.33%)	83.91% (+/- 9.21%)	0.76 (+/- 0.11)
	Resnet50	74.17% (+/- 4.77%)	52.50% (+/- 7.19%)	85.20% (+/- 9.75%)	0.80 (+/- 0.03)
	Densenet121	74.17% (+/- 4.23%)	51.17% (+/- 8.62%)	85.89% (+/- 7.68%)	0.82 (+/- 0.06)
	Inception_V3	73.75% (+/- 6.17%)	52.75% (+/- 2.30%)	84.55% (+/- 6.06%)	0.78 (+/- 0.05)
	Inception_resnet_V2	71.01% (+/- 4.17%)	47.42% (+/- 0.80%)	83.13% (+/- 6.43%)	0.75 (+/- 0.04)
Naïve 3D CNN Models	Sequential_1	77.38% (+/- 4.01%)	50.03% (+/- 4.95%)	91.41% (+/- 7.22%)	0.81 (+/- 0.06)
	Sequential_2	75.69% (+/- 4.62%)	51.98% (+/- 0.49%)	87.78% (+/- 9.54%)	0.77 (+/- 0.08)
	Sequential_3	74.12% (+/- 4.63%)	42.68% (+/- 8.07%)	90.28% (+/- 6.95%)	0.73 (+/- 0.07)
	Inception_1	76.49% (+/- 5.15%)	54.83% (+/- 0.13%)	87.50% (+/- 0.06%)	0.79 (+/- 0.09)
	Inception_2	74.76% (+/- 5.25%)	44.12% (+/- 22.49%)	90.36% (+/- 10.42%)	0.75 (+/- 0.09)
	Inception_resnet_1	80.17% (+/- 3.98%)	65.12% (+/- 13.50%)	87.81% (+/- 8.46%)	0.83 (+/- 0.06)
	Inception_resnet_2	78.16% (+/- 4.03%)	57.37% (+/- 13.10%)	88.75% (+/- 7.61%)	0.80 (+/- 0.07)

The results of outer cross-validation on the IMH dataset are listed with mean (+/- standard deviation). Naïve 3D CNN models obtained higher accuracy than both

handcrafted feature-based machine learning and deep feature models. The highest accuracy obtained by each approach is in bold. The highest accuracy is obtained by Inception_resnet_1 in general.

Supplementary Table 4.4 Single modal (sMRI) independent testing results on the NUSDAST dataset.

		ACC	SP	SE	ROC-AUC
HANDCRAFTED FEATURE- BASED MACHINE LEARNING	Linear SVM	64.00%	64.18%	63.83%	0.70
	Nonlinear SVM (RBF kernel)	65.45%	73.88%	57.45%	0.69
DEEP FEATURE BASED ON PRE-TRAINED 2D CNN	VGG16	63.64%	44.78%	81.56%	0.68
	Xception	61.45%	60.45%	62.41%	0.66
	Resnet50	64.00%	47.76%	79.43%	0.71
	Densenet121	64.00%	53.73%	73.76%	0.68
	Inception_V3	62.91%	54.48%	70.92%	0.67
	Inception_resnet_V2	62.55%	67.16%	58.16%	0.69
NAÏVE 3D CNN MODELS	Sequential_1	60.36%	87.31%	34.75%	0.68
	Sequential_2	54.55%	96.27%	14.89%	0.70
	Sequential_3	62.91%	88.06%	39.01%	0.71
	Inception_1	67.64%	77.61%	58.16%	0.72
	Inception_2	67.27%	82.09%	53.19%	0.72
	Inception_resnet_1	68.36%	76.87%	60.28%	0.72
	Inception_resnet_2	57.09%	26.12%	86.52%	0.66

The testing results on the NUSDAST dataset using ensemble approach with models trained on the IMH dataset are listed. Both handcrafted feature-based machine learning approach and deep feature approach have low accuracy comparing to the performance on the IMH dataset. The performance of naïve 3D CNN models also decreased. The best testing accuracy is achieved by Inception_resnet_1, indicating better generalizability of it.

Supplementary Table 4.5 Brain regions whose grey matter volume contribute to classification at the group-level via gradient activation map.

<i>Brain Regions (MNI coordiantes)</i>	<i>Hemisphere</i>	<i>Cluster Size</i>	<i>Peak T Value</i>
<i>Cluster 1: (25 12 -1)</i>	L&R	5315	30.1721
<i>Insula</i>	R	722	24.3532
<i>Putamen</i>	R	719	30.1721
<i>Putamen</i>	L	627	28.2751
<i>Caudate nucleus</i>	L	410	20.4788
<i>Caudate nucleus</i>	R	348	19.6374
<i>Insula</i>	L	231	13.2613
<i>Olfactory cortex</i>	L	204	15.5389
<i>Olfactory cortex</i>	R	193	14.7561
<i>Superior frontal gyrus, medial orbital</i>	R	169	8.2930
<i>Amygdala</i>	R	141	11.6035
<i>Hippocampus</i>	R	107	10.1247
<i>Amygdala</i>	L	93	9.1939
<i>Rectus</i>	R	88	15.3316
<i>Cluster 2: (2 -13 6)</i>	L&R	1404	30.5640
<i>Thalamus</i>	L	553	30.4824
<i>Thalamus</i>	R	629	30.5640
<i>Cluster 3: (25 -65 -24)</i>	R	322	7.1269
<i>Cerebellum 6</i>	R	220	7.1269
<i>Cerebellum crus 1</i>	R	89	7.1236
<i>Cluster 4: (-25 -65 -30)</i>	L	209	7.7426
<i>Cerebellum 6</i>	L	154	7.4538
<i>Cerebellum crus 1</i>	L	55	7.4726

Clusters thresholded at $p < 0.01$ (familywise error corrected) were listed with peak MNI coordinates, cluster size, and peak T values.

Supplementary Table 4.6 Brain regions whose FA contribute to classification at the group-level via gradient activation map.

<i>Brain Regions</i>	<i>Hemisphere</i>	<i>Cluster Size</i>	<i>Peak T Value</i>
<i>Splenium of corpus callosum</i>		1532	391.5022
<i>Body of corpus callosum</i>		1586	318.6496
<i>Genu of corpus callosum</i>		1356	308.4362
<i>Pontine crossing tract (a part of MCP)</i>		1004	253.8701
<i>Corticospinal tract</i>	R	509	150.4916
<i>Cerebral Peduncle</i>	R	414	141.4642
<i>Medial lemniscus</i>	L	448	141.1224
<i>Fornix (column and body of fornix)</i>		573	138.2648
<i>Superior cerebellar peduncle</i>	L	292	137.2089
<i>Medial lemniscus</i>	R	359	136.6568
<i>Superior cerebellar peduncle</i>	R	318	128.0944
<i>Anterior corona radiata</i>	R	706	124.6363
<i>Retrolenticular part of internal capsule</i>	R	471	119.1647
<i>Posterior limb of internal capsule</i>	L	579	118.9369
<i>Posterior corona radiata</i>	R	382	118.4336
<i>Inferior cerebellar peduncle</i>	R	290	112.4366
<i>Cerebral Peduncle</i>	L	412	107.7200
<i>Middle cerebellar peduncle</i>		2320	107.7028
<i>Retrolenticular part of internal capsule</i>	L	502	103.7576
<i>Sagittal stratum (include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus)</i>	R	270	102.5899
<i>Inferior cerebellar peduncle</i>	L	317	101.7558
<i>Cingulum (cingulate gyrus)</i>	R	123	100.7076
<i>Anterior corona radiata</i>	L	683	100.0775
<i>Superior Corona Radiata</i>	L	805	99.7424
<i>Posterior thalamic radiation (include optic radiation)</i>	L	392	99.1640
<i>External capsule L</i>	L	135	94.8347
<i>External capsule</i>	R	200	93.3602

<i>Corticospinal tract</i>	L	501	91.1342
<i>Superior corona radiata</i>	R	800	86.6730
<i>Cingulum (cingulate gyrus)</i>	L	123	84.5676
<i>Sagittal stratum (include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus)</i>	L	183	84.4917
<i>Posterior limb of internal capsule</i>	R	584	79.0643
<i>Posterior thalamic radiation (include optic radiation)</i>	R	418	76.9420
<i>Posterior corona radiata</i>	L	395	75.9523
<i>Cingulum (hippocampus)</i>	L	94	69.8030
<i>Anterior limb of internal capsule</i>	R	447	66.3511
<i>Anterior limb of internal capsule</i>	L	448	65.4247
<i>Fornix (cres) / Stria terminalis</i>	R	134	62.7618
<i>Superior longitudinal fasciculus</i>	R	340	62.0168
<i>Superior Longitudinal Fasciculus</i>	L	309	59.4590
<i>Cingulum (hippocampus)</i>	R	54	48.8614
<i>Fornix (cres) / Stria terminalis</i>	L	86	41.3852

Overlapping regions of FA clusters (familywise error corrected at $p < 0.01$) and Johns Hopkins University (JHU) white-matter atlas are listed in the table with cluster sizes and peak T values.

Supplementary Figure 4.1 Prediction probability distribution of schizophrenia and controls in the replication experiment across all approaches. Random predictions for both controls (blue) and patients (orange) have a distribution peak at around 0.5 (first column). Y-axis represents the predicted probability of being patient from 0 to 1. Prediction probability distributions are presented in the following order: handcrafted feature-based machine learning are in the green box, deep feature based on pre-trained 2D CNN are in the red box, and naïve 3D CNN models are in the purple box. **Row A** represents cross-validation results on the IMH dataset on sMRI models. Predictions generated by the proposed models demonstrated higher than randomness accuracy, which had wider gaps between the predicted probability distributions of controls and patients. Naïve 3D CNN models performed the best with clear separation of patients and controls. **Row B** represents independent testing results on the NUSDAST dataset on sMRI models trained with the IMH dataset. Handcrafted feature-based machine learning approaches and deep feature based on pre-trained 2D CNN performed similarly to random predictions. Naïve 3D sequential models categorize all subjects into one class. Inception models and Inception_resnet models obtained better classification results with wider gaps between the predicted probability distributions of controls and patients.

Appendix B: Publications and Manuscripts

PEER REVIEWED JOURNALS

Published:

Hu, M., Cheng, H. J., Ji, F., Chong, J. S. X., Lu, Z., Huang, W., ... & Zhou, J. H. (2021). Brain functional changes in stroke following rehabilitation using brain-computer interface-assisted motor imagery with and without tDCS: a pilot study. *Frontiers in human neuroscience*.

Hu, M., Qian, X., Liu, S., Koh, A. J., Sim, K., Jiang, X., ... & Zhou, J. H. (2021). Structural and diffusion MRI based schizophrenia classification using 2D pretrained and 3D naive Convolutional Neural Networks. *Schizophrenia research*.

Under Review:

Hu, M., Jiang, X., Zhou, J.H., Sim, K., Guan, C. Decomposition of 3D Neural Image to 2+1D for Feature Extraction for Schizophrenia Detection. *IEEE Transactions on Biomedical Engineering*.

CONFERENCE PAPERS

Hu M, Ji F, Lu Z, Huang W, Khosrowabadi R, Zhao L, Ang KK, Phua KS, Nasrallah FA, Chuang KH, Stephenson MC, Totman J, Jiang X, Chew E, Guan C, Zhou J. Differential Amplitude of Low-Frequency Fluctuations in brain networks after BCI Training with and without tDCS in Stroke. *Annu Int Conf IEEE Eng Med Biol Soc*. 2018 Jul;2018:1050-1053. doi: 10.1109/EMBC.2018.8512395. PMID: 30440571.

Hu M, Sim K, Zhou JH, Jiang X, Guan C. Brain MRI-based 3D Convolutional Neural Networks for Classification of Schizophrenia and Controls. *Annu Int Conf IEEE Eng*

Med Biol Soc. 2020 Jul;2020:1742-1745. doi: 10.1109/EMBC44109.2020.9176610.

PMID: 33018334.