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Identifying Functional Imaging Markers in Psychosis Using fMRI

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Abstract

Major types of psychotic disorders include schizophrenia (SCZ), bipolar disorder (BP) and schizoaffective disorder (SZA). These disorders have profound and overlapping symptoms with marked cognitive deficits, and their diagnosis relies on symptom clusters. The treatments for psychosis are usually focused on positive symptoms such as delusions and hallucinations. Although cognitive impairments underlie both positive and negative symptoms, functional brain imaging biomarkers that can reliably predict a patient's cognitive deficits are still lacking. Therefore, this project used functional MRI to explore the feasibility of using functional connectivity (FC) to predict cognitive performance.

A total of 207 subjects (BP: 79, SZ/SZA: 48, and HC: 80) with high functional MRI image (fMRI) quality (SNR> 100, motion < 0.3) were selected from the McLean MATRICS dataset. Subjects were divided into a discovery cohort (n=104) and an age, gender, and head motion matched validation cohort (n=103). The hypothesis was that FC could predict cognitive performance in the discovery cohort and that the prediction models could be generalized to the validation cohort. The connectomes for each subject were obtained by calculating the whole-brain connectivity using networks from the individualized functional parcellation as region of interests (ROIs). Models were trained to predict the 8 cognitive scores in the discovery cohort, respectively. The generalizability of these models was tested by applying these models to the validation cohort.

The trained models were able to predict 6 out of 8 cognitive scores using a LOOCV procedure. Models for working memory, composite score and attention score could be generalized to the validation cohort. A total of 35 FC features were identified as important for predicting performance in these cognitive domains. Significant differences between patients and controls were found for 13 of these features when considered individually.

In summary, this project has established a framework for biomarker discovery that may have clinical relevance for the diagnosis of psychosis early in the disease process by providing possible FC features that can be detected using fMRI and may help guide therapeutic interventions. The identified biomarkers also provide convergent evidence for network dysfunction in psychosis and suggest personalized treatment targets.

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Chapter 1. Introduction

1.1 Definition of psychosis and bipolar disorder

According to the National Institute of Mental Health, a person is considered to have psychosis when they have developed conditions that affect the mind and lost contact with reality. Major types of psychosis include SZ, BP and SZA. These disorders have profound symptoms with marked cognitive deficits (National Institude of Mental Health, 2019). SCZ is characterized by having lost contact with reality (McCutcheon et al., 2020), while BP is associated with extreme mood changes between mania and depression (McIntyre et al., 2020). SZA is mainly marked by mood disorders along with common SCZ symptoms (Miller & Black, 2019). Usually, the diagnosis of psychosis relies on symptom clusters and requires the use of psychological assessment scales.

1.2 Epidemiology

The prevalence of SCZ and BP in the US is around 1% (Rowland & Marwaha, 2018) and 1 in 300 people is affected by the disease worldwide. The rate increases to 1 in 222 people for adults because onset usually happen during late adolescences. Men also tend to develop the disease earlier than women. Despite low prevalence, these disorders take a tremendous toll on patients, families, and society as a whole. The economic burden of SCZ in the U.S. reached $340 billion in 2019, with BP not far behind (Moreno-Kustner et al., 2018). Many individuals with psychotic disorders have difficulty functioning in society due to cognitive deficits that are

commonly seen in psychosis. According to a meta-analysis in 2019, there is a high prevalence of 21% in homeless people that are diagnosed with psychosis (Ayano et al., 2019).

SCZ patients have reduced life expectancy around 15 to 20 years shorter than healthy people (Hjorthoj et al., 2017). Also, with around 5% to 10% life-time risk of death by suicide (Hjorthoj et al., 2017), SCZ patients are more likely to commit suicide compared with the general population with suicide rate less than 0.01% (U.S. Department of Health and Human Services, 2021). SCZ is associated with risk factors in multiple dimensions including genetics, brain development, birth complication and environmental factors. People who have a family history of SCZ are more likely to develop SCZ with a heritability of around 80%. GWAS studies showed that over 100 loci are associated with SCZ but each with only small effect (Schizophrenia Working Group of the Psychiatric Genomics, 2014). Based on this information, GWAS could construct a polygenic risk score and gives a genetic risk summary of the disorder. Some genetic variants involving some sections of DNA duplication and deletion could also increase the risk of SCZ but not in all cases (only 2% to 3% of SCZ cases) (Bassett & Chow, 2008). Although SCZ typically diagnosed in late adolescence to early thirties, there is evidence indicating that pathogenesis begins in neurodevelopment. Birth complication could be one of the potential causes that increase the risk of developing SCZ. For example, studies suggested that people with psychosis are more likely to have experienced utero adversity like maternal infections, starvation during pregnancy, preterm birth and etc. (Xu et al., 2009). However, SCZ can also be trigged by stress and substance abuse. Environmental factors like injury, urban living, and minority status could all increase the risk of developing psychosis (Lederbogen et al., 2011). Thus, even

identical twins could have different chances of getting psychosis (Hilker et al., 2018), suggesting the importance of environmental factors in psychosis development.

Similarly, a combination of genetic, biological, and environmental factors may contribute to the development of BP. People who have a close relative with the condition have a 5% to 10% chance to develop BP themselves, which is much higher than healthy people (Craddock & Jones, 1999). BP can occur at any age, but it typically develops in late adolescence or early adulthood (Leboyer & Kupfer, 2010; National Institude of Mental Health). Just like SCZ, BP is likely influenced by many different genes. Recent research has identified multiple genes that may contribute to BP risk. Some specific gene variations have been associated with an increased risk of BP. For example, the CACNA1C gene is involved in calcium signaling in the brain and has been linked to the disease (K. L. Bigos et al., 2010). Trauma, stress, substance abuse, and other environmental factors may also play a role in the development of BP (Jiang et al., 2019) (Fass et al., 2014). Certain medical conditions, such as thyroid disorders, multiple sclerosis, and traumatic brain injury, have been linked to an increased risk of BP (Hu et al., 2013; McIntyre et al., 2008). Medications such as antidepressants and corticosteroids may also trigger manic episodes in some people (Bowers et al., 2003; Peet & Peters, 1995).

1.3 Symptoms

1.3.1 Positive and negative symptom

There are many symptoms involved in psychotic disorders, but the two primary symptoms are the hallucination and delusion (Larkin & Read, 2008; Whitfield et al., 2005). These are positive symptoms of psychosis which refers to gain of abnormal functions. Other positive symptoms include disorganized speech, Examples of negative symptoms include reduced motivation, lack of emotion, social isolation (Lencz et al., 2004; Piskulic et al., 2012) where patients start to lose their normal functions of life. These symptoms usually vary in different patients. This is one of the most recognized barriers in the field is phenotypic heterogeneity, where two patients with a diagnosis of SZ can present with completely non-overlapping symptom clusters (Chand et al., 2020). This suggests that multiple disease processes may exist for patients within the same diagnostic category. On the other hand, genetic, radiological, and neuropathological studies suggest psychotic disorders may not be biologically independent entities but can be considered as a continuum of overlapping syndromes (Craddock & Owen, 2007). The positive symptoms of SCZ are related to the recognition of "happy" faces, while patients with obvious negative symptoms often have negative beliefs when returning to society, thus affecting their social functions.

1.3.2 Cognitive symptoms

The focus of research within the field is usually on improving the positive symptoms like delusions and hallucinations because there are antipsychotic medications that could manage these aspects affectively. However, underlying the positive and negative symptoms are the cognitive impairments. Cognitive deficits in multiple domains are involved in psychotic disorders, including processing speed (Montalvo et al., 2014), attention (Rodriguez-Blanco et al., 2017), working memory (Brewer et al., 2005; González-Ortega et al., 2013; Niendam et al., 2006; Rodriguez-Blanco et al., 2017), verbal learning (Niendam et al., 2006; Sommer et al., 2001), visual learning (Niendam et al., 2006), problem solving (Chien et al., 2016) and social cognition (Addington & Addington, 2008).

1.4 Diagnosis

According to the DSM-5, a diagnosis of SCZ requires a combination of at least two characteristic symptoms (delusions, auditory hallucinations, speech disorders, behavioral disorders, negative symptoms) lasting for more than one month (symptoms must include one of the three). Prodromal symptoms or impaired social, occupational, or self-care function lasting for up to 6 months (including 1 month when symptoms are evident). The diagnosis of BP has two types. BP I has mainly manic episode with (at least one) along with depressive episode. A manic episode is defined as a distinct period of abnormally elevated mood that lasts at least one week, accompanied by other symptoms such as increased energy, decreased sleep, and etc. BP II has mainly depressive episode with at least one hypomanic episode. A hypomanic episode is similar

to a manic episode, but the symptoms are less severe and do not cause significant impairments in social or occupational functioning (American Psychiatric Association, 2013). The cognitive symptoms are not typically used as criterion for the diagnosis of psychosis because cognitive symptoms can be present in a variety of conditions and may not be specific to psychosis. However, cognitive symptoms are often evaluated as part of the overall assessment of a diagnosed patient, as they may provide important information about the severity and nature of the illness, as well as potential treatment targets (McCleery & Nuechterlein, 2019).

1.5 Assessments

There are many assessments that are commonly used in clinical diagnosis to evaluate symptoms of SCZ and BP. The most representative assessment is the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). It can assess the severity of SCZ and is usually used to assess the efficacy of antipsychotic treatments. Other scales include the young mania rating scale (YMRS) which assess patient's mania symptoms, Montgomery-Asberg Depression Rating Scale (MADRS) (Young et al., 1978) which assess patient's depression symptoms, and Multnomah Community Ability Scale (MCAS) (Barker et al., 1994) which measures patient's functioning with in the community.

The National Institute of Mental Health's Measurement and Treatment Research to Improve Cognition in SCZ (MATRICS) together evaluated also over 90 tests and selected the most promising tests to discover the MATRICS Consensus Cognitive Batter (MCCB). The MCCB produces 7 domain scores including processing speed, attention, working memory,

verbal learning, visual learning, problem solving, social cognition and a composite score which is the average of all the scores. It is now used as a standard battery in clinical assessments for cognitive deficits (Nuechterlein et al., 2008).

1.6 Magnetic resonance imaging (MRI)

There are many types of MRI techniques used in neuroscience: including diffusion MRI, myelin water imaging, arterial spin labeling, susceptibility weighted imaging, magnetization transfer, structural MRI (sMRI) and fMRI. The ones that were used in this project were sMRI and fMRI. Researchers usually compare the brain structure or function of subjects with certain types of illness to those without the illness. Differences identified by MRI can provide insight into their pathogenesis or identify biomarkers that can guide subsequent treatment. Changes in the intrinsic functional connectivity (FC) of the brain are associated with cognition in a wide range of psychiatric disorders. Therefore, the changes in resting state FC can be used as a method to explore the mechanism of the disease.

1.6.1 Structural MRI

The mechanism of sMRI is that the scanner takes magnetic resonance values of different areas of the brain and combine these data into an output that produces a high-resolution T1 image of the brain. Scientists can look at the gray matter (which mainly contains the bodies of nerve cells) and the white matter (which mainly contains the synapses that connect different parts of the brain) separately as needed. T1 images can also provide shape and size information of different areas of the brain. For example, the hippocampus, which is responsible for memory, is typically smaller in Alzheimer's patients than healthy people (Schuff et al., 2009).

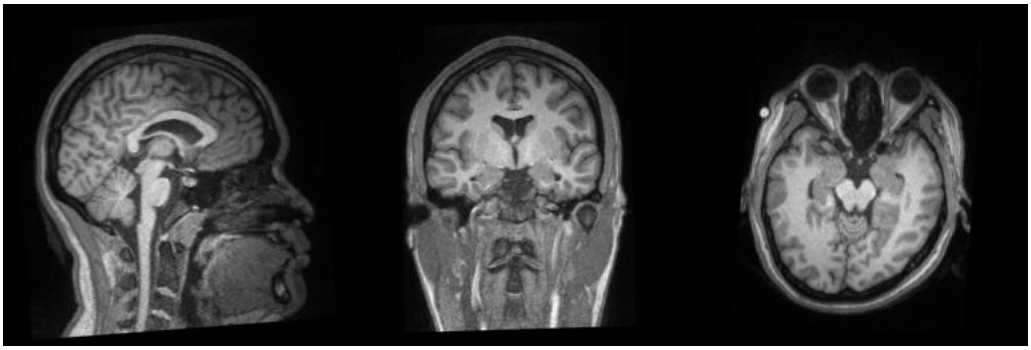


Figure 1. Visualization of an original T1 image. A structural T1 image view showing one slice each from in (a) sagittal, (b) coronal, and (c) axial plane.

1.6.2 Blood-Oxygen-Level-Dependent signal

When a certain brain region is activated, the synaptic activity of neurons will increases. This will cause energy consumption and oxygen consumption of the area increase, thus causing a large increase in the blood supply of this brain region. The increase thus affecting the up-regulation of oxygen metabolic rate in this brain region. As the energy generation process depletes the local oxygen reserves, waste products build up, causing vasodilation reactions. Cerebral blood flow increases, making oxygen supply greater than oxygen consumption. Thus, when neurons fire, the ratio of oxygenated hemoglobin to deoxygenated hemoglobin in this brain region increases (Bren et al., 2015).

fMRI imaging is based on this large rebound of local tissue oxygenation. Studies have shown that oxygenated hemoglobin is diamagnetism and deoxygenated hemoglobin is para-magnetism (Bren et al., 2015). This will allow the formation of the local magnetic field gradient, causing hydrogen protons in these different substances to feel different magnetic field intensity. When a brain region is activated, oxygenated hemoglobin is much higher than deoxygenated hemoglobin, resulting in a slower dephasing of hydrogen protons. The changes can be detected using T2-weighted imaging sequences to locate functional brain activity (Glover, 2011). Thus, the BOLD functional image that we often hear about is also a T2* image.

1.6.3 Functional MRI

Functional magnetic resonance imaging (fMRI) is a technique that used to record the BOLD signals of the brain related to certain tasks. It has been one of the leading methods for studying whole-brain function in humans since its inception in 1992. There are two primary types of fMRI, resting-state fMRI, and task-based fMRI. Resting-state fMRI is collected in the absence of any experimental task. The subject is usually asked to rest quietly with their eyes opened. Initial experiments suggest that various regions of the brain remain active during this process, expressed in low frequency BOLD fluctuations of around 0.01-0.1 Hz (Fransson, 2005; Kajimura et al., 2023). It is believed that temporal correlations between these fluctuations reveal the intrinsic functional organization of the brain (Biswal et al., 1995); thus, the most common method for analyzing resting-state fMRI is to measure the temporal correlation between BOLD signals in different brain regions. Task-based fMRI is a powerful tool to study neural activity in related to sensory, motor, or cognitive tasks over time. The scanning is done when the participant is instructed to perform tasks. The hemodynamic response is a key concept in task-based fMRI because it is used to identify which brain regions are activated in response to these tasks. It describes the time course of the changes of the BOLD signals in response to a neural stimulus. The BOLD response peaks around 3s to 5s after the stimulus is given, and persist before returning to baseline level. (West et al., 2019). In task-based fMRI analysis, researchers usually convolve onsets of task-specific conditions with the hemodynamic response function to generate statistical models (for example, the general linear model) that identify brain activations related with each condition (Calhoun et al., 2004).

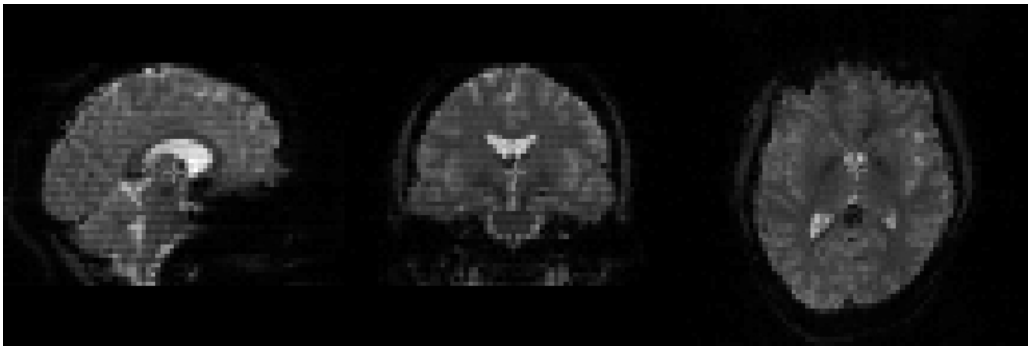


Figure 2. Visualization of an original BOLD image. A functional BOLD image view showing one slice each from in (a) sagittal, (b) coronal, and (c) axial plane.

1.6.4 Individual variability in functional connectivity architecture of the human brain

Our lab has investigated the individual differences in brain FC and found high levels of individual differences especially in the higher order association areas in the cortical networks (Mueller et al., 2013). The raw inter-subject variability across 23 healthy subjects was calculated by analyzing their functional connectivity calculated from the resting-state fMRI data. Then the intra-subject variability from the 5 scans of the same subject was obtained and regressed out from the inter-subject variability to get the pure inter-subject variability. We found large functional inter-subject variability in frontoparietal network, ventral attention network, default network and dorsal attention network. In contrast, the limbic system, motor sensory and visual areas demonstrated less inter-subject variability across individuals. We then compared the inter-subject variability map with the evolutionary cortical expansion map (evolutionary cortical expansion compared between an adult macaque and the average human adult PALS-B12 atlas) (Hill et al., 2010; Van Essen, 2005) and also found a high correlation ($r = 0.52$, $p < 0.0001$). Then we investigated the relationship between functional and anatomical variability. Individual variability in functional connectivity is found to be associated with the sulcal depth variability, but not associated with cortical thickness. These two analyses suggest that the evolution of the brain is characterized by the expansion of the cortical surface but the same cortical thickness. Lastly, to confirm whether our individual difference map overlaps with the known brain regions with large individual differences, we searched the literature for studies that are related to personality traits, memory performance, intelligence, and perception, and quantified them on the brain surface. The results showed that 73% of the regions found in these studies were consistent

with the regions with high differences. Areas of high variance are those with differences greater than the overall mean, which collectively cover 51% of the cerebral cortex.

1.6.5 Parcellating cortical networks in individuals

Our laboratory has implemented an initial version of the homologous parcellation algorithm using fMRI data from a publicly available dataset consisting of 10 healthy, young adults (Gordon et al., 2017). We first derived a group-level atlas using these 10 subjects, which included 213 parcels. Homologous regions of these 213 parcels in each individual's brain were then identified using the iterative algorithm, lobe by lobe. To examine reliability of the results, each participant's data was partitioned into two halves and assessed the within-subject overlap between parcellations derived from each half. The test-retest reliability, measured by the Dice coefficient, was 85.7% ± 1.9%. Homology of parcels between subjects was then examined using task-based fMRI data. The rationale is that the same task should activate homologous functional regions across individuals. We first tested this in the motor domain. Each participant moved different body parts (e.g., hand, tongue) in the scanner for a total duration of 76 min, allowing for robust mapping of task-activated regions. Brain regions activated by hand and tongue movements showed variable topographies across individuals. However, these activations fell within the same two parcels in every subject. Across all 10 subjects, 95.1% ± 4.0% of the top 10% most activated vertices fell within these two parcels. This high convergence suggests that the parcels derived from rs-fMRI can reflect homologous motor functions across individuals. We next examined the language domain. Using 3 subjects as the Discovery sample, we found 3 parcels that were significantly activated by the language task. We predicted that the same task would activate the same parcels in

a sample of new subjects. Our results showed that these parcels were indeed all activated in the 3 previously unseen, testing subjects, supporting the homology of these parcels across individuals.

1.7 Brain changes related to psychosis

1.7.1 Structural change in psychosis

Psychosis is often accompanied by structural brain abnormalities. However, it remains unclear when these structural changes occurred and how they developed over time. Thus, the question of SCZ as a progressive brain disorder remains unresolved. Studies from the preclinical phase to the regression phase of psychosis have shown that the loss of cortical gray matter is more significant in patients who later transitioned to SCZ. Patients with first-episode psychosis revealed a decrease in multiple gray-matter regions (e.g., frontal lobes and thalamus) with disease progression, as well as progressive cortical thinning of the superior and inferior frontal gyri. Also, visual hallucination was found to be associated with lower white matter integrity in the inferior longitudinal fasciculus in SCZ patients (Ashtari et al., 2007). Recently, a quantitative review of magnetic resonance imaging studies in SCZ demonstrated significantly structural changes in volume changes of several brain structures, such as intracranial, lateral, and third ventricle volumes, relative to controls. (Kuo & Pogue-Geile, 2019). There is sufficient evidence that SCZ is associated with abnormality in the gray matter especially in the early stages of the disease (Blakemore & Choudhury, 2006). Few studies investigated in white matter microstructure in long-term psychosis. However, the relationships between structural changes and the course of chronic psychosis should be concluded with caution. Prolonged treatment,

higher doses of antipsychotic drugs, or concomitant epiphenomena of illness may confound the results (Stroup & Gray, 2018).

Structural changes in the brain have also been observed in people with BP. Studies have found reduced gray matter in certain regions of the brain, particularly in the prefrontal cortex, and this might be caused by mood state (Wang et al., 2019). The prefrontal cortex is responsible for decision-making and emotional regulation. Abnormality in the prefrontal cortex may result in disrupted communication between different parts of the brain, mood instability and other symptoms of BP (Fernandes et al., 2019). Studies also found that dysregulation of salience network is associated with reduction in grey matter thickness in insular and anterior cingulate cortex. amygdala, and hippocampus (Matsubara et al., 2016). These regions are involved in mood regulation, emotional processing, and memory. The lateral ventricle volumes were also larger in BP than healthy people (Hibar et al., 2016). But this is this is found to be associated with more hospitalization and unemployment, but not with the severity of the illness (Pearlson et al., 1984).

1.7.2 Functional change in psychosis

Previous research has shown that patients with BP have cognitive impairments involving multiple areas of attention, verbal learning and memory, executive function, and social cognition during the acute phase of depressive or manic episodes, which persist even in remission (Sanches et al., 2015). For example, imaging studies have shown that certain areas of the brain may exhibit functional abnormalities in people with BP. For example, the amygdala, which is involved in emotional processing, may be more active in people with BP, particularly during manic episodes

(Altshuler et al., 2005). Other studies have found reduced amygdala-prefrontal connectivity, particularly during episodes of depression (Dannlowski et al., 2009). In the default mode network, Decreased connectivity were found between the medial prefrontal cortex (mPFC) and PCC in BP compared with healthy controls, and this was found to be associated with decreased processing speed (Nguyen et al., 2017; Zhang et al., 2022). The connectivity between ACC and PCC were found to be decreased in BP patients and this is associated with disrupted mood (Gong et al., 2019; Rey et al., 2016). The decrease connectivity between the salience and limbic network were related with greater severity of mood dysregulation (Anand et al., 2009). In frontal parietal network, increased activity was found in DLPFC, and decreased activity was found in dorsal medial prefrontal cortex (DMPFC), mPFC and precuneus in a n-back working memory task. These abnormalities are associated with the working memory function, difficulty in regulating emotions and dysregulation in response to emotional stimuli (Rodríguez-Cano et al., 2017).

Patients with SCZ have extensive cognitive impairment which is related to the progression of SCZ and the stage of the disease. They usually show obvious negative symptoms and beliefs when returning to society, thus affecting their social functions. Researchers have found that the ability of emotional face recognition and emotion management in SCZ patients was lower than that in healthy control group (Hargreaves et al., 2016). In a study where participants were asked to perform a visual oddball task, SCZ patients showed reduced activity in dorsal and ventral attention networks compared with healthy controls (HCs). Visual oddball task is a common task used to evaluate participant's cognitive and attention functions (Wynn et

al., 2015). Studies have also found hypoactivation in dorsolateral prefrontal cortex (DLPFC) (Carter et al., 1998) and hyperactivation in the ventrolateral prefrontal cortex compared with HCs during verbal working memory tasks. The tasks involved memory encoding and manipulation of the information (Tan et al., 2005). In addition, BOLD activity in posterior cingulate cortex (PCC) was found to be positively correlated with regions within the default mode network including surrounding regions, precuneus, anterior cingulate cortex, and medial prefrontal cortex in general population. However, SCZ patients had less correlation between those regions comparing with HCs. Positive symptoms in SCZ were found to be positively correlated with connectivity between PCC and regions including the bilateral premotor and bilateral temporal gyrus. Negative symptoms were found to be positively correlated with connectivity between PCC and right fusiform gyrus, and negatively correlated with connectivity between PCC and right premotor region, right middle and left superior temporal gyri, left inferior frontal gyrus and right dorsal anterior cingulate gyrus. Dysfunction in dorsal lateral prefrontal cortex is associated with cognitive disorganization, but not associated with positive or negative symptoms (Perlstein et al., 2001). Decreased activation in dorsal lateral prefrontal cortex is associated with abnormal working memory function (Callicott et al., 2000).

However, we still could not gather a unified understanding of network dysfunction in psychosis. Many studies that examine functional networks in psychotic patients have produced inconsistent findings, suggesting increases or decreases in FC at rest, and hyper- and hypo-activity across a variety of brain regions during task performance. For example, sustained attention tasks were designed to test patients' ability to focus and respond to specific cognitive command or stimuli. Several studies reported increased activation in anterior cingulate cortex

(ACC) and PCC in SCZ patients during sustained attention tasks comparing with HCs (Honey et al., 2005; Wolf et al., 2008), while others reported decreased activation (Gur et al., 2007; Liddle et al., 2006; Morey et al., 2005). In another study, researchers found larger deactivation in PCC in SCZ patients when performing attention tasks with respect to HCs (Harrison et al., 2007). Lesh et al. in 2013 have found reduced activation in DLPFC and inferior parietal cortex in first episodic psychotic patients (FEP) (Lesh et al., 2013), while Keedy et al. in 2015 found increased activation in DLPFC in FEP patients (Keedy et al., 2015). Similarly, insular cortex was found to have increased (Wolf et al., 2008) and decreased (Liddle et al., 2006) activation bilaterally, showing how inconsistent results have been. In fact, abnormal functional activity and connectivity have been reported in almost every major network, rendering an extremely complex and obscure picture of "network dysfunction".

Overall, these studies all provide valuable insights into the cognitive impairments observed in psychosis. The cognitive impairments observed in these disorders are complex and multifaceted, affecting various cognitive domains and functional networks. Understanding the network dysfunction underlying these deficits is necessary for the treatment of psychosis.

1.8 Commonalities between SCZ and BP

The classification of SCZ and BP originates from Kraepelin's classification of psychoses (Kendler, 2020). However, research has shown that there are commonalities between the two disorders, which has led some studies to suggest a disease continuum between the two (Craddock et al., 2006; de Sousa et al., 2023). Studies have shown that both SCZ and BP have similar

genetic factors and share some overlapping genes (Kristin L. Bigos et al., 2010; Chumakov et al., 2002; Hattori et al., 2003). Brain imaging studies have also found similar abnormalities in white matter (Anderson et al., 2013; Cui et al., 2011; Ellison-Wright & Bullmore, 2010) and brain connectivity patterns between the two disorders (Wagner et al., 2015). Dysfunctional features in neurotransmitter systems, such as dopamine (Jauhar et al., 2017), serotonin (Patrick & Ames, 2015), GABA (Fatemi et al., 2017), and glutamate (Fiorentino et al., 2015), are present in both disorders. These findings suggest that there may be underlying mechanisms that contribute to both SCZ and BP. Understanding the relationship between the two disorders may lead to improved diagnosis, treatments, and managements of these common conditions.

Chapter 2. Methods

2.1 Datasets

The MATRICS dataset has been acquired at McLean hospital in Belmont, Massachusetts. The dataset includes imaging, clinical and cognitive data from 232 subjects. Cognition scores comprised of 7 domain scores (Processing Speed, Attention, Working Memory, Verbal Learning, Visual Learning, Reasoning/Problem Solving, Social Cognition) and a composite score were measured using the MATRICS Consensus Cognitive Battery (Nuechterlein et al., 2008) in all patients and HCs. Clinical symptoms were measured in patients include the Positive and Negative Syndrome Scale (PANSS), the Young Mania Rating Scale (YMRS), Montgomery-Asberg Depression Rating Scale (MADRS), and the Multnomah Community Ability Scale (MCAS).

2.1.1 Participants

Participants included HCs, BP, SCZ and SZA patients. After quality control, data from 207 subjects (77 women; age: 18 ~ 68 yrs; BP: 79, SCZ/SZA: 48, HC: 80) with high fMRI imaging quality were retained for analysis (SNR> 100, mean motion < 0.3mm). These participants' demographic characteristics are summarized in Tables 1. The purpose of having cross-diagnostic groups in the analysis was to see how cognitive scores from different groups would fit into the overall distribution and to compare cognitive deficits in those groups with respect to healthy controls.

Subjects were divided into two group: a Discovery cohort (n =104, 41 women, age: 18 ~ 68 yrs, BP: 40, SCZ/SZA: 24, and HC: 40) and a Validation cohort (n =103, 36 women, age: 18 ~ 68 yrs, BP: 39, SCZ/SZA: 24, and HC: 40) to test the generalizability of the models. Subjects within each dataset were matched in age, gender, and head motion across BP, SZC/SZA, and HCs to ensure the results were not driven by differences in demographics and head motion.

Discovery: n = 104, age, gender and motion matched

	SCZ/SZA (n=24)		BP (n=40)		HC (n=40)		p
	M	SD	M	SD	M	SD	
Age, yr	30.91	9.47	27.30	9.57	26.52	7.29	0.334
Gender	Male: 17; Female: 7		Male: 24; Female: 16		Male: 22; Female: 18		0.540
Mean FD	0.105	0.060	0.084	0.050	0.089	0.059	0.463

Validation: n = 103

	SCZ/SZA (n=24)		BP (n=39)		HC (n=40)		p
	M	SD	M	SD	M	SD	
Age, yr	31.79	9.96	26.84	8.31	27.25	8.70	0.216
Gender	Male: 19; Female: 5		Male: 23; Female: 16		Male: 25; Female: 15		0.333
Mean FD	0.115	0.077	0.093	0.057	0.074	0.054	0.851

Table 1. Demographics. (Top) Discovery Cohort: n=104. (Bottom) Validation Cohort: n=103. Subjects within each dataset were matched in age, gender, and head motion across BP, SZ/SZA, and HCs (one-way ANOVA test, $p > 0.2$) to ensure the results were not driven by differences in demographics and head motion in scanner. FD: framewise displacement.

2.2 Imaging data analysis

2.2.1 MRI data acquisition and preprocessing

MRI data were acquired using a 3T Siemens scanner with 12-channel head coil. The T2-weighted imaging of TR = 2500 msec, flip angle = 82.00 degrees, voxel size = 3.5x3.5x3.5 mm^3, nframes = 240, FOV = 64, orientation = LPS, were used for BOLD fMRI. Participants were instructed to remain still with eye their open and perform two 6-mins resting-state scanning.

Structural MRI data were processed via the FreeSurfer software environment (Dale et al., 1999; Fischl, 2012) using the recon-all command. Recon-all stands for reconstruction, like the reconstruction of a two-dimensional cortical surface from a three-dimensional volume. The images we collected from the MRI scanner were 3D blocks, which were converted by recon-all into smooth, continuous two-dimensional surfaces. In brief, the following steps was applied to each subject: 1) Motion correction and conform. Small movements were corrected and the images were averaged if the same subject has multiple images. 2) multiple intensity normalization. Scale the intensity of all voxels. 3) Skull strip. 4) White matter segmentation. Separating white matter from everything else. 5) Creating original cortical and subcortical mass. The midbrain is cut off from the brain, and the two hemispheres of the brain were cut off from each other. 6) Tessellation. Creating the original surface, which is created by filling hemispheres with triangles. The point where the points of a triangle meet is called a vertex. 7) Smooth. After tessellation, vertex position needs to be adjusted to smooth the jagged surface filled by the

triangles. 8) Spherical inflation and registration. This step is for registering the surface to the spherical template atlas. 9) Contralateral surface registration. Registering to the contralateral atlas for comparing the corresponding regions in both hemisphere of the brain and studying functional connectivity and asymmetry between the two hemispheres. 10) Cortical parcellation and statistics. Create anatomical labels for each location on the cortical surface, and a statistical table for anatomical information including structure name, number of vertices, surface area, gray and white volume, cortical thickness, and curvature information. Reconstruction would allow individual's resting-state fMRI data to be projected onto their cortical surface anatomy.

Resting-state fMRI data were preprocessed using a series of steps developed in a previously published pipeline (Mueller et al., 2015; Mueller et al., 2013; Wang et al., 2015; Wang et al., 2013; Wang et al., 2014) from our laboratory. In brief, the following preprocessing was applied for each subject: 1) The first 4 volumes of the BOLD scans was discarded to account for magnetization stabilization. 2) Motion correction. In the scanner, participants moved their bodies as they acquired the images, which led to mismatches in the subsequent images over time. This type of motion artifact could be partially corrected by a simple rigid body transformation. The transformation estimates six correction parameters by three translations in the X, Y, and Z directions and three rotations around the X, Y, and Z axes, aligning each individual image with a reference image. 3) Slice-timing correction. In a TR (Repetition time) of scanning, several brain slices were usually scanned. Since only one brain slice could be scanned at a time, there will be some difference in scanning time between each brain slice. Interpolation was used to align brain slices scanned at different time points within the same TR. 4) Spatial smoothing was used to eliminate interference signals generated by the hardware instability and physiological motion. It

was achieved by applying a Gaussian kernel to the data, which weights the intensity values of surrounding voxels to reduce noise. The number of voxels that were smoothed or blurred is determined by the size of the kernel, defined by the half-valued full width (FWHM) of the Gaussian kernel. The FWHM is defined as the width of the pick at half of its maximum value. A larger FWHM corresponds to a larger kernel and a greater degree of smoothing.

2.2.2 Quality control

BOLD signal is known to be highly sensitive to motion-related artifacts and physiological noise, as well as equipment instability due to random processes. Therefore, fMRI data denoising is not only essential for improving data quality, but also helps to improve the repeatability and reliability of the study. The quality control involves a series of steps: 1) Exclusion for subjects that have mean head motion > 1 mm and SNR < 100, 2) Visual inspection for T1, BOLD raw images to look for possible motion-related artifacts such as blurring or ghosting that might affect the quality of the data and the FC maps in the next step. 3) Check whole-brain FC maps for ROIs in ACC, PCC of the default network, and motor cortex. These seeds were commonly used in fMRI quality control because they provide consistent and robust connectivity maps that can seve as a reference for brain activity (Andrews-Hanna et al., 2014; Buckner et al., 2008). These steps increased the likelihood that the data included in the analysis were of good quality and that the results would not be affected by head motion and imaging artifacts.

2.2.2 Individualized fine-grained parcellation

Our laboratory has established a series of technologies to localize fine-grained cortical functional networks at the single-subject level using rs-fMRI (Brennan et al., 2019; Langs et al., 2016; Li et al., 2019; Wang et al., 2015; Wang et al., 2018; Wang et al., 2020). These methods show high within-subject reproducibility and can be validated using invasive cortical stimulation mapping in surgical patients. These novel techniques were used in this project to map the homologous, fine-grained functional regions in the discovery dataset.

The goal is to parcellate an individual subject's brain into 92 functional clusters based on rs-fMRI. The following constraints were applied in the individualized functional network parcellation to maximize between-subject homology of the resulted parcels. First, the iterative parcellation procedure is initially guided by a group-level, fine-grained functional network atlas from the fMRI data of 10 healthy, young adults (Gordon et al., 2017). The group-level atlas was projected to each individual's brain and then an iterative algorithm gradually adjusted the network boundaries, allowing individual-specific information to replace the group information. To maximize homology between subjects, the iterative parcellation was performed within each lobe of the cortex. This constraint ensured that for a functional region in a given lobe, its homologous region in a different subject will be located in the same lobe. The Desikan Killiany atlas (Desikan et al., 2006) was used to segment each hemisphere into the frontal, temporal, parietal, and occipital lobes. A fifth "lobe" which consists of regions surrounding the central sulcus (i.e., pre-, post-, and para-central regions) was also included. After each lobe was parcellated into multiple functional regions, the regions at the borders of the lobes were merged

based on functional correlation. During the subject-level parcellation, for each cluster, I used the group-level FC signature of that cluster as a potential indicator for determining inclusiveness. In other words, a voxel is more likely to be assigned to a cluster if its connectivity to the rest of the brain resembles the cluster's connectivity signature observed at the group-level.

The reliability of parcellation was evaluated using Dice's coefficient. We partitioned the rs-fMRI data of each subject into two halves. Test-retest reliability was calculated as the similarity of the network parcellation derived from the two halves of the data. Specifically, we compared the dice similarity of the parcellation between two segments in each subject (intra-subject reliability) and variability across different subjects (inter-subject variability).

2.2.3 Resting-state connectomes

The 92 functional networks generated above were analyzed as 92 ROIs. The time courses for each network were extracted, and the correlation between any two ROIs was calculated to obtain a unique 92×92 functional connectomes for each subject.

2.3 Prediction models

Support Vector Machine for Regression (SVR) and Leave-One-Out cross validation (LOOCV) was used to construct prediction models. Permutation tests were also be applied to avoid overfitting. These analyses were done through MATLAB and Python. A trans-diagnostic approach was used, by combining all the groups to construct prediction models, as there is often overlap in clinical symptoms and cognitive impairments in psychosis. In the case of SCZ and BP, both are associated with similar cognitive impairments, which makes it reasonable to combine the patient groups for prediction. Including healthy controls in the prediction model allowed us to compare between psychotic patients and general population. This can help distinguish cognitive impairments that are associated with the disorders themselves versus those that are within the range of normal cognitive functioning. Additionally, it could also provide a larger sample size and increase the statistical power to draw more definitive conclusions for the findings.

2.3.1 Support Vector Machine (SVR) and Leave-One-Out Cross Validation (LOOCV)

Cross-validation is widely used to assess the validation performance of the models/biomarkers. However, internal LOOCV accuracy is not equivalent to an assessment of how the model will perform on new data, as excellent models obtained by internal cross-validation may perform substantially worse on held-out datasets. Therefore, to assess biomarkers' generalizability, other than test them with internal cross-validation, it is crucial to additionally test the final model on a completely held-out dataset.

Support Vector Machine is a supervised learning model that is widely used for fMRI data classification (Song et al., 2011) and regression analysis (Vergun et al., 2013). The LOOCV procedure will also be adapted in the training process to estimate the prediction performance of the model.

Specifically, I constructed the model with a set of labelled training data that consists of the input data (resting-state connectomes) and a selected output (a specific cognitive score). The machine learning algorithm adjusted the weights for features that contribute to prediction in the input data based on the desired output. For the LOOCV procedure, n-1 subjects were used to train the model and then the resulting model was applied to the 1 subject to predict the subject's cognitive score. The correlation between the observed scores and the predicted scores were evaluated with Pearson correlation.

2.3.2 Permutation test

The cognition scores of all the subjects in the Discovery cohort were randomly reshuffled 1000 times, and correlation between predicted cognition scores and observed cognitive scores were rerun. The permutation *p* value was estimated by calculating the percentage of permutations that yielded a predicted-observed score absolute correlation value higher than the real predicted-observed score absolute correlation.

Chapter 3. Results

3.1 Score Prediction

3.1.1 Parcellation Reliability

The intra-subject similarity was 0.67±0.05 ranged from 0.48 to 0.78. The inter-subject variability was 0.52±0.02 ranged from 0.43 to 0.56.

3.1.2 Internal validation - Cognitive Score prediction on discovery dataset

Using the Discovery cohort, we constructed prediction models based on the resting-state functional connectomes and the 8 cognitive scores. Correlations between the predicted cognitive scores and observed cognitive scores are shown in Figure 1. FC could predict six ouf of eight cognitive scores using LOOCV within the discovery sample. The correlation values for the successful models were verbal learning score ($r = 0.29$, $p = 0.002$), working memory score ($r = 0.42$, $p < 0.001$), attention score ($r = 0.24$, $p = 0.011$), processing score ($r = 0.27$, $p = 0.004$), social cognition score ($r = 0.26$, $p = 0.006$) and composite score ($r = 0.33$, $p < 0.001$). Visual score ($r = 0.17$, $p = 0.081$) had a lower correlation value and problem-solving score ($r = -0.27$, $p = 0.005$) had a negative correlation value.

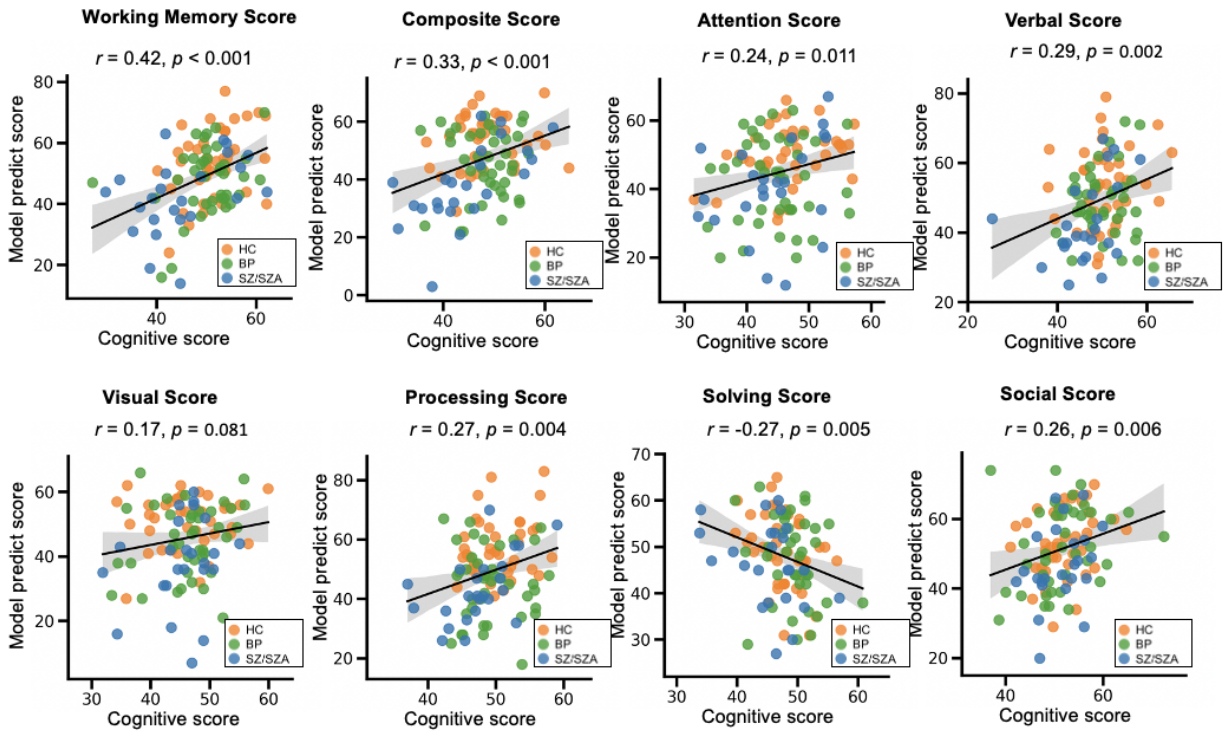


Figure 3. Cognitive score prediction based on FC from the discovery cohort. Models were trained to predict the eight cognitive scores using FC data of 104 subjects from the discovery cohort. The models were validated within the discovery data using the LOOCV approach. The scatter plots showed the correlation between the predicted cognitive score and observed cognitive score. Each dot represents one subject. Three subject groups (SCZ/SA, BP, and HC) were color-coded. The line and shadow indicated the linearly fitted value with a 95% confidence interval for the mean. Six out of eight cognitive scores could be predicted from FC.

3.1.3 External validation

The performance of the prediction models was then evaluated with the validation cohort to estimate the generalization performance of the models to independent populations. These models could successfully predict working memory ($r = 0.23$, $p = 0.016$), composite score ($r = 0.25$, $p = 0.008$) and attention score ($r = 0.24$, $p = 0.014$) in the validation dataset. Three of the prediction models constructed using the discovery sample can be generalized to the validation sample. The correlations for the other models were verbal learning ($r = 0.20$, $p = 0.041$), visual learning ($r = 0.17$, $p = 0.076$), processing speed ($r = 0.011$, $p = 0.233$), problem solving ($r = -0.10$, $p = 0.272$), and social cognition ($r = 0.10$, $p = 0.302$)

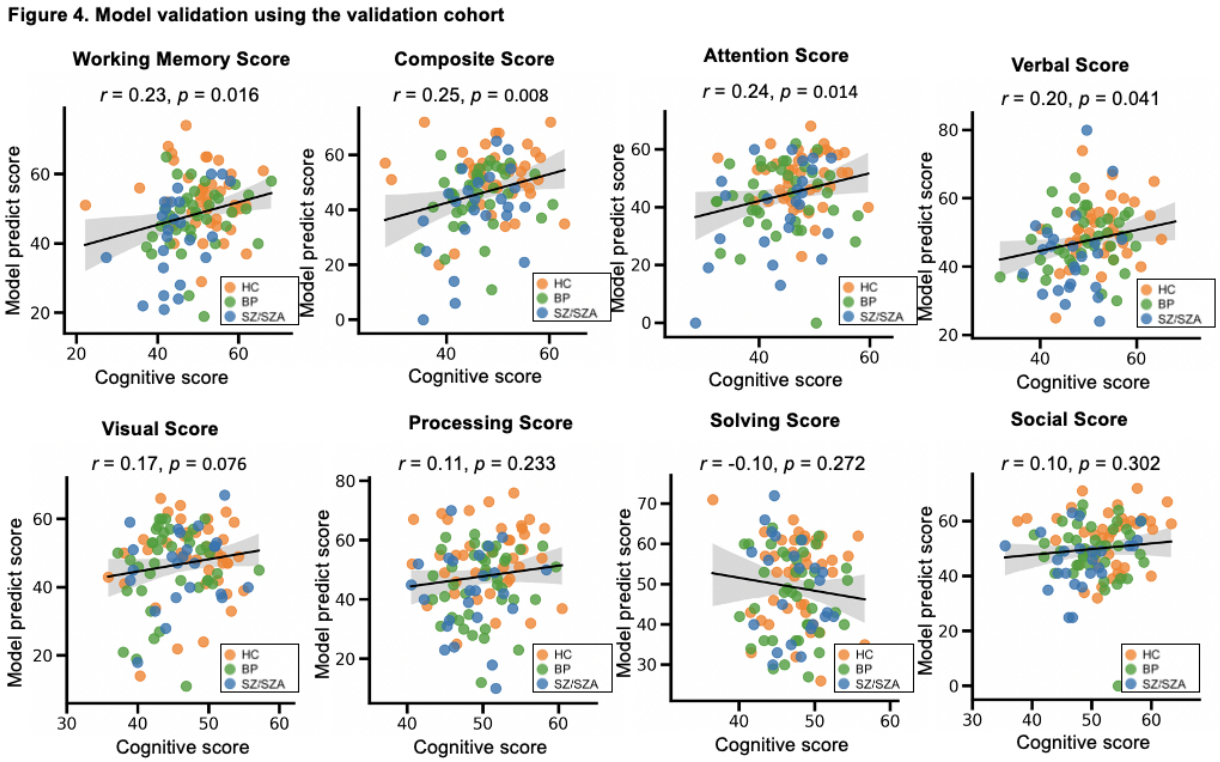


Figure 4. Model validation using the validation cohort. Prediction models trained from the discovery cohort were directly applied to 103 subjects in the validation cohort to predict eight cognitive scores. The scatter plots showed the correlation between the predicted cognitive score and observed cognitive score. Each dot represents one subject. Three subject groups (SCZ/schizoaffective disorder, BP, and HC) were color-coded. The line and shadow indicated the linearly fitted value with a 95% confidence interval for the mean. Three models trained in the discovery cohort can be generalized to predict cognitive scores in previously unseen data.

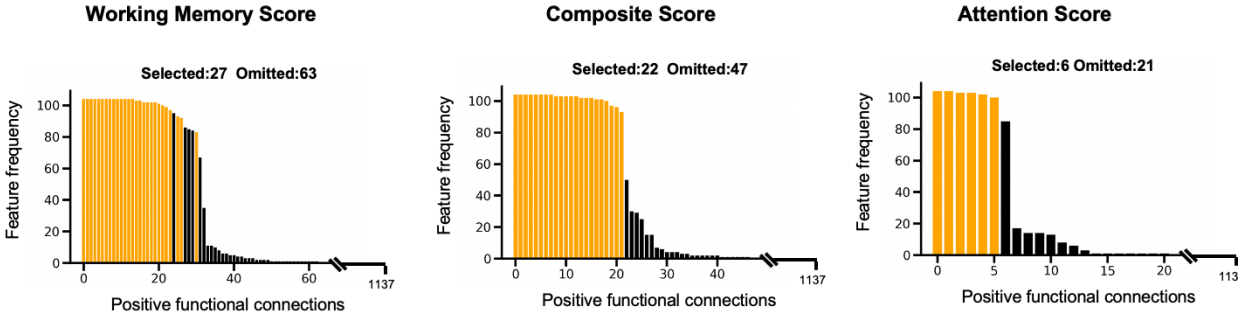
3.2 Analysis on selected features

3.2.1 FC features involved in the prediction of three cognitive scores

Using the LOOCV, we predicted one subject's score using the rest of the subjects and generated a prediction model for each subject in the discovery dataset. This allow us to compare between the models and extract functional connections (features) that were frequently selected during the training. The 1137 positive functional connections from all the connections that were related to working memory score, attention score and composite score were shown in Figure 2. Out of all the positive connections, 27 connections for working memory score, 16 connections for composite score, and 6 for attention score trained from the discovery sample were the frequently selected features in LOOCV (orange). Figure also shows an important subset of features that were selected at least once in all LOOCVs (black) but were not considered features due to low weight of the connection during the training, suggesting the stability of the selected features across cross-validations in discovery.

Figure 5. Within- and between- network connections involved in the prediction models

(a) Stability of the selected features across 104 cross-validation sets in Discovery



(b) Identified features related to cognitive symptoms in Discovery

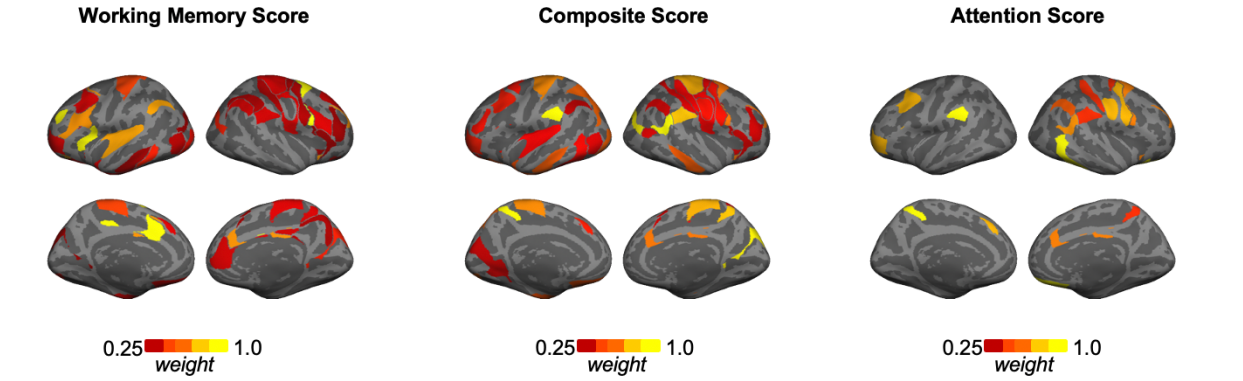


Figure 5. Brain connections involved in the prediction of three cognitive scores were reliable (a). The histogram plots show brain connections that were involved in the prediction models during model training. Connections that were frequently selected during LOOCVs and remained in the final model were shown in orange. Connections that were selected at least once in all LOOCVs but didn't reach the significant feature weights for prediction to be included in the final models were marked grey. The plots show that connections in the final models (orange bars) were reliably selected in LOOCVs in the discovery data. (b). Brain regions involved in the prediction models for working memory score, composite score and attention score were visualized on brain surface. The regions involved in the prediction of working memory include

regions in the left frontal parietal control network, whereas regions involved in the prediction of attention include regions in the right dorsal attention network.

3.2.2 Identification of cognitive related brain features

The Connections related to working memory score, composite score and attention scores based on the entire discovery sample were shown in Figure 6. Yeo's 7-network parcellation, which divides the brain into 7 large-scale functional networks, was used for visualization purpose to illustrate the overall connectivity patterns between different brain regions and networks (Yeo et al., 2011). The large-scale networks could provide a more accessible and interpretable way of presenting the results. There were cross-hemisphere connections for working memory score and composite score. There were also several connections that connect to the default, motor, attention, and the visual network. For composite score, connections related to default, motor, visual, attention and frontal parietal networks were found at similar regions but with different connection patterns. Connections for attention scores were mainly located in the right hemisphere. Two of them connected to the left hemisphere (Figure 6 top). For all three scores, selected connections were mainly between networks. Connections related to working memory were mainly involved in left frontal parietal networks, whereas connections identified by the attention score model were mostly involved in the attention network. Importantly, frontal parietal networks showed many within-network connections for working memory scores only.

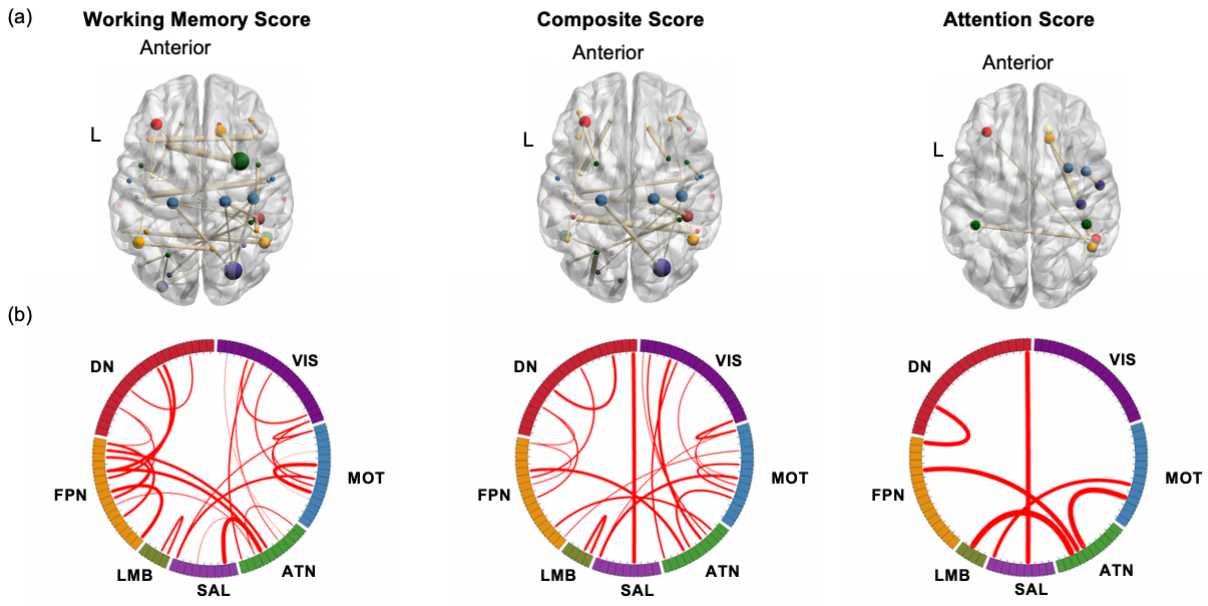


Figure 6. Within- and between- network connections involved in the prediction models. (a, upper). Connections selected by the prediction model were illustrated in the brain. Colors indicated brain regions in visual network (VIS, purple), somatomotor network (MOT, blue), attention network (ATN, green), salience network (SAL, violet) and frontoparietal network (FPN, orange), according to Yeo's 7-network parcellation of the human cerebral cortex. The size of the sphere represented how many connections are involved in this region, while the thickness of the connecting lines represented the feature weight of each connection in the prediction models. (b, lower). Selected connections were shown in the chord graph. The brain regions of the seven networks were represented on a circle. The weights of connections were represented by the thickness of the line. The connectivity markers include both within- and between- network connections.

3.2.3 Feature comparison between patients and HCs

The identified FCs that track cognitive performance of working memory (27 FCs), attention score (6 FCs) and composite scores (22 FCs) were then combined into 35 non-overlapping FCs. They were considered as the trustworthy biomarkers in characterizing cognition in this project. We next investigated whether these cognitive FCs were changed in patients based on the whole dataset.

These 35 FCs were then compared between patients vs. HC. 13 FCs were found to be significantly different in patients ($p < 0.05$) as compared to controls. The connected functional regions of the changed FCs were shown in the chord graph in Figure 4. Compared to the HCs, patients have decreased FC in frontal parietal network, salience network, attention network, visual network, and default network. Our results also show that there was increased FC especially in frontal parietal network and attention network in patients. Connections in patients were still mainly between networks except that there was one increased connection in frontal parietal network, one increased connection in default network, and one decreased connection in limbic system. Because the identified FCs related to the working memory, attention, and composite scores were effectively generalized to the independent cohort, these 13 FCs were considered as a marker for cognitive impairment.

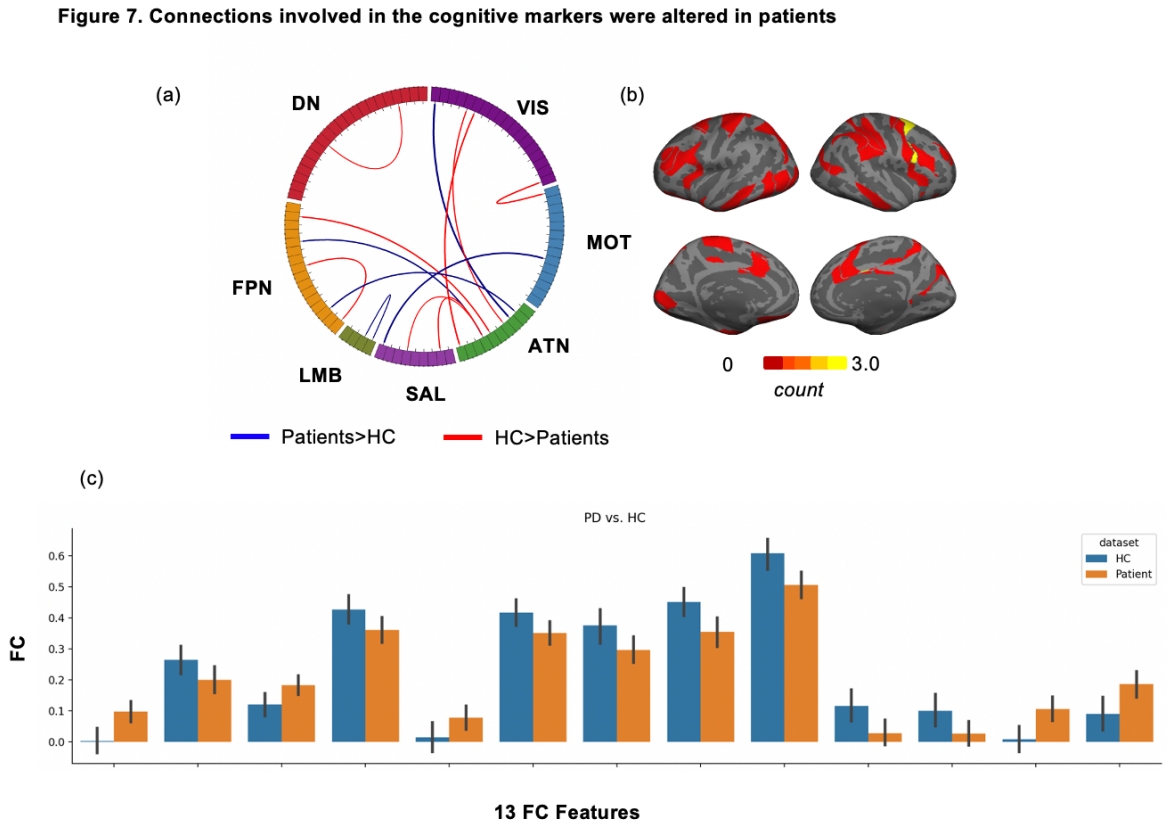


Figure 7. Connections involved in the cognitive markers were altered in patients. a) 35 non-overlapping FCs that track cognitive performance of working memory score (27 FCs), composite score (22 FCs) and attention scores (6 FCs) were identified and compared. Chord graph showed 13 FCs selected from the three prediction models that were significantly changed in patients. These 13 FCs track working memory score, attention score and composite score. Red lines represented the positive connections and blue lines represented the negative connections. b) Brain regions involved in these 13 connections were shown on the brain surface. c) These 13 connections were compared between patients and controls (127 patients vs. 80 HCs) and shown in bar plots. All 13 FCs were significantly changed in patients (all $p < 0.05$). These connections mainly involved in attention and salience networks. There were four connections that were stronger in patients and nine connections that were stronger in HC.

Chapter 4. Discussion

4.1 Summary of results

This project revealed a method for predicting cognitive performance using fMRI and found FC markers that contributes to cognitive deficits in psychosis. fMRI data were separated into discovery cohort and validation cohort. First, an individualized approach was used to construct resting-state functional connectomes for each subject. LOOCV and SVR algorithms were then applied to train prediction models for MCCB cognitive scores the discovery dataset. Within the eight cognitive domains, models for could be successfully predicted using the LOOCV during the internal validation. For external validation, we applied the same prediction models on the validation dataset. Results showed that models for working memory score, composite score and attention score could predict the cognitive scores in independent datasets. Then we compared the models developed during each LOOCV and selected multiple brain connections that were predictive to these cognitive scores. By visualizing the connections (working memory score: 27; composite score: 22; attention score: 6) on the brain, we found that these frequently selected features were mainly located in the frontal parietal network, dorsal attention network and ventral attention network. To investigate how those connections differ between patients and HC, we combined the FCs into 35 non-overlapping FCs. Within the 35 FCs, 13 FCs were significantly changed in patients. Four connections were significantly increased in patients and nine connections were significantly decreased.

4.2 Results interpretation

Within the three cognitive prediction models that were able to be generalized to independent datasets, the working memory network was known to be the most complicated and required the coordination of multiple brain regions. This was shown in our results were multiple brain regions were shown to be related to working memory scores. Many of the FCs in the selected features were associated with prefrontal cortex as this region is involved in the selection, maintenance, and manipulation of information in working memory. Regions like medial frontal gyrus, inferior and middle frontal gyrus were all highly weighted in the working memory prediction model. These were all consistent with previous research related to working memory (Chen et al., 2021; Emch et al., 2019). Studies have also shown that damage to the DLPFC could impair working memory performance (Perlstein et al., 2002).

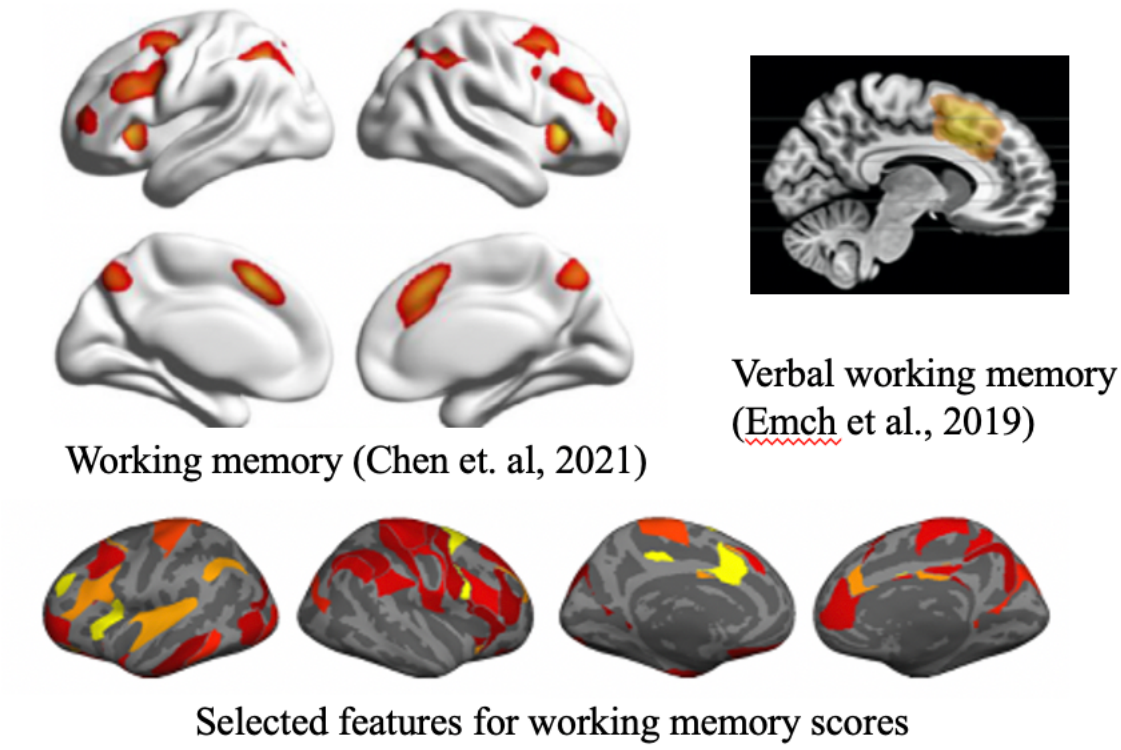


Figure 8. Comparing between selected features for working memory scores and working memory task-related activation. (a, upper left) Activated brain regions in both hemisphere from a n-back working memory task including frontal pole, middle frontal gyrus, frontal eye field, superior parietal lobule, insular, precuneus and anterior cingulate cortex. (b, upper right) Significant activation of superior frontal gyrus and anterior cingulate cortex. (c, bottom) Selected features from our working memory model showing consistent regions with related studies.

The selected features for attention scores were mainly located in frontal and parietal cortex. This is consistent with previous research as frontal cortex is responsible for attention control and parietal cortex is responsible for visual attention and integrating sensory information from multiple modalities. Additionally, ACC was also known to be involved in attention. These features were also consistent with an attention related task as shown in Figure 6 In this study,

researchers have found that frontal parietal regions were mainly involved in alerting, while parietal cortex were associated with alerting and orienting (Fan et al., 2005). Executive controls were associated with frontal areas as well as ACC (Fan et al., 2005). Most features selected were located on the right hemisphere. There could be explained by lateralization of attentional processes such as language processing or spatial attention which were mainly lateralized toward the right hemisphere (Petit et al., 2015).

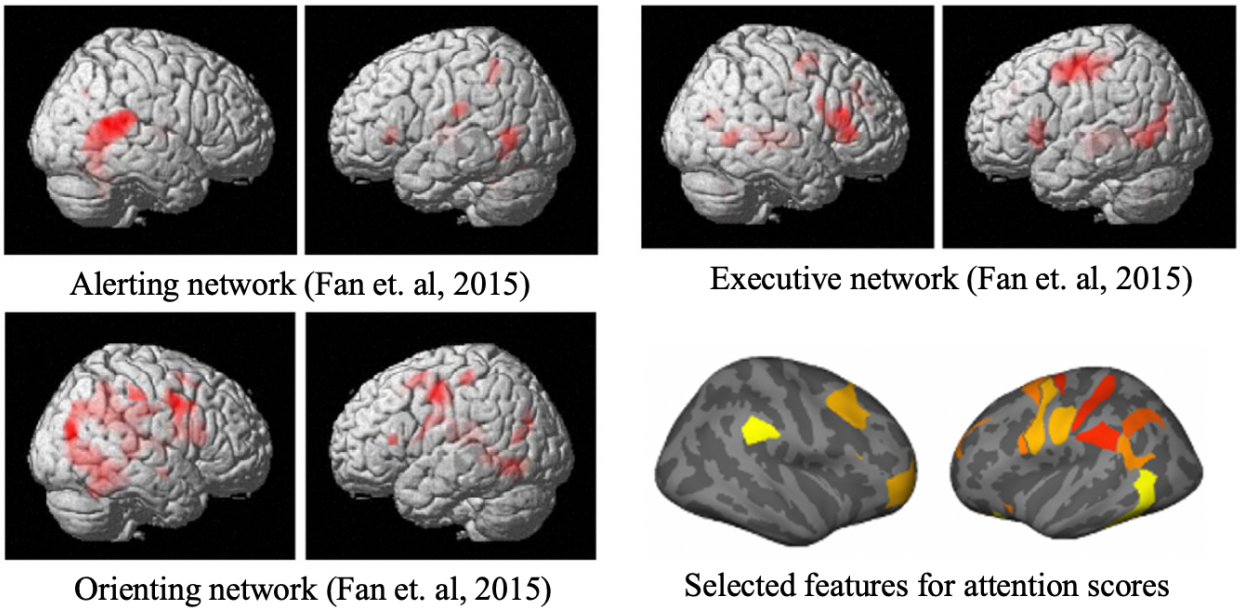


Figure 9. Comparing between selected features for attention scores and attention task-related activation. (a, upper left) Frontal-parietal cortical regions were activated during the alerting cues in the attention task. (b, upper right) Frontal area and ACC (shown in a separate cross-section view in the paper) were activated for the executive cues. (c, bottom left) Regions involved the left and right superior parietal lobe were found to be associated with orienting during the attention task. (d, bottom right) Selected features from our attention model showing consistent regions with related studies.

4.3 Significance of findings

4.3.1 Why is this work important and novel

It is known that many neuroimaging findings are poorly reproducible (Button et al., 2013; Marek et al., 2022) and that many imaging biomarkers have low generalizability (Dukart et al., 2021). This is an important issue that needs to be addressed in the field. If a biomarker is not generalizable, then it will be of limited utility. One of the main reasons is the low reliability of results derived from group templates. There was growing evidence that the functional brain networks vary greatly among individuals, particularly in higher order regions (Mueller et al., 2013). Using group templates to analyze data could neglect important individual features that might affect the findings. At the same time, many of the clinical symptom scores that used to analyze fMRI data were based on patients' subjective judgment (Charpentier et al., 2021). More inaccurate results will be produced when analyzing group results with individual's subjective symptom scores. To address these issues, we used the individualized parcellation approach to construct the functional connectomes. This individualized approach has a higher reliability and could better capture individual differences in brain networks than a traditional group atlas approach.

4.3.2 Clinical benefits

The findings of this project have the potential to be applied in clinical treatment in several ways. The first is to find targets for transcranial magnetic stimulation (TMS). TMS is a non-invasive brain stimulation technique used to treat many neurological diseases (Hallett, 2007). By providing potential targets for TMS using the identified biomarkers and locating individualized target with the individualized parcellation approach, this could help improve the precision and efficacy of TMS treatment. Second, the biomarkers identified in the project may help researchers gain a better understanding of the underlying mechanism of psychosis. This could lead to the development of better therapies or interventions that could improve patient outcomes.

4.4 Limitation and future work

Although all eight cognitive scores were successfully predicted using the discovery dataset, not all models could be generalized to the validation dataset. Models for verbal learning score, visual learning score could still predict scores but with less significant correlation and p values. Scores for processing speed, problem solving and social cognition could not be successfully predicted at all. Many studies in the field have discovered the related brain areas for these cognitive functions. For example, social cognition has been proved to be associated with temporal-parietal junction and the medial prefrontal cortex (Van Overwalle, 2009). One possible explanation was that our individualized parcellation approach focused only on cortical regions,

while sub-cortical structures also play critical roles in many cognitive processes. For example, hippocampus is important in the formation and retrieval of new memories (Wiltgen et al., 2010). Thalamus acts as a relay station for sensory information to enter the brain and is involved in a wide range of cognitive processes including attention, memory, and learning (Fama & Sullivan, 2015). Amygdala is important in emotional processing, but also plays a role in learning and memory (Baxter & Croxson, 2012; Tyng et al., 2017). Basal ganglia, a group of subcortical structures that involved in motor control, have also been linked to working memory processes such as maintenance and updating of information (Lanciego et al., 2012; McNab & Klingberg, 2008). However, parcellating sub-cortical regions could be challenging with our current technology, especially since they are small and located deep within the brain. Their omission from the parcellation could limit the ability of using functional connectivity to predict cognitive scores. Alternative approaches such as combining data from multiple imaging modalities or using machine learning algorithms to identify subcortical regions should be considered as a future step of this study.

Another important limitation came from data selection. The scanning time of each subject in the MATRICS data was only around twelve minutes. Although many analyses can be done with this scanning length, it is not enough to calculate the test-retest reliability where the data should be segmented into two halves and be compared. If the scanning time could be extended to thirty minutes, the reliability of the research would be greatly improved. Recent research has also demonstrated that a large sample of dataset might be needed to get an accurate prediction result (Marek et al., 2022). The future plan for these issue is to enroll more fMRI data with longer scanning time and replicate the analysis with a larger group of subjects. Increasing scanning time

could improve the quality of the data, while increasing sample size and using independent data sets for validation could ensure that the biomarker is not specific to a particular sample but could also be generalized to other populations. While the imaging features for psychosis identified in half of the dataset could be validated to the other half, would this framework still work when testing with independent datasets? Another future plan could be enrolling an independent dataset to see if models could be generalized to those new data.

4.4 Conclusion

In this project, multiple prediction models were constructed to estimate cognitive scores using resting-state fMRI. Models for working memory score, composite score and attention score could be successfully applied to independent datasets with a significant correlation between the predicted score and observed score. Based on the models, thirteen FCs were found to be different between psychotic patients and HC. These connections were seen as imaging markers for psychosis and were mainly located in frontoparietal, dorsal attention and ventral attention networks.. However, the size of the dataset and the length of the scanning might limit the accuracy of the prediction. More data might be needed and more research is necessary to have a more accurate imaging biomarker for psychosis.

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