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Trans-Diagnostic Relations Between Functional Brain Network Integrity and Cognition

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by

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Abstract

Cognitive impairment occurs across the psychosis spectrum. However it is unknown whether these shared manifestations of cognitive dysfunction also reflect shared neurobiological mechanisms, or whether the source of impairment differs. One common feature of cognitive impairment across psychotic disorders is that the impairments are often “generalized”, indicating deficits in a range of cognitive domains, including executive functioning, processing speed, memory, and attention. The goal of the current study was to determine whether the similar generalized cognitive deficit observed across psychotic disorders is also associated with a shared putative mechanism of functional brain network integrity. To address this question, we estimated resting-state functional network integrity of the cingulo-opercular and fronto-parietal networks -- two networks widely implicated in cognitive ability -- in 201 healthy controls, 143 schizophrenia, 103 schizoaffective, and 129 bipolar disorder with psychosis participants from the Bipolar and Schizophrenia Network on Intermediate Phenotypes (BSNIP1) consortium. Cognitive ability was measured using the Brief Assessment of Cognition in Schizophrenia (BACS), and generalized cognitive ability was estimated as the first factor (54% variance explained) in a principal axis factor analysis of all BACS subtests. Graph theory algorithms were used to estimate the global and local efficiency of the whole brain, cingulo-opercular network (CON), fronto-parietal network (FPN), and the auditory network (AUD), as well as participation coefficient of the anterior insula, dorsal anterior cingulate cortex, and dorsolateral prefrontal cortex. We observed significantly reduced CON global efficiency in schizophrenia and psychotic bipolar patients compared to healthy controls (p’s<.01), but none of the clinical groups differed from one another (p’s>.21). All psychotic disorders had significantly reduced CON local efficiency (p’s<.03), but the clinical groups did not differ from one another. CON global efficiency was significantly associated with general cognitive ability across all groups (β=.099, p=.009), and significantly mediated the relationship between psychotic disorder status and general

cognition ($p<.05$). Exploratory analyses revealed that global efficiency of the subcortical network was also significantly reduced in psychotic disorders ($p=.007$), and positively predicted cognitive ability ($\beta=.094$, $p=.009$). These findings provide evidence of a role for reduced CON and subcortical network efficiency in the generalized cognitive deficit observed across the psychosis spectrum. They also support the hypothesis that a shared neurobiological mechanism underlies the dimension of cognitive impairment in psychotic disorders.

1. Introduction

In the United States, approximately 4% of the population suffers from a psychotic disorder ("The Numbers Count: Mental Disorders in America", 2014), costing the country millions of dollars in emergency room and psychiatric hospital visits, ongoing pharmacotherapies, and lost income and productivity (Millier et al., 2014). Psychotic disorders also generate large costs on the well-being of patients and their families, who are often deeply affected by the chronic symptoms manifest across the psychosis spectrum. Even in the context of effective treatments, the recurrent nature of disorders like schizophrenia, schizoaffective disorder, and bipolar disorder can drastically impact patients' quality of life, through disturbance in reality testing, social skills deficits, reward processing abnormalities, and cognitive dysfunction.

Schizophrenia, schizoaffective disorder, and bipolar disorder represent distinct diagnostic categories as described in the current Diagnostic and Statistical Manual-5 (DSM-5) (Association, 2013), however all share the feature of psychotic experiences. Psychosis is broadly defined as distortions in thought, typically captured by the constructs of delusions and hallucinations. Although all psychotic disorders are characterized by the presence of psychosis, which is often the most prominent or noticeable feature of these disorders, other symptoms help distinguish these diagnostic groups. For instance, schizophrenia and schizoaffective disorder patients sometimes present with negative symptoms, which is not a symptom characteristic of a bipolar disorder diagnosis. Negative symptoms are characterized by the absence of typical emotional processes, such as anhedonia, flattened affect, and amotivation (Andreasen, 1982). By definition, schizoaffective disorder and bipolar disorder are also characterized by disturbances in mood, namely depression and mania, while schizophrenia is not. The diagnostic distinction between schizoaffective and bipolar disorder is captured by the timing of mood and psychotic symptoms; schizoaffective patients present with chronic psychotic symptoms regardless of current mood state, whereas bipolar patients experience psychosis only in the context of a mood episode.

One notable aspect of these three psychotic disorders, however, is the frequent difficulty clinicians face in determining a differential diagnosis (Heckers, 2009). Therefore, although considered distinct disorders, the amount of symptom overlap, similar timing of symptom onset, and chronic trajectory of these illnesses beg the question of whether they exist on a common spectrum of mood and psychotic disturbances. Similar questions about the validity and reliability of current psychiatric classifications have recently been taken on by the National Institute of Mental Health (NIMH), who introduced the Research Domain Criteria (RDoC) initiative in 2010 (Insel et al., 2010). RDoC is a framework for understanding psychiatric disorders, designed to encourage researchers and clinicians to think beyond the boundaries of strict diagnostic criteria. Psychiatric disorders are instead conceptualized as manifestations of disturbances in neural systems, and understanding the quality and etiology of these brain circuit abnormalities will hopefully lead to improved treatments and interventions. The current investigation, funded by an NIMH F31 fellowship, utilized an RDoC framework to test hypotheses about brain-based abnormalities associated with a dimension of impairment common across schizophrenia, schizoaffective disorder, and bipolar disorder: cognitive deficits.

1.1 Cognitive Deficits in Psychotic Disorders

A major impetus for the project's focus on cognitive deficits, in the context of an RDoC framework, is the similarity in the pattern of cognitive impairment observed across patients with schizophrenia, schizoaffective disorder, and psychotic bipolar disorder. Individuals with psychotic disorders from all of these diagnostic groups exhibit deficits in the vast majority of cognitive domains, with similar patterns of relative impairment in areas of executive functioning, working memory, cognitive control, verbal memory, attention, and processing speed (Daban et al., 2006) (Heinrichs, Ammari, McDermid Vaz, & Miles, 2008) (Barch & Sheffield, 2014). For instance, one study that measured cognitive ability in all three diagnostic groups observed the greatest impairment in processing speed across all groups and the relatively least impairment in

verbal fluency across all groups, with intermediate relative deficits in working memory and verbal memory (Hill et al., 2013).

Large studies of neurocognitive functioning within single diagnostic groups have emphasized, not just the pattern of impairment, but how many domains are affected. In a sample of 1,493 individuals with schizophrenia from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, patients displayed significant impairments ($p<.0001$) in all neurocognitive tests where normative comparison data was available. These tests ranged from a grooved pegboard measuring motor speed to verbal learning, digit symbol processing speed, and executive functioning tasks (Keefe et al., 2006). In a meta-analysis of euthymic bipolar disorder patients, a similar pattern of broad impairments was observed, such that bipolar subjects were significantly impaired ($p<.0001$) on all tasks measuring domains of executive functioning, working memory, processing speed, attention, and memory (Torres, Boudreau, & Yatham, 2007). The broad nature of these impairments in psychotic disorders stands in contrast to other mental health disorders that are characterized by more specific cognitive impairments, such as attention and memory deficits in PTSD (Horner & Hamner, 2002) and executive dysfunction in ADHD (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Therefore, this global nature of cognitive impairment may be a particularly important feature in understanding the mechanisms underlying cognitive deficits across the psychosis spectrum.

The generalized nature of cognitive impairment in psychotic disorders has not always been apparent, and is a concept that continues to be debated within the field (Green, Horan, & Sugar, 2013) (Gold & Dickinson, 2012). Decades of research, particularly in schizophrenia subjects, has tested hypotheses of specific deficits, with the idea that a specific deficit might expose a focal lesion or abnormality associated with the disorder. Following years of productive research, an active debate has emerged regarding the interpretation of this body of work, which has largely converged to reveal deficits in the majority of domains tested. On the one hand, some researchers argue that the broad impairments reflect a “generalized deficit”, indicating a

shared mechanism that produces the impairments observed in multiple cognitive domains (Gold & Dickinson, 2012). Evidence for the generalized deficit can be seen in factor analyses of neurocognitive batteries, which often reveal a single factor of cognitive performance in schizophrenia that explains at least 40% of the variance in cognitive ability (e.g. (Keefe et al., 2006) (Dickinson, Ragland, Gold, & Gur, 2008) (J. M. Sheffield et al., 2015)). On the other hand, the notion of a generalized deficit has been dismissed, based primarily on the fact that some areas of cognition are preserved in schizophrenia (Green et al., 2013). For instance, patients with schizophrenia appear to have intact functioning in attentional selection for working memory storage, speed of attention shifting, in the moment emotional experience, and some forms of implicit learning (Gold, Hahn, Strauss, & Waltz, 2009). While this debate will not be adjudicated here, hypotheses in the current study are based on the existence of a generalized deficit that can be measured through shared variance in task performance (although relationships with specific domains are also explored). One rationale for focusing on the generalized deficit across psychotic disorders, as opposed to specific deficits, is that a generalized deficit is increasingly apparent in bipolar disorder (Robinson et al., 2006), again suggesting that these disorders may share a common abnormality underlying cognitive impairment.

1.1.2 Cognitive Deficits and Functional Outcome

One of the most important aspects of cognitive deficits is that they contribute to the disabling nature of psychotic disorders, such that individuals with more severe cognitive impairment have more difficulty accomplishing daily tasks, thereby hindering their independence (Bowie, Reichenberg, Patterson, Heaton, & Harvey, 2006). In previous work investigating this relationship, I demonstrated that memory, cognitive control, and processing speed ability were all significantly associated with functional outcome in patients with schizophrenia (J. M. Sheffield et al., 2014). Functional outcome was measured through simulation of real-world skills, two self-report measures, and an informant report. Relational memory, cognitive control, and processing

speed ability significantly correlated with schizophrenia patients' ability to simulate real-life skills, while verbal learning was associated with self-report measures of daily functioning. These findings, in addition to those presented in a multitude of other studies (Bowie et al., 2008; Green, 2006; Green, Kern, & Heaton, 2004), reveal that greater cognitive impairment in the context of psychotic disorders is associated with greater impairment in daily functioning. An important complementary finding, however, is that cognitive remediation (i.e. cognitive skills training designed to treat cognitive impairment) is associated with improvements in functional outcome, particularly when those cognitive skills are practiced and integrated into real-world settings (Medalia & Saperstein, 2013). Therefore, understanding the neural mechanisms underlying cognitive impairment may improve targets for treatment, perhaps in conjunction with current remediation protocols.

1.1.3 Time Course of Cognitive Impairment in Psychotic Disorders

Aside from their association with functional outcome, the time course of cognitive impairment in psychotic disorders may make them a particularly important target for understanding the etiology and progression of schizophrenia, schizoaffective disorder, and bipolar disorder. In schizophrenia, research shows that cognitive deficits exist prior to a patient's first episode of psychosis (Bora & Murray, 2014). Cognitive impairment is not specific enough to schizophrenia that its presence could alone predict disease onset; however its presence early in life suggests that it may be an important marker of the developmental changes and neurobiological abnormalities that ultimately coalesce during a patient's first break. If the mechanisms underlying cognitive impairment in schizophrenia can be determined, they can be monitored and potentially targeted earlier on. Schizoaffective patients most likely also experience cognitive impairment prior to their first episode, however researchers' propensity to combine schizophrenia and schizoaffective patients into one group make differentiation in the time course of cognitive deficits difficult.

Cognitive deficits are also observed in the early stages of illness in bipolar disorder patients, with a recent meta-analysis revealing cognitive impairment within two years of the first bipolar episode (Bora, 2015). These impairments persist even during euthymic states (Lee et al., 2014), suggesting that the mechanisms underlying cognitive deficits in bipolar disorder represent a stable change in cognitive functioning that is independent of mood state. Meta-analyses (Lee et al., 2014) (Bora, 2015) and a recent review (Bora & Pantelis, 2015) point to a similar neurodevelopmental course of cognitive impairment in bipolar disorder, as is seen in schizophrenia, although the data is somewhat mixed (e.g. (Goodwin, Martinez-Aran, Glahn, & Vieta, 2008). Some studies, for instance, have observed superior cognitive ability in individuals who have later developed bipolar disorder (Tiihonen et al., 2005) (Kumar & Frangou, 2010), and other studies have demonstrated worsening cognitive ability with illness progression (Bearden et al., 2006; Cavanagh, Van Beck, Muir, & Blackwood, 2002; Martinez-Aran et al., 2004). Although research has not yet adjudicated whether cognitive deficits in bipolar disorder are neurodevelopmental or neurodegenerative in nature, they are clearly present during the chronic state. While not in the scope of the current report, research elucidating differences (and similarities) between the course of cognitive deficits across the psychosis spectrum will be important for determining whether or not these are truly distinct disorders with distinct etiologies, or should instead be considered along a common dimension of mood and psychotic disturbances.

1.1.4 Cognitive Deficits in First-Degree Relatives

Research has also established that cognitive deficits are present, not only in patients with psychotic disorders, but in their first degree relatives as well. Schizophrenia, schizoaffective disorder, and bipolar disorder are heritable, with heritability estimates at 37% for first degree relatives, when taking into account family history of both schizophrenia and bipolar disorder (G. Light et al., 2014). Cognitive deficits in healthy first-degree relatives are less severe than those

seen in the psychosis proband, but represent significant impairment compared to healthy individuals without a family history of psychosis (Bora, Yucel, & Pantelis, 2009; Snitz, Macdonald, & Carter, 2006). These findings suggest a genetic component to the mechanisms underlying cognitive deficits across the psychosis spectrum. In fact, a meta-analysis from 2004 demonstrated that the areas of cognition that were the most impaired in schizophrenia patients were also the most impaired in first degree relatives (e.g. verbal memory, executive functioning, and attention) (Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004). Similar patterns of cognitive impairment within patients and relatives provide further support for genetic factors contributing to the mechanisms underlying these deficits. Work in relatives also validates that cognitive impairments in psychotic disorders are not the consequence of psychiatric medication, and are independent of other symptoms.

1.1.5 Magnitude of Cognitive Impairment Across Psychotic Disorders

While similar in *pattern* of impairment, schizophrenia, schizoaffective disorder, and bipolar disorder patients exhibit differences in the *magnitude* of impairment (Bora et al., 2009; Heinrichs & Zakzanis, 1998; Robinson et al., 2006). Data previously published using the Bipolar and Schizophrenia Network for Intermediate Phenotypes (B-SNIP) dataset, for instance, has revealed that bipolar patients are less impaired in all cognitive domains than patients with schizophrenia, and that schizoaffective patients have intermediate deficits compared to bipolar and schizophrenia patients (Hill et al., 2013). This pattern has been observed across a multitude of studies in a variety of cognitive domains (e.g. (J. M. Sheffield, Williams, Cohen, & Heckers, 2012)). Differences in magnitude of impairment, in the context of similar patterns of impairment, may map onto the severity of abnormalities in the underlying mechanism. In other words, if a common mechanism underlies the generalized deficit in psychotic disorders, the degree to which that mechanism is abnormal should be related to the degree of impairment observed in cognitive ability. Therefore, one would expect to see evidence of the most abnormalities in

schizophrenia patients, followed by schizoaffective and bipolar patients, as compared to healthy controls. Here, as discussed in more detail below, I hypothesize that abnormalities in functional brain networks, as measured through resting state functional magnetic resonance imaging (fMRI) and quantified using graph theoretical metrics, represent a shared mechanism underlying the generalized deficit observed in schizophrenia, schizoaffective disorder, and bipolar disorder.

1.2 Resting state functional connectivity networks

Functional brain networks can be examined using resting state fMRI data, which measures blood oxygen-level dependent (BOLD) activity in the brain while an individual lies quietly in an fMRI scanner, estimating on-going, intrinsic neural activity in each voxel (Smith et al., 2013). The resulting BOLD activity from each brain region can be correlated to estimate resting state functional connectivity (rs-fc), an indirect measure of communication between brain areas. In a paper published in 2016, I describe rs-fc methods in depth (J. M. Sheffield & Barch, 2016), and therefore will mention them here only briefly. One of the most important aspect of rs-fc, for the purposes of the current report, is that rs-fc reveals stable networks of brain regions that demonstrate consistently high connectivity within and across individuals (Cole, Bassett, Power, Braver, & Petersen, 2014). These networks have been widely studied in healthy subjects, and appear to support relatively distinct cognitive processes (Power et al., 2011). In the creation of their atlas, Power and colleagues utilized both meta-analysis of task-based data and fc-Mapping techniques to define 264 putative functional nodes that comprise 13 functional networks. These networks largely corresponded with previously described functional networks that had been identified based on their coordinated BOLD activity in different cognitive contexts. For instance, visual, auditory, and somatosensory networks were identified that included well-defined functional areas for these sensory systems (Burton, Sinclair, Wingert, & Dierker, 2008) (Lowe, Mock, & Sorenson, 1998). The default mode network, dorsal and ventral attention networks, and salience network were also identified in accordance with previous literature

(Corbetta, Patel, & Shulman, 2008; Fox et al., 2005; Greicius, Krasnow, Reiss, & Menon, 2003; Seeley et al., 2007). This atlas therefore capitalizes on the broad scope of published fMRI data to approximate reliable functional networks that support human cognition. In the current study, we focus our analyses on two networks from the Power atlas, the fronto-parietal network (FPN) and the cingulo-opercular network (CON), that appear to support relatively generalized cognitive processes, and therefore whose connectivity is critical for cognitive ability in a multitude of cognitive domains (Cocchi, Zalesky, Fornito, & Mattingley, 2013).

1.2.1 Fronto-Parietal and Cingulo-Opercular Networks

The fronto-parietal network (FPN) and the cingulo-opercular network (CON) have been hypothesized to form a "core task-set system" to facilitate domain-general higher-order cognitive functioning (N. U. Dosenbach et al., 2007). Regions within the FPN, which include the dorsolateral prefrontal cortex (DLPFC) and the intraparietal sulcus, exhibit increased BOLD activity during task start-cues and in response to error feedback. In a study by Dosenbach and colleagues (2006), this pattern was seen across 10 cognitive tasks measuring distinct cognitive domains, suggesting a domain-general role of the FPN in adaptive task control. In the same study, regions that comprise the CON (such as the anterior insula (AI), dorsal anterior cingulate cortex (DACC), and anterior prefrontal cortex) showed sustained increased BOLD activity throughout the duration of the task epoch. The CON is therefore hypothesized to provide sustained task control to help maintain goal-directed behavior. Together, these two networks appear to flexibly support domain-general higher-order cognitive functioning, and therefore represent a putative mechanism underlying generalized cognitive ability, making them excellent candidate networks for understanding the generalized cognitive deficit in psychotic disorders.

Previous research has already revealed abnormalities in the FPN and CON in schizophrenia, schizoaffective disorder, and bipolar disorder, providing further support for their role in the pathophysiology of psychotic disorders. Prior work demonstrated that individuals with

schizophrenia have significantly reduced functional connectivity between the FPN and CON, as well as between the FPN, CON and cerebellum (Repovs, Csernansky, & Barch, 2011). This pattern was also observed in healthy first-degree relatives. In a follow-up study in patients with bipolar disorder, bipolar subjects demonstrated significantly reduced functional connectivity within the CON, as well as between the CON and the cerebellum and saliency networks (Mamah, Barch, & Repovs, 2013). Others have demonstrated reduced functional connectivity within the FPN in schizophrenia (Woodward, Rogers, & Heckers, 2011) and schizoaffective patients (Baker et al., 2014), as well as reduced cortico-striatal connectivity with the CON in schizophrenia (Tu, Hsieh, Li, Bai, & Su, 2012). In addition to abnormalities during resting state, one study in schizophrenia patients revealed reduced functional connectivity between the insula and DACC during an information processing task (White, Joseph, Francis, & Liddle, 2010). Importantly, decreased functional connectivity between the FPN and cerebellum in schizophrenia was associated with greater impairment in executive function, working memory, episodic memory, and on a vocabulary task (Repovs et al., 2011), supporting the hypothesis that functional connectivity of these networks play a role in the generalized cognitive deficit.

1.3 Network Science Approach

While most studies quantify functional connectivity by averaging connectivity strength between network regions, this approach is agnostic to the "structure" of the network, ignoring information regarding which regions (or nodes) are inter-connected. In the past decade, a growing literature of studies have utilized network science to quantify properties of functional connectivity networks (Bullmore & Sporns, 2012). This approach is particularly attractive for analyzing resting state data, which is believed to reveal stable networks that are characteristic of that individual's "intrinsic" network topology (Cole, Bassett, et al., 2014). Unlike average functional connectivity, which measures bivariate connection strength between two nodes, network science borrows tools from the mathematical literature of graph theory, which provides

metrics for characterizing more diverse network properties (Bullmore & Sporns, 2009). Graph theory is being increasingly used for understanding network correlates of cognitive processes such as memory, attention, and cognitive control (for review, see (Medaglia, Lynall, & Bassett, 2015)). For instance greater whole brain global efficiency has been shown to be significantly associated with higher IQ in healthy subjects (van den Heuvel, Stam, Kahn, & Hulshoff Pol, 2009). Decreased memory encoding and recognition were associated with increased path length and lower network efficiency in aging individuals (Wang, Li, Metzak, He, & Woodward, 2010). And in a clever study utilizing individuals who had suffered a stroke, Warren and colleagues demonstrated that patients with lesions affecting "hub" nodes (i.e. nodes that are highly inter-connected between networks) experienced worse functional outcome than patients whose lesions affected more peripheral network nodes (Warren et al., 2014). Together, this literature has pointed to the utility of graph theory metrics in describing network properties, and their associations with behavior.

1.3.1 Application of Network Science to Understanding Psychopathology

One reason graph theory is attractive for studying psychotic disorders, is that a heterogeneous literature has arisen to reveal both increased and decreased functional connectivity in psychotic disorder patients (for reviews, see (J. M. Sheffield & Barch, 2016) (Karbasforoushan & Woodward, 2012)). The emergent complexity of connectivity patterns in psychotic disorders have led schizophrenia and schizoaffective disorder to be considered disorders of "dysconnectivity", implying abnormal functional integration in the brain (K. E. Stephan, Friston, & Frith, 2009). Given increasing awareness of the importance of functional brain networks in supporting complex behavior, graph theory metrics provide a new perspective for understanding connectivity abnormalities, that can take into account the multifaceted patterns of functional connectivity differences observed in these disorders.

My research program has focused on developing our understanding of network abnormalities in psychotic disorder patients, and how those abnormalities relate to cognitive ability. I began my investigation of this question in the summer after my first year of graduate school. During that time, I was curious about mechanisms underlying the generalized cognitive deficit in schizophrenia, and was interested in exploring the role of functional connectivity abnormalities in this context. When reading the literature, I was struck by the heterogeneous findings of both increased and decreased functional connectivity in schizophrenia, making it challenging to determine any locus or pattern of disturbance. Simultaneously, through the Cognitive and Computational Systems Neuroscience (CCSN) pathway, I learned more about the application of graph theory to functional connectivity data, as a means of describing the brain as a complex network. Inspired by studies from Danielle Bassett (Bassett et al., 2008; Bassett, Nelson, Mueller, Camchong, & Lim, 2012) , Martin van den Heuvel (van den Heuvel, Mandl, Stam, Kahn, & Hulshoff Pol, 2010; van den Heuvel et al., 2009), and Alex Fornito (Fornito, Zalesky, Pantelis, & Bullmore, 2012), and review papers from Bullmore & Sporns (Bullmore & Sporns, 2009, 2012), I wondered whether graph theory would provide a more holistic view of functional connectivity abnormalities in schizophrenia. A paper from van den Heuvel and colleagues (van den Heuvel et al., 2009) demonstrated that whole brain global efficiency, for instance, was positively associated with IQ in healthy individuals. Work from Bassett and colleagues highlighted abnormalities in network properties in schizophrenia patients, and demonstrated relationships between network abnormalities and deficits in attention and memory (Bassett et al., 2012; Lynall et al., 2010). Bolstered by this literature, and the minimally explored role of the FPN and CON in schizophrenia, I wondered whether global efficiency of these networks may be related to the generalized deficit. I also wondered whether hub nodes within these networks had reduced participation coefficients, based on a paper that had recently been published by researchers at Washington University (Power, Schlaggar, Lessov-Schlaggar, & Petersen, 2013).

I chose the metrics of efficiency and participation because of their theoretical relevance to my questions of interest. Global efficiency, for instance, is a metric that measures the potential for information transfer and integration within a network, and local efficiency measures the fault tolerance of a network in terms of local information processing (Rubinov & Sporns, 2010). Global efficiency had previously been shown to be related to IQ (van den Heuvel et al., 2009), and there is literature suggesting reduced network integration in schizophrenia (G. A. Light et al., 2006). Participation coefficient is a nodal property that quantifies the connectedness of a node with other networks, with higher participation indexing that node's importance in transferring information between networks (Power et al., 2013). Dosenbach and colleagues had identified critical hub nodes in the FPN and CON, and participation of these hubs allowed me to test both within- and between-network abnormalities in schizophrenia. With this research, I also hoped to assess whether global efficiency of specific networks (as opposed to the whole brain) had predictive power in describing behavior. The decision to analyze efficiency of sub-networks, as opposed to the whole brain, was a conceptual correlate to analyses assessing average functional connectivity changes in the CON and FPN in schizophrenia. By analyzing sub-networks important for cognition, I could test more specific relationships between network topology abnormalities and cognitive ability.

My first attempt at answering this question was done in a population of schizophrenia patients and healthy controls. Because resting-state data was not available, the study utilized pseudo-resting state data, which involves the regression of task-dependent signal from concatenated task fMRI data to approximate resting state. I then measured the global and local efficiency of the whole brain, FPN, CON, and auditory network (AUD), as well as the participation coefficient of the insula, DACC, and DLPFC. In that study, I demonstrated that FPN, CON, and whole brain global and local efficiency were significantly positively associated with overall cognitive ability (J. M. Sheffield et al., 2015). Overall cognitive ability was quantified as the shared variance in cognitive performance across multiple cognitive domains, to estimate

the generalized cognitive deficit. This study also revealed a positive association between the participation coefficient of the right anterior insula and overall cognitive ability. These findings in healthy controls and patients with schizophrenia or schizoaffective disorder not only showed the importance of CON and FPN network properties in generalized cognitive ability, but also demonstrated the utility of graph theory tools in explaining variance associated with complex behavior.

Since this initial study, I have published several papers revealing network properties associated with cognitive ability and psychosis, particularly within the CON. Using the same sample as described above, I observed a robust differential association between CON global efficiency and age in schizophrenia patients and healthy controls (J. M. Sheffield et al., 2016). This cross-sectional study revealed a significantly stronger negative association between age and CON global efficiency in schizophrenia, as compared to healthy controls. These findings added to the literature on "accelerated aging" in schizophrenia, and provided support for the notion that processes of normal aging, such as reducing functional integration of higher-order cognitive networks (Andrews-Hanna et al., 2007), may occur earlier and/or more rapidly in schizophrenia; a finding that had been observed in structural connectivity data (Kochunov et al., 2013) but never before using functional connectivity or graph theory. I further extended my research into the role of network efficiency for cognition across the psychosis spectrum, in a large sample of healthy young adults from the Human Connectome Project. In this project I showed that CON global efficiency (calculated from resting-state data) was significantly associated with both cognitive ability and psychotic-like experiences, and mediated the relationship between psychotic-like experiences and cognition (J. M. Sheffield, Kandala, S., Burgess, G. C., Harms, M. P., & Barch, D. M, 2016). This study provided support, not only for an association between CON global efficiency and cognitive ability, but also for the CON's role in the psychotic and cognitive symptoms observed across the psychosis spectrum.

With my dissertation, I hope to add to this growing program of research to elucidate associations between CON and FPN network properties and the generalized cognitive deficit in a large sample of individuals with "distinct" psychotic disorders. To this end, the current study extends my previous findings of relationships between global cognition and network efficiency by 1) analyzing these relationships in large groups of individuals with psychotic bipolar disorder and schizoaffective disorder, allowing me to further assess this putative mechanism across the psychosis spectrum, 2) use a robust measure of cognition to estimate the generalized deficit, and 3) further work to replicate my previous findings in an independent dataset.

1.4 Specific Aims

Here, I present a study aimed to reveal whether network properties of the FPN, CON and whole brain are abnormal in three distinct psychotic disorders, and whether those abnormalities are related to generalized cognitive impairment. Using a large dataset from the Bipolar and Schizophrenia Network on Intermediate Phenotypes (B-SNIP), I analyzed resting state functional connectivity data using graph theory tools, in healthy controls, bipolar disorder subjects, schizoaffective subjects, and schizophrenia subjects. Network properties analyzed in the study include global and local efficiency of the FPN, CON, whole brain, and AUD, and participation coefficient of the bilateral DLPFC, bilateral AI, and DACC. These network metrics were selected for two main reasons: 1) they capture properties of global and local functional integration both within the network, as well as between networks, which are critical properties for supporting cognitive ability, 2) they have previously been shown to be associated with cognitive impairment in schizophrenia (J. M. Sheffield et al., 2015), and therefore can be extended to patients with bipolar disorder to assess continuity along the psychosis spectrum. If supported, these findings would provide evidence of a common dimensional neurobiological source associated with the generalized cognitive deficit across psychotic disorders.

Specific Aim 1: To test the hypothesis that impairments in efficient information integration in fronto-parietal and cingulo-opercular networks are associated with the generalized cognitive deficit in psychotic disorders, both within and across diagnostic groups. We defined efficiency metrics of functional brain connectivity in subjects using graph analysis of resting state functional connectivity data, through previously validated methods and definitions of functional areas (Power et al., 2011). We calculated both local and global efficiency within the fronto-parietal and cingulo-opercular networks and tested hypotheses about associations between efficiency metrics and generalized cognitive ability, based on performance on working memory, verbal memory, executive functioning, and processing speed tasks. These efficiency metrics reflect information integration between neighbors of a node (local efficiency) and across all nodes in a network (global efficiency). We predicted that these relationships would be present within each individual diagnostic group and would not interact with diagnostic group.

Specific Aim 2: To test the hypothesis that reductions in the communication of specific "hub" regions across networks are associated with the generalized cognitive deficit in psychotic disorders, both within and across diagnostic groups. We focused on three specific *a priori* regions: anterior insula, dorsal anterior cingulate cortex, and dorsal lateral prefrontal cortex, as prior work has shown that these are hub regions that display high levels of communication with multiple functional networks (Cole, Reynolds, et al., 2013) (van den Heuvel et al., 2010). We assessed the "hubness" of these regions using participation coefficients, which index the distribution of a node's edges with other communities in the whole brain network (Guimera & Amaral, 2005). We tested the hypothesis that these regions participate with fewer communities in individuals with mental disorders, as compared to healthy controls, and that the degree of participation would be associated with the generalized cognitive deficit. We predicted

that these relationships would hold across all participants, would not interact with diagnostic group, and would be present within each individual diagnostic group.

2. Methods

2.1 Participants

Participants were collected as part of the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP1) project, a multi-site study focused on identifying intermediate phenotypes across the psychosis spectrum (Tamminga et al., 2013). Following quality-control procedures for the MRI data, the final sample for the current study included 201 healthy control (HC), 143 schizophrenia, 103 schizoaffective, and 129 psychotic bipolar disorder participants. All participants completed similar behavioral and MRI protocols across 6 sites (Baltimore, Boston, Chicago, Dallas, Detroit, and Hartford), as reported in previous papers (Meda et al., 2014), and signed informed consent documents prior to study enrollment.

As described in detail previously (Tamminga et al., 2013), clinical status was determined using the Structured Clinical Interview of the DSM-IV (SCID (First, Spitzer, Gibbon, & Williams, 1995)) which was reviewed by at least two experienced research clinicians to establish a consensus diagnosis. Patients were stable outpatients, referred by mental health providers or recruited through the community. HC were recruited through community advertisements and research registries, and had no history of a psychotic disorder or recurrent depression, and no immediate family history of these disorders.

Inclusion/exclusion criteria for all participants included: no history of seizures or head injury resulting in >10 minutes loss of consciousness, negative drug screen on the day of testing, no diagnosis of substance abuse in the past 30 days or substance dependence in the past 6 months, no history of serious medical or neurological disorder that would likely affect cognitive functioning, sufficient fluency in English, and an age-corrected Wide-Range Achievement Test (4^{th} edition) reading test standard score >65. Additionally, participants could

not have had a medication change and needed to be clinically stable over the past month.

2.2 Cognitive and Clinical Measures

Cognitive ability was measured using the Brief Assessment of Cognition in Schizophrenia (BACS (Keefe et al., 2004)), a well-validated cognitive battery. The BACS takes approximately 30 minutes to complete in healthy subjects, and involves assessment of cognitive ability in the domains of working memory, processing speed, motor speed, executive functions, verbal fluency, and verbal memory (Keefe et al., 2004). Working memory is assessed through a digit sequencing task, and processing speed is measured through a symbol coding task lasting 90 seconds. Motor speed is measured through a token motor task where subjects are given 100 plastic tokens and are asked to rapidly pick up one token at time, with each hand simultaneously, for 60 seconds. Executive functions are assessed through a tower test, and verbal fluency is assessed through both category and letter fluency over the course of 60 seconds. Verbal memory is assessed through a list learning task that includes 15 words. All BACS scores were age-adjusted and z-scored using published norms (Keefe et al., 2008), and z-scores >|4.0| were truncated to minimize the impact of outliers (Hill et al., 2013). Based on research showing a single cognition factor in BACS data from the B-SNIP dataset (Hochberger et al., 2016), general cognition was defined as the factor score from an exploratory principal axis factor analysis that included all six BACS tasks. This single factor (the only factor with an eigenvalue >1) explained 54% of the variance in cognitive ability.

Clinical symptoms were measured using the Positive and Negative Syndrome Scale (PANSS (Kay, Opler, & Lindenmayer, 1989)), the Young Mania Rating Scale (YMRS (Young, Biggs, Ziegler, & Meyer, 1978)), and the Montgomery-Asberg Depression Rating Scale (MADRS (Montgomery & Asberg, 1979)). Psychotic disorder patients were non-acute with regard to episode, and were stably medicated, which likely reduced individual differences in symptom severity.

2.3 Imaging Data Acquisition and Processing

All participants completed a 5-minute resting-state fMRI scan and a T1-weighted structural scan on a 3T scanner. Participants were instructed to keep their eyes focused on a crosshair. Scanning parameters differed slightly across sites (Table 2.1 (Meda et al., 2015)), and these differences were taken into account during preprocessing.

Structural scans were segmented through FreeSurfer53 (Fischl, 2012). Data preprocessing was completed using in-house scripts at Washington University. Preprocessing included slice timing correction, removal of the first four images from each run to allow data to reach a steady state, adjustment for odd/even slice acquisition, rigid body motion correction, normalization of data to a whole brain mode value of 1000, registration of structural image to Talariach space, and co-registration of functional volumes to atlas space using 3mm cubic resampling in a one-step interpolation

To further improve signal-to-noise ratio, additional preprocessing steps were applied to functional images based on published recommendations (Power et al., 2014): data were voxel-wise demeaned and detrended, followed by nuisance regression including 24 motion parameters (six rigid body estimates, their preceding timepoints, and their squares), and whole brain, white matter, ventricle signals and their temporal derivatives. Frequency filtering was applied, retaining frequencies in the $0.009 < f < 0.08$ Hz band. Data were additionally spatially smoothed with a Gaussian kernel (6mm FWHM in all directions). Additional motion-correction was applied based on procedures suggested by Power and colleagues (Power et al., 2014), in which frames exceeding a frame displacement (fd)>0.4mm were excluded from that subject's data. Subjects with <50 total frames following data scrubbing were removed from all analyses. Based on this criteria, 116 participants (18 HC, 37 schizophrenia, 26 schizoaffective, and 35 bipolar) were removed from the original B-SNIP dataset, due to excessive motion. These individuals did not significantly differ from those who passed motion scrubbing on age, personal

education, parental education, SES, or BACS composite scores (i.e. cognitive ability). For the subjects that passed the data scrubbing threshold, there were significant differences in the number of frames retained across groups ($F(3,590)=6.438$, $p<.001$). On average, healthy controls retained 167 frames, schizophrenia subjects retained 147, schizoaffective subjects retained 161, and bipolar subjects retained 165. Post-hoc pairwise analysis revealed that the schizophrenia group was driving this group difference (healthy vs. schizophrenia ($p<.001$) bipolar vs. schizophrenia ($p=.001$), schizophrenia vs. schizoaffective ($p=.014$)). Number of frames retained did not significantly correlate with cognitive ability across groups ($r=.07$, $p=.097$) or CON global efficiency ($r=.078$, $p=.057$).

Table 2.1: Data Collection Parameters Across B-SNIP Sites

fMRI	TR (ms)	TE (ms)	FA (degree)	Slices (N)	slice order	Acq matrix (mm)	Voxel Size (mm)	Vendor
Baltimore	2210	30	70	36	Interleaved ascending	64x64	3.4x3.4x3	Siemens Triotim
Hartford	1500	27	70	29	Sequential ascending	64x64	3.4x3.4x5	Siemens Allegra
Detroit	1570/1720	22	60	29	Sequential ascending	64x64	3.4x3.4x4	Siemens TrioTim
Dallas	1500	27	60	29	Sequential ascending	64x64	3.4x3.4x4	Philips
Chicago	1775	27	60	29	Sequential ascending	64x64	3.4x3.4x4	GE Signa HDX
Boston	3000	27	60	30	Sequential ascending	64x64	3.4x3.4x5	GE Signa HDX
T1-Weighted Structural	**TR (ms)**	**TE (ms)**	**FA (degree)**	**Slices (N)**	**slice order**	**Acq matrix (mm)**	**Voxel Size (mm)**	**Vendor**
Baltimore	2300	2.91	9	160	N/A	256x240	1x1x1.2	Siemens Triotim
Hartford	2300	2.91	9	160	N/A	256x240	1x1x1.2	Siemens Allegra
Detroit	2300	2.94	9	160	N/A	256x240	1x1x1.2	Siemens TrioTim
Dallas	6.6	2.8	8	170	N/A	256x256	1x1x1.2	Philips
Chicago	6.98	2.84	8	166	N/A	256x256	1x1x1.2	GE Signa HDX
Boston	6.98	2.84	8	166	N/A	256x256	1x1x1.2	GE Signa HDX

Table 2.1: Information on data acquisition parameters across all B-SNIP sites.

2.4 Network Analysis

Following fMRI and functional connectivity preprocessing, Blood Oxygen-Level Dependent (BOLD) timecourses were extracted from 264 ROIs, using 6mm spheres, based on coordinates from the Power atlas (Power et al., 2011). The Power atlas was selected due to the robustness of its networks across both resting-state and task data, indicating good reliability (Cole, Bassett, et al., 2014), and because we have previously shown relationships between the Power-designated FPN and CON efficiency and cognitive ability, allowing us to test for reproducibility (J. M. Sheffield et al., 2015). BOLD timecourses were averaged across all voxels within the ROIs, and the resulting timeseries were correlated to create a 264x264 correlation matrix of functional connectivity values. Power atlas ROI assignments for the fronto-parietal network (FPN, 25x25), cingulo-opercular network (CON; 14x14), and auditory network (AUD; 13x13) were used to construct network graphs, in addition to the 264x264 whole brain graph. Global efficiency, local efficiency, and participation coefficient were computed on weighted, undirected graphs thresholded at 5-10% strongest positive connections (in 1% increments) for each individual subject, using algorithms from the Brain Connectivity Toolbox 2016_01_16 (Rubinov & Sporns, 2010). This thresholding range was selected for several reasons: 1) Power and colleagues (2011) identified this range as most appropriate for isolating meaningful networks, with higher thresholds resulting in noisy and fragmented graphs, 2) Bassett and colleagues (2012) have shown this range best differentiates between schizophrenia and healthy subjects whole brain networks. Because there is no “correct” threshold, CON and FPN global efficiency are presented at every threshold in Figure 2.1, revealing a stable pattern of group differences across thresholds.

Following thresholding of each subject’s whole brain graph, ROIs/nodes from the FPN, and CON graphs were isolated from the whole brain graph. Global and local efficiency were calculated for each individual graph, at each threshold. Global efficiency yields a single metric for the entire graph, while local efficiency is calculated on a nodal basis; therefore local

efficiency was averaged across all nodes within each network to yield a single metric.

The CON and FPN were selected *a priori* to be associated with cognitive ability, however global and local efficiency of the 10 other networks from the Power atlas were also analyzed to assess specificity of our findings. Graph creation was the same as described above, and group differences in average network efficiency can be found in Figure 3.3.

Figure 2.1: Cingulo-Opercular and Fronto-Parietal Networks Across Thresholds

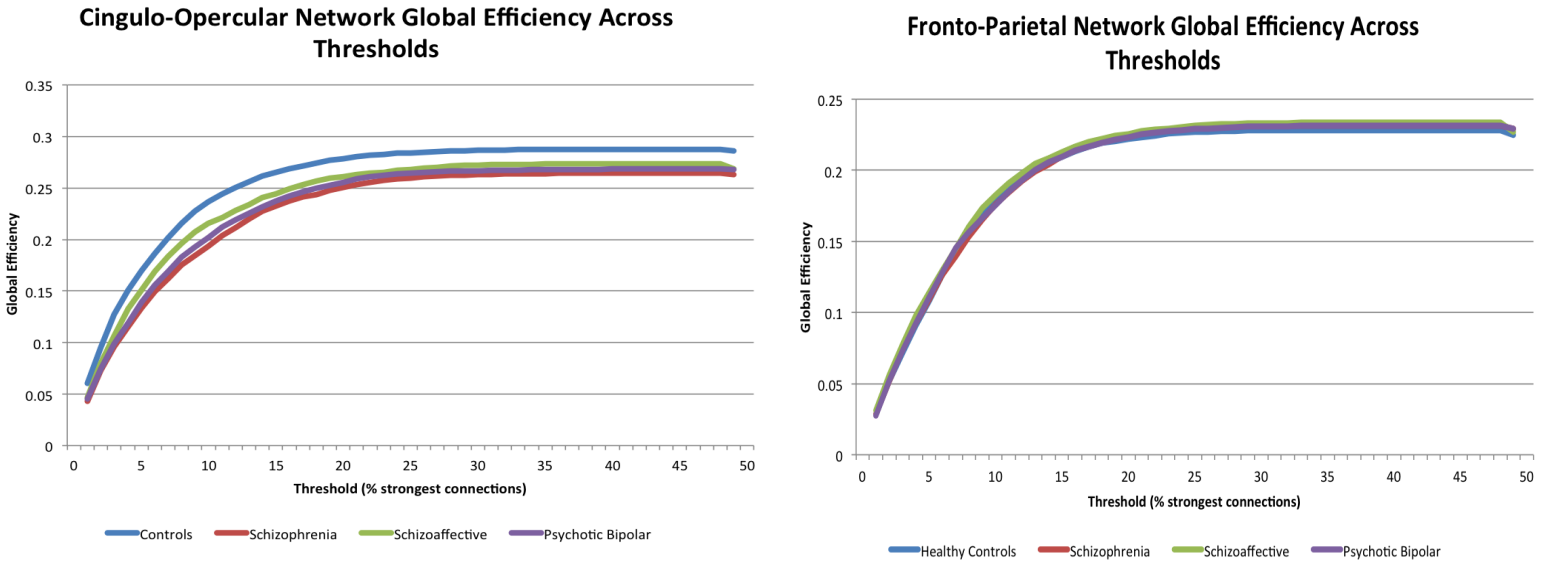

Figure 2.1: Global efficiency of the CON and FPN across thresholds 1%-49% strongest positive connections. Group differences are stable across thresholds. Thresholds 50%-100% begin to include negative functional connectivity values which are difficult to interpret in how they contribute to network metrics.

Two processes were used for calculating participation coefficient. First, *a priori* Power-networks were used to determine each node's module assignment, in order to determine the node's connectedness with Power networks outside of its primary network. This also allowed us to make direct comparisons of participation coefficient across subjects, because all subjects had the same community structure. Second, Louvain's modularity algorithm was used for every subject, creating data-driven communities. This algorithm increases within-module connectivity and reduces between-module connectivity, based on the individual's thresholded, whole brain

graph. Therefore, Louvain-based participation values are based on different community assignments for each individual.

Finally, we completed exploratory analyses to assess network properties associated with the FPN, CON, and DMN. As described further in the Section 4.2, the FPN, CON and DMN are believed to have a dynamic, reciprocal relationship, in which activity in the CON aids in "switching" between task-positive and task-negative activity in the FPN and DMN, respectively (Menon & Uddin, 2010). Therefore, we created a network comprised of the CON, FPN, and DMN nodes (97x97) and calculated global efficiency of this network. We also calculated the degree (i.e. the number of connections) of our *a priori* nodes, but only in the context of this network. In other words, we calculated how many nodes the AI, DACC, and DLPFC were connected to, among all the nodes in the thresholded CON, FPN, and DMN networks. We chose not to utilize participation coefficient, as there are only two outside networks, limiting the range of this metric. Once calculated, we analyzed group differences in global efficiency and hub degree, as well as relationships with cognition.

2.5 Volume Analysis

Exploratory analyses were completed to assess relationships between cognitive ability, network metrics, and gray matter volume. In particular, we wanted to investigate whether participation coefficients would be related to node volume for any hub nodes that showed significant associations with cognitive ability and/or that were significantly reduced in psychotic disorders. We hypothesized that nodes with higher volume would show both higher participation coefficient and would be related to higher network efficiency. We also wanted to explore whether significant relationships between network efficiency and cognitive ability were independent of gray matter volume, and whether gray matter volume predicted cognitive ability beyond the variance explained by network efficiency.

Volume data was calculated in FreeSurfer53, through segmentation of each individual's

T1 structural image based on the Destrieux atlas (Destrieux, Fischl, Dale, & Halgren, 2010). Gray matter parcels from the Destrieux atlas were selected that best approximated hub nodes: anterior insula, anterior cingulate, middle frontal sulcus, and middle frontal gyrus. When assessing group differences and relationships with cognition, right and left hemisphere volumes for each parcel were summed to create a single variable.

2.6 Data Analysis

Analyses were performed using SPSS v.23. Group differences in demographic and clinical characteristics were analyzed using a one-way analysis of variance (ANOVA) and chi-square tests. Group differences in network metrics were calculated in four multivariate ANOVAs (MANOVA): global efficiency of our four networks, local efficiency of our four networks, Power-based participation coefficient of the five hubs, and Louvain-based participation coefficient of the five hubs. Group differences were also assessed through four repeated-measures ANOVAs, to determine the significance of network by diagnostic group interactions. Race, sex, age, B-SNIP site, and head motion were included as covariates in all analyses.

Linear regression analysis was used to test associations between graph metrics and cognition. Regressions included cognitive ability as the dependent variable, with network metric, sex, head motion, and dummy codes for diagnostic group, site, and race as predictors. Interaction variables were included in a second block of regression models to assess interactions between group and network metric. Bonferroni correction was determined for each *a priori* metric analysis, making our threshold $p<.0125$ for global and local efficiency, given four networks within each metric, and $p<.01$ for participation coefficient, given five hubs. Mediation analysis was completed using the PROCESS macro for SPSS (Preacher & Hayes, 2004), with 1000 bias-corrected bootstrap sample for significance-testing. Average functional connectivity of the CON was calculated by averaging connectivity strength across all nodes, and then averaged across 5-10% thresholds. Relationships with gray matter volume, BACS subdomains, and

clinical symptoms were also explored.

3. Results

3.1 Participant Characteristics

Groups differed significantly on sex, race, age, personal education, and socioeconomic status (SES), but not parental education. Clinical groups also differed on symptom scores (Table 3.1).

Table 3.1: Participant Characteristics

	Healthy Controls N=201	Schizophrenia N=143	Schizoaffective N=103	Psychotic Bipolar Disorder N=129	Omnibus Statistic
Age (in years)	36.54 (11.68)	33.39 (11.92)	33.59 (11.19)	35.71 (13.07)	F(3,572)=2.58, p=.05
Sex (M/F)	86/115	103/40	49/54	43/86	X^2=46.20, p<.001
Race (Caucasian/African American/Other)	58/124/19	61/70/12	36/60/7	26/94/9	X^2=19.22, p=.004
Personal Education	14.79 (2.31)	13.08 (2.22)	13.13 (2.17)	14.23 (2.42)	F(3,569)=20.89, p<.001
Mother Education	13.55(3.56)	13.91(3.08)	13.56(4.32)	14.32(3.90)	F(3,486)=1.17, p=.321
Father Education	13.23(3.23)	13.58(2.75)	13.35(3.34)	14.09(2.90)	F(3,536)=2.12, p=.10
Socioeconomic Status (SES)	36.20(14.56)	52.11(15.61)	48.82(15.10)	43.03(16.25)	F(3,540)=32.29, p<.001
PANSS Positive[a]	N/A	16.30(5.57)	18.21(5.13)	12.48(4.12)	F(2,362)=39.84, p<.001
PANSS Negative[b]	N/A	16.34(6.04)	15.91(4.83)	12.08(3.68)	F(2,362)=27.76, p<.001
PANSS General[c]	N/A	31.06(8.67)	34.94(9.10)	28.49(8.09)	F(2,361)=15.73, p<.001
PANSS Total[d]	N/A	63.79(17.02)	68.99(16.34)	53.05(13.46)	F(2,361)=31.07, p<.001
MADRS[e]	N/A	8.46(7.53)	14.33(9.70)	10.48(8.79)	F(2,367)=13.89, p<.001
YMRS[f]	N/A	5.29(5.80)	7.80(6.49)	5.30(5.98)	F(2,365)=6.33, p=.002

Table 3.1: SES was measured using the Hollingshead Index on Social Position, in which higher scores indicate a lower social position (Hollingshead, 1975). PANSS = Positive and Negative Syndrome Scale (Lancon et al., 2000); MADRS = Montgomery Asberg Depression Rating Scale (Montgomery & Asberg, 1979); YMRS = Young Mania Rating Scale (Young et al., 1978)

[a]*Post-hoc Tukey: all groups differ from one another (all p<.02)*
[b]*Post-hoc Tukey: bipolar differs from schizophrenia and schizoaffective (p<.001)*
[c]*Post-hoc Tukey: all groups differ from one another (all p<.05)*
[d]*Post-hoc Tukey: all groups differ from one another (all p<.03)*
[e]*Post-hoc Tukey: schizoaffective differs from schizophrenia and bipolar (p<.01)*
[f]*Post-hoc Tukey: schizoaffective differs from schizophrenia and bipolar (p<.01)*

3.2 Cognitive Ability

General cognition was measured by the factor score of the first and only factor with an eigenvalue >1 from a principal axis factor analysis that included all BACS subtests. Groups significantly differed from one another overall ($F(3,559)=66.39$, $p<.001$), and post-hoc LSD tests revealed significantly reduced cognitive ability in all clinical groups compared to healthy controls (all p's<.001). The schizophrenia patients were the most cognitively impaired (Cohen's d=1.40), bipolar the least (Cohen's d=0.83), and schizoaffective were intermediate (Cohen's d=1.28), but statistically similar to schizophrenia. Group differences in factor scores and BACS sub-test scores are shown in Figure 3.1.

Figure 3.1: Group Differences in Cognitive Ability

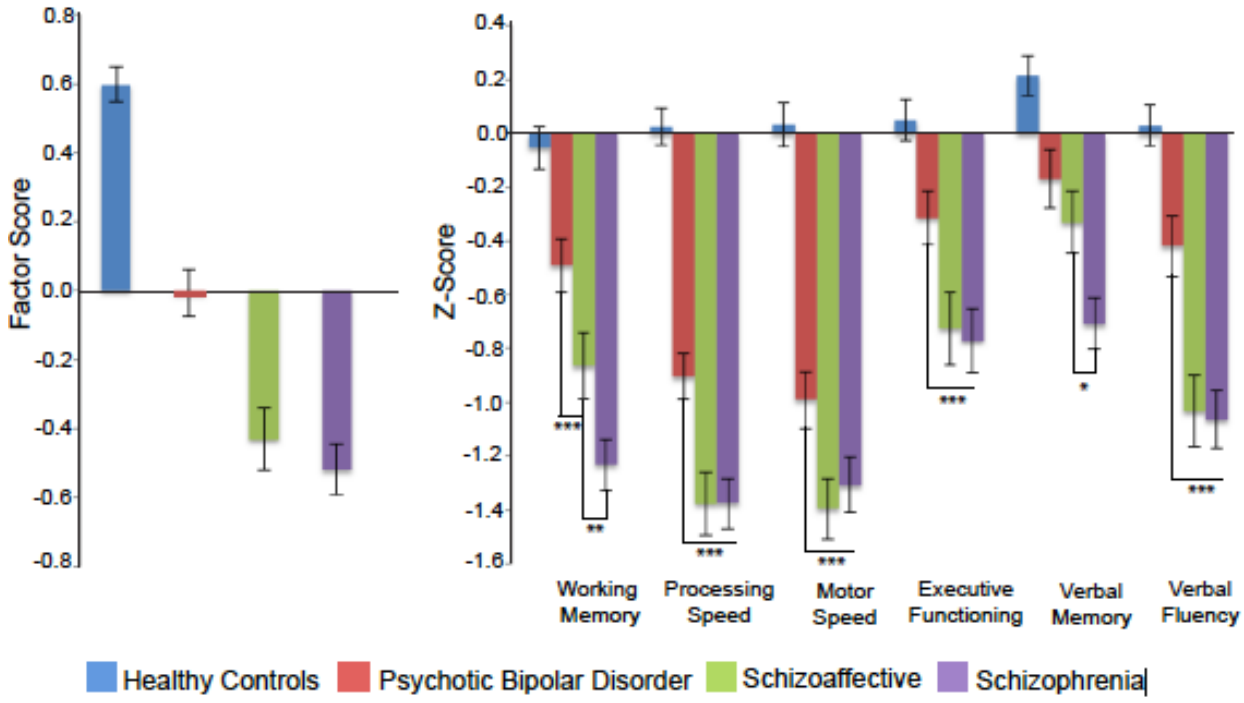

*Figure 3.1: Group differences in cognitive ability across all four diagnostic groups. Left panel shows differences in the factor score used to measure general cognitive ability ($F(3,559)=66.39$, $p<.001$). Right panel shows group differences in specific cognitive domains as measured by the BACS. *p<.05, **p<.01, ***p<.001.*

3.3 Group Differences in Network Metrics

Multivariate analysis revealed a significant omnibus difference in global efficiency across all diagnostic groups ($F(4,575)=2.62$, $p=.002$) (Figure 3.2), and repeated-measures ANOVA revealed a significant network by diagnosis interaction ($F(9,1731)=2.939$, $p=.002$). Follow-up univariate tests revealed a significant difference in CON global efficiency ($p<.001$), but no difference in Whole Brain, FPN or AUD ($p's>.121$). Post-hoc tests revealed significantly reduced CON global efficiency (Cohen's $d=0.36$, $p<.001$) in schizophrenia, compared to HC. Bipolar subjects also had significantly reduced CON global efficiency compared with HC (Cohen's $d=0.33$, $p=.002$), and schizoaffective subjects were trending (Cohen's $d=0.18$, $p=.063$). However, none of the clinical groups differed from each other ($p's>.201$).

Multivariate analysis of local efficiency also indicated significant differences across all groups ($F(4,575)=2.75$, $p=.001$) (Figure 3.2), which was further supported by a significant network by diagnosis interaction in the repeated-measures ANOVA ($F(9, 1731)=2.944$, $p=.002$). This omnibus difference in local efficiency and significant interaction were driven by a significant group difference in local efficiency of the CON ($p=.001$), with no difference for Whole Brain, FPN or AUD ($p's>.113$). CON local efficiency was significantly higher in HC when compared to all groups (schizophrenia: $p=.027$, schizoaffective: $p=.009$; bipolar: $p<.001$), but did not significantly differ between clinical groups ($p's>.183$).

Figure 3.2: Group Differences in *a priori* Network Efficiency

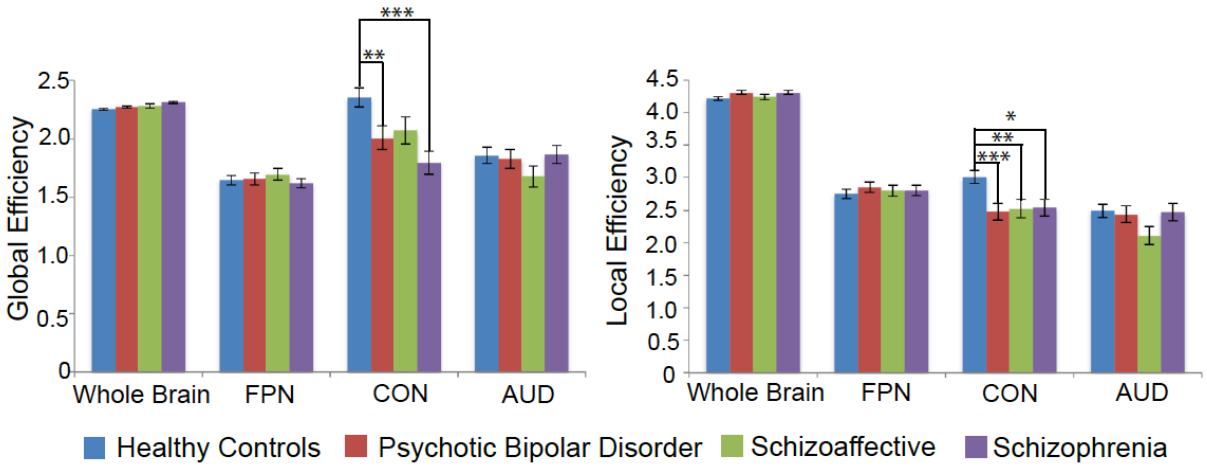

Figure 3.2: As compared to healthy controls, individuals with schizophrenia and bipolar disorder had significantly reduced CON global and local efficiency. Individuals with schizoaffective disorder had significantly reduced CON local efficiency. None of the psychosis groups significantly differed from one another.

No significant group differences were observed in the participation coefficients of the rDLPFC, lDLPFC, DACC, rAI, or lAI. This was true when calculating participation using *a priori* network assignments ($F(15,1704)=1.23$, $p=.24$) or when detecting communities based on a modularity algorithm ($F(15,1704)=.65$, $p=.83$). No significant interaction was observed between hub participation and diagnostic group in repeated-measures ANOVA for either participation calculation (power networks: $F(12,1728)=0.95$, $p=.495$); modularity algorithm: $F(12,1728)=0.763$, $p=.69$)).

Exploratory analysis of all Power networks revealed significantly reduced global efficiency of the subcortical network in all psychotic disorder groups ($F(3,587)=4.756$, $p=.003$). The somatosensory motor network (SSM), which includes only five nodes, also showed significantly reduced global ($F(3,587)=8.30$, $p<.001$) and local efficiency ($F(3,587)=6.861$, $p<.001$) in psychotic disorders (Figure 3.3).

Figure 3.3: Group Differences in all Power Networks

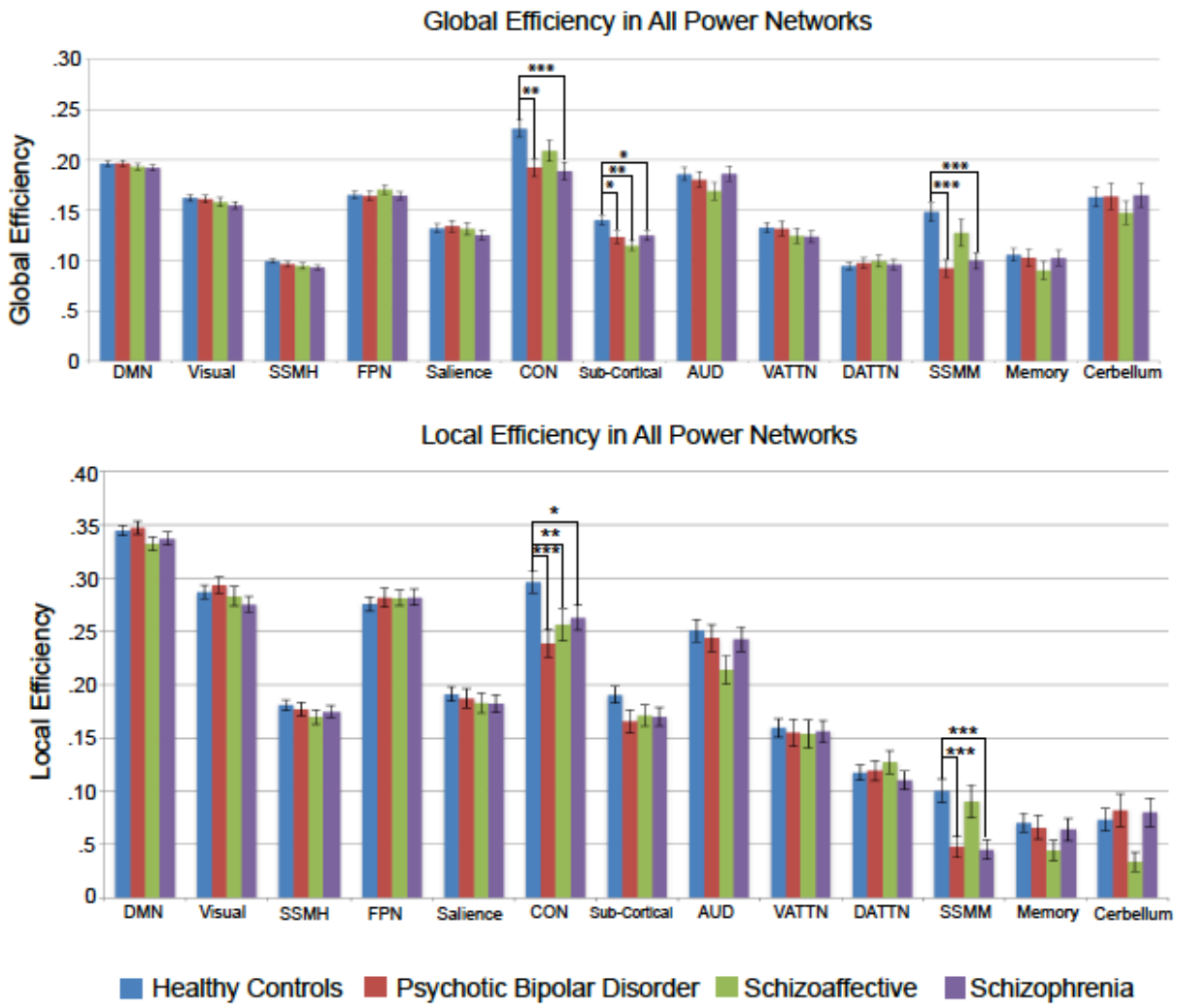

*Figure 3.3: Exploratory analyses revealed significantly reduced global efficiency of the subcortical network in all psychotic disorder groups, compared to controls. Somatosensory Motor network global and local efficiency were also significantly reduced in psychosis patients, however this network includes only five nodes, and therefore efficiency values are interpreted with caution. DMN=Default Mode Network; SSMH = Somatosensory Hand; FPN = Fronto-Parietal Network; CON= Cingulo-Opercular Network; AUD = Auditory Network; VATTN= Ventral Attention Network; DATTN= Dorsal Attention Network; SSMM = Somatosensory Motor. *p<.05, **p<.01, ***p<.001*

3.4 Network Efficiency and Cognition

CON global efficiency positively predicted general cognitive ability, when controlling for sex, race, site, head motion, and diagnosis (standardized β=.099, p=.009). No interactions

between group and CON global efficiency were observed for the schizoaffective or bipolar groups, however a significant interaction was observed for the schizophrenia group (β=.195, p=.032), driven by a stronger positive association between general cognition and CON global efficiency in the schizophrenia group, compared to HC (Figure 3.4). Interestingly, CON global efficiency continued to predict general cognition even when average CON functional connectivity was included as a predictor (β=.179, p.=05). The same was true when CON local efficiency was included in the model, CON global efficiency continued to significantly predict cognition (β=.206, p=.006). Whole brain, FPN, and AUD global efficiency did not significantly predict general cognition across all groups (whole brain: β=-0.029, p=.467; FPN: β=-.004, p=.997; AUD: β=.039, p=.306). Follow-up analyses including chlorpromazine equivalent (CPZ) values as a covariate indicated a similar relationship between CON global efficiency and cognition (β=.125, p=.057), suggesting that this finding cannot be attributed to current antipsychotic therapy.

No significant associations were observed between network local efficiency and cognitive ability for *a priori* networks: CON (β=.053, p=.157), whole brain (β=.009, p=.791), FPN (β=.001, p=.966), or AUD (β=.032, p=.372) local efficiency.

Exploratory linear regressions predicting cognitive ability were performed for the networks that revealed significant group differences in efficiency (subcortical and SSM). Subcortical network global efficiency significantly positively predicted cognitive ability (β=.094, p=.009), with no significant group interactions (p's>.239). Interestingly, when both subcortical and CON global efficiency were included in the same model, both continued to predict cognitive ability, suggesting independent contributions of each network to cognition (CON: (β=.092, p=.021); Subcortical: (β=.079, p=.028)). In terms of explanation of variance, the whole model explained 31.7% of the variance in cognitive ability (R^2 = .317), and together CON and subcortical network global efficiency explained 1.6% of the variance in the model (R^2 = .016).

Separately, CON global efficiency had an R^2 of .01 and subcortical network efficiency had an R^2 of .009. Therefore, these metrics each explain approximately 1% of the variance in cognitive ability. SSM global and local efficiency did not significantly predict cognition (p's >.285). Associations between cognition and global efficiency of all Power networks are shown in Table 3.2.

Table 3.2: Associations Between Power Network Global Efficiency and Cognition

	DMN	Visual	SSMH	FPN	Salience	CON**	Subcortical*	AUD	VATTN	DATTN	SSMM	Memory	Cerebellum
Cog. Ability	β=.06 p=.108	β=.034 p=.359	β=-.028 p=.439	β=-.004. p=.997	β=.025, p=.518	β=.099, p=.009	β=.077, p=.038	β=.039 p=.306	β=.046 p=.232	β=.037 p=.307	β=.028 p=.472	β=-.014, p=.710	β=-.066 p=.065

Table 3.2: Relationships between network global efficiency and general cognitive ability were estimated from linear regression analyses controlling for diagnostic group, sex, race, head motion, and B-SNIP site.

3.5 Participation Coefficient and Cognition

General cognition was not significantly associated with participation of the rDLPFC, lDLPFC, DACC, rAI, or lAI when using Power network assignments (all t's <|1.83|, all p's>.07) or Louvain-derived communities (all t's< |1.31|, all p's>.19).

3.6 Mediation Analysis

Given the significant group differences in CON and subcortical network global efficiency and cognitive ability, in conjunction with the positive association between CON and subcortical network global efficiency and cognitive ability, we assessed whether CON and/or subcortical global efficiency significantly mediated the relationship between clinical status (patient or control) and cognition. We found that CON global efficiency significantly mediated group differences in general cognition (95% CI [-.0764, -.0140]) (Figure 3.4). Subcortical network global efficiency also significantly mediated group differences in cognition (95% CI[-.0544, -

.0043]). When included in the same mediation model, both CON and subcortical global efficiency continued to be significant independent mediators (p<.05).

Figure 3.4: Cingulo-Opercular Network Global Efficiency and Cognition

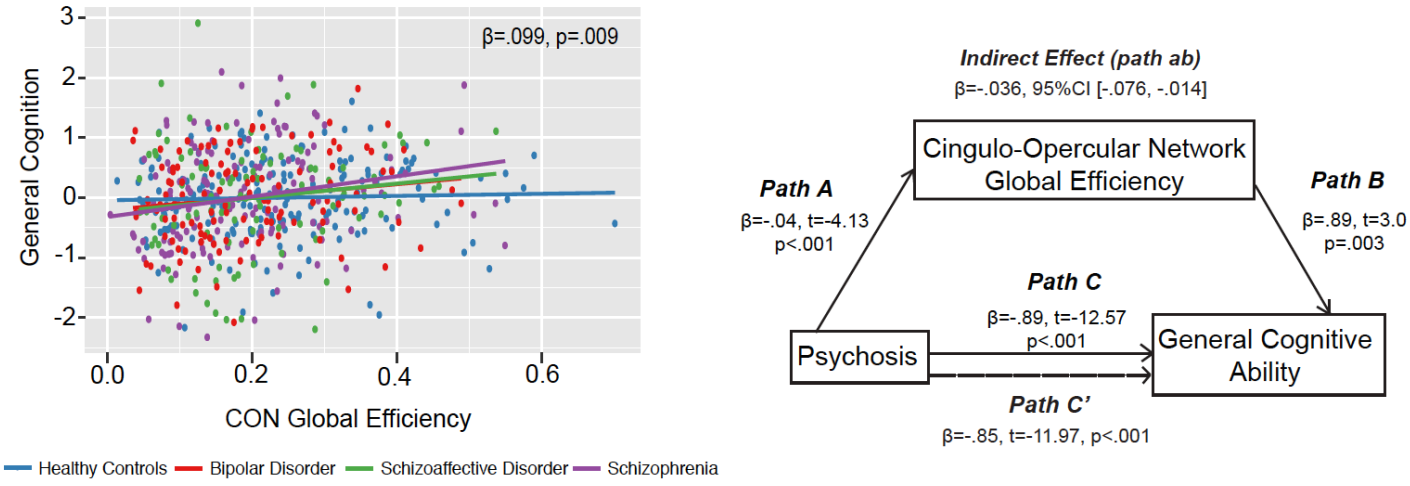

Figure 3.4: Left panel shows significant association between CON global efficiency and general cognition. Right panel shows significant mediation analysis, with CON global efficiency mediating the association between psychotic disorder status and cognitive ability.

3.7 Task-Positive/Task-Negative Networks

In order to probe relationships between the CON, FPN and the DMN, three networks that comprise a dynamic push-pull system to support cognitive function, we calculated global efficiency of these three networks' inter-connections as well as node degree of the anterior insula, DACC, and DLPFC, in the context of these three networks. There were no significant group differences in global efficiency (F(3,590)=.846) or omnibus hub degree (F(3,577)=.694, p=.556). Global efficiency did not significantly predict cognitive ability (β=.035, p=.322), and none of the hubs significantly predicted cognitive ability: rAI (β=.068, p=.061), lAI (β=.032, p=.371), rDLPFC (β=-.042, p=.236), lDLPFC (β=-.018, p=.636), DACC (β=.045, p=.214). These findings do not support the notion that network properties of this larger system, at least as

measured during resting state, are specifically abnormal in psychotic disorders and/or related to the generalized deficit.

3.8 Gray Matter Volume Analysis

When controlling for age and sex, groups significantly differed in total gray matter volume ($F(3,575)=9.188$, $p<.001$). Post-hoc pairwise analysis revealed significantly reduced total gray matter volume in schizophrenia ($p=.005$) and schizoaffective ($p<.001$) subjects, but not bipolar subjects ($p=.274$), when compared to healthy controls. Schizoaffective subjects also had significantly reduced gray matter volume compared to bipolar subjects ($p<.001$). All regions of interest (AI, DACC, DLPFC) showed significant group differences when controlling for age and sex, but the differences were no longer significant when controlling for total gray matter volume (with the region of interest's volume subtracted), suggesting that these differences are a reflection of globally smaller brain volume in schizophrenia and schizoaffective subjects, not a specific abnormality in our *a priori* hubs.

Whole brain gray matter volume was significantly positively associated with overall cognitive ability, when controlling for sex, age, race, head motion, diagnosis, and B-SNIP site ($\beta=.214$, $p<.001$). Gray matter volume of the middle frontal gyrus, anterior insula, and anterior cingulate were all significantly positively associated with cognitive ability ($p's<.03$), but these relationships were no longer significant when controlling for total gray matter volume ($p's>.596$).

Correlations between brain volume and network metrics were also explored in all subjects, controlling for age, sex, race, and psychosis group (control or patient). Of all the pairwise correlations, only six associations passed the lenient significance level of $p<.05$: DACC power-derived participation and anterior cingulate volume ($r=-.099$, $p=.018$), DACC Louvain participation and middle frontal gyrus volume ($r=.098$, $p=.019$), DACC Louvain participation and middle frontal sulcus volume ($r=.091$, $p=.029$), whole brain global efficiency and anterior cingulate volume ($r=-.086$, $p=.038$), whole brain global efficiency and anterior insula volume ($r=-$

.105, p=.012), whole brain local efficiency and anterior insula volume (r=-.138, p=.001).

We also assessed whether the significant association between CON global efficiency and overall cognitive ability was independent of, or influenced by, individual differences in gray matter volume. To do this, we ran a series of partial correlations, controlling for age, sex, and the brain variable of no interest. When controlling for CON global efficiency, overall cognition was still significantly associated with total gray matter volume (r=.321, p<.001), anterior insula volume (r=.192, p<.001), and anterior cingulate volume (r=.243, p<.001). When controlling for both anterior insula and anterior cingulate cortex volume, CON global efficiency was still significantly correlated with total cognition (r=.18, p<.001); the same was true when controlling for total gray matter volume (r=.164, p<.001).

Finally, in a multiple regression, we assessed whether CON global efficiency, subcortical network global efficiency, and total gray matter volume independently predicted total cognition. We found that CON global efficiency (β=.099, p.=007) and total gray matter volume (β=.183, p<.001) independently significantly predict cognition, but this was not true for the subcortical network (β=.052, p.=152). In this model, which explained 34% of the variance in cognitive ability, total gray matter volume explained 2.2% (R^2 = .022) and CON global efficiency explained 1% of the variance (R^2=.01) and subcortical global efficiency explained an additional .3% (R^2 = .003). These findings suggest that gray matter volume, although related to cognitive ability, does not influence the association between CON global efficiency and cognition. Therefore, these brain relationships appear to be relatively independent in their influence on the generalized cognitive deficit. It is possible, however, that total gray matter volume explains some of the relationship between subcortical global efficiency and cognition, as subcortical global efficiency is significantly positively associated total gray matter volume (r=.114, p<.001).

3.9 CON and Subcortical Global Efficiency and Specific Cognitive Domains

To unpack the observed association with general cognition, we assessed relationships between CON and subcortical network global efficiency and the specific cognitive domains that comprise our general cognition measure. CON global efficiency was significantly positively associated with processing speed (β=.113, p=.003), executive functioning (β=.120, p=.004), and verbal fluency (β=.107, p=.012), but not with any other cognitive domains. We did not find significant group interactions in the prediction of these cognitive variables. Further, mediation analyses revealed that CON global efficiency significantly mediated the relationship between psychotic disorder status and processing speed (95% CI [-.0917, -.0178]), executive function (95% CI [-.1126, -.0254]), and verbal fluency (95% CI [-.1009, -.0157]).

Using methods from Meng and colleagues (Meng, Rosenthal, & Rubin, 1992) to compare the strength of correlations, we observed no significant differences in the strength of bivariate correlations between CON global efficiency and the factor score, compared to any specific cognitive domains (all p's >.239). In addition, we explored whether these specific cognitive domains were significantly associated with CON global efficiency after controlling for overall cognition, to assess their specificity beyond the generalized deficit. Once this factor was included in the model, processing speed (β=.027, p=.162), executive functioning (β=.038, p=.261), and verbal fluency (β=.035, p=.298) were no longer significantly associated with CON global efficiency.

Subcortical network global efficiency was also significantly associated with processing speed (β=.084, p=.024), but not with any other specific domain. Subcortical global efficiency was also a significant mediator in the relationship between psychotic disorder status and processing speed (95% CI [-.0710, -.0072]).

3.10 Relationships with Symptoms

Using partial correlation analyses controlling for sex and race, we observed no

significant associations between any of our clinical variables and global or local efficiency of our *a priori* networks or the subcortical network. We did observe some significant associations between clinical symptoms and cognitive ability, however the effect sizes were small and most would not survive multiple comparison correction. All associations are shown in Table 3.3. Assuming a stringent Bonferroni correction, in which 7 cognitive variables and 6 clinical variables are considered, significant thresholds is ($p < (.05/6*7) = p<.0012$). Therefore, only the relationships between verbal fluency and negative symptoms and between motor speed and PANSS total are considered statistically significant. Despite the small effect sizes, all relationships were negative, suggesting that more severe symptoms were associated with worse cognitive ability across all psychotic disorders.

Table 3.3: Correlations Between Cognition and Clinical Symptoms

	Overall Cognition Factor Score	BACS Digit Sequencing	BACS Symbol Coding	BACS Token Motor	BACS Tower Task	BACS Verbal Fluency	BACS Verbal Memory
PANSS Positive Symptoms	r=-.111* p=.038	r=-.110* p=.041	r=-.047 p=.386	r=-.15* p=.005	r=-.081 p=.133	r=-.051 p=.348	r=-.132* p=.014
PANSS Negative Symptoms	r=-.159* p=.003	r=-.111 p=.039	r=-.121* p=.024	r=-.118* p=.029	r=-.019 p=.723	r=-.188** p<.001	r=-.146 p=.006
PANSS General Symptoms	r=-.111* p=.04	r=-.081 p=.134	r=-.091 p=.092	r=-.162 p=.002	r=-.059 p=.278	r=-.04 p=.458	r=-.092 p=.086
PANSS Total Symptoms	r=-.144* p=.007	r=-.113 p=.036	r=-.101 p=.061	r=-.17** p=.001	r=-.063 p=.244	r=-.096 p=.074	r=-.137 p=.011
MADRS Depression Symptoms	r=.028 p=.605	r=-.009 p=.866	r=.023 p=.671	r=.015 p=.785	r=.062 p=.252	r=.041 p=.442	r=.005 p=.927
YMRS Mania Symptoms	r=.084 p=.12	r=.008 p=.885	r=.106* p=.049	r=.012 p=.83	r=-.036 p=.502	r=.098 p=.068	r=.091 p=.091

*Table 3.3: Correlations controlled for sex and race and only included psychotic disorder patients (N=344). *p<.05, **p<.0012 (Bonferroni correction for significance level).*

4. Discussion

The presented findings are the first to investigate the role of brain network integrity in the generalized cognitive deficit across multiple psychotic disorders. In line with my first hypothesis, we demonstrated that individuals with psychotic disorders had significantly reduced global and local efficiency of the cingulo-opercular network (CON), a network that has been implicated in both cognitive impairment and psychotic symptoms (Palaniyappan & Liddle, 2012) (Menon, 2011). As predicted, global efficiency of the CON was positively associated with overall (i.e.

generalized) cognitive ability across all groups with no group interactions amongst psychotic disorders. These findings suggest that lower efficiency of the CON observed in psychotic disorders contributes to the generalized cognitive deficit across multiple diagnostic categories. Exploratory analyses also revealed a significant role of the subcortical network in psychotic disorders and cognition, but not in the other Power exploratory networks. We observed significantly reduced global efficiency of the subcortical network, as well as a positive association between subcortical network global efficiency and cognitive ability. Although not hypothesized, these findings fit well with a growing literature on the role of subcortical structures, particularly the thalamus and basal ganglia, in the pathophysiology of psychotic disorders (Anticevic et al., 2015) (Woodward, Karbasforoushan, & Heckers, 2012).

Contrary to my hypotheses, FPN and whole brain global and local efficiency were not significantly reduced in psychotic disorders and did not correlate with cognitive ability. In addition, hub node participation coefficients did not show group differences and were not associated with cognitive ability. These findings were surprising, particularly the lack of associations between cognitive ability and the FPN, given the strong literature suggesting a role of FPN abnormalities in cognitive ability generally (N. U. Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008), and psychiatric disorders specifically (Baker et al., 2014; Cole, Repovs, & Anticevic, 2014). In an independent dataset, we have previously shown associations between FPN efficiency and cognition; however this was found in pseudo-resting state data, which involved the regression of task-related BOLD signal from the time series. The FPN is a network comprised of flexible hubs that rapidly update based on task-demands (Cole, Reynolds, et al., 2013). We speculate that “pure” resting-state data may be less reflective of these flexible, adaptive dynamics, and therefore FPN efficiency measured using resting-state may be less sensitive to associations with cognition. However, follow-up studies that more directly compare resting state and pseudo-resting state data would be needed to support this hypothesis.

Together, these data provide evidence that the functional efficiency of information

transfer within the CON, as measured during rest, is reduced in three “distinct” psychotic disorders, and that lower functional efficiency contributes to the generalized cognitive deficit. These findings further my line of research revealing that lower CON global efficiency is associated with more severely impaired overall cognitive ability across the psychosis spectrum, as seen now in three distinct datasets (J. M. Sheffield et al., 2015) (J. M. Sheffield, Kandala, S., Burgess, G. C., Harms, M. P., & Barch, D. M, 2016). These findings also point to a previously uninvestigated role of reduced subcortical network global efficiency in psychotic disorders that appears to independently (i.e. beyond CON global efficiency) predict cognitive impairment. Finally, the lack of an interaction between psychotic disorder groups and global efficiency in predicting cognition provides support for a dimensional interpretation of the relationship between global efficiency and cognitive impairment, in line with the current aims of the RDoC initiative.

4.1 The Generalized Deficit

The goal of the current research was to assess a putative mechanism underlying the generalized cognitive deficit across psychotic disorders. One motivation for investigating this question was to replicate our previous findings of associations between network efficiency and overall cognitive ability in schizophrenia. However another major aim of the study was to assess whether these relationships existed across multiple psychotic disorders. To our knowledge, this is the first investigation of abnormal efficiency of functional networks in psychotic bipolar disorder and relationships with cognitive impairment. Therefore this study is the first to report that psychotic bipolar disorder patients have significantly reduced global and local efficiency of the CON and reduced global efficiency of the subcortical network, and that these reductions are related to cognitive ability. These findings fit within a growing literature indicating a generalized cognitive deficit in psychotic bipolar disorder, similar to that observed in schizophrenia and schizoaffective disorders (Reilly & Sweeney, 2014).

The generalized cognitive deficit describes the significant impairment of cognitive ability

within a multitude of cognitive domains, and implies a common mechanism contributing to the range of impairments (Gold & Dickinson, 2012). In the current study, we quantified the generalized deficit as the first factor in a principal axis factor analysis that included individual performance on all six cognitive domains measured in the BACS. This first factor was the only factor with an eigenvalue >1, indicating that it was the only factor explaining significant variance (54%) in cognitive ability across tasks. We chose to use the first factor as our measure of generalized cognition, as it isolated the shared variance in cognitive ability across multiple domains. This corresponds with the conceptualization of the generalized deficit as reflecting a shared mechanism that contributes to performance in multiple cognitive domains (Dickinson et al., 2008).

This finding of a single cognitive factor in psychotic disorders was initially reported by Dickinson and colleagues in 2004 (and later replicated in an independent sample in 2008) in a group of 97 subjects with schizophrenia or schizoaffective disorder and 87 healthy controls (Dickinson, Iannone, Wilk, & Gold, 2004) (Dickinson et al., 2008). Through structural equation modeling, they found that a single common cognitive factor from subdomains of the Wechsler Adult Intelligence Scale-III and the Wechsler Memory Scale mediated the relationship between diagnostic status and cognitive ability in 18 subdomains. In addition, they found that approximately two thirds of the diagnosis-related variance in cognitive ability could be accounted for by the common factor, and that this effect was stronger than any contribution by specific cognitive domains. These findings are convergent with our observation that CON and subcortical network global efficiency significantly mediated the relationship between psychotic disorder status and the general cognition factor. CON global efficiency is therefore a neurobiologically-based mechanism that accounts for significant variance in disorder-related generalized cognitive impairment.

In our dataset, CON and subcortical network global efficiency were significantly associated with the overall cognitive ability factor, but also showed specific relationships with

cognitive domains, including processing speed, executive functioning, and verbal fluency. If associations between cognitive scores on these subtests were independent (i.e. not contributing to a generalized deficit), they would show relationships with CON global efficiency after accounting for the shared variance attributed to the generalize deficit. Instead, we found that relationships between CON global efficiency and specific cognitive domains were not significant after controlling for our generalized deficit factor. This suggests that the associations between CON global efficiency and specific domains can be accounted for by the generalized deficit, as opposed to representing specific associations. In other words, the general cognition factor is identifying variance in specific cognitive abilities that are most related to CON global efficiency. Our current findings therefore support the hypothesis that CON global efficiency is associated with the generalized cognitive deficit in psychotic disorders.

The importance of this generalized deficit is (at least) two-fold. First, knowing that cognitive impairment across domains is due to a shared mechanism alters hypothesis-generation when working to understand the neurobiological underpinnings of cognitive deficits across the psychosis spectrum. By focusing on shared variance in a cognitive battery, researchers may have more power to detect relationships with putative mechanisms. Second, using a single cognitive factor of shared variance allows for the exploration of relationships with other relevant variables, such as symptom severity, to determine how the complex symptom constellations in psychotic disorders are interrelated. In the B-SNIP sample, although we saw no significant relationships between symptom severity and network metrics, we did observe significant associations between symptoms and general cognition. More specifically, we found that overall cognitive ability was significantly associated with both negative symptom severity and total symptom expression on the PANSS, suggesting that a more severe generalized cognitive deficit was related to more severe negative and total symptoms. Effect sizes for these relationships were small, but in this large sample were statistically significant at $p<.05$. While the relationship between cognitive deficits and clinical symptoms remains a difficult web to untangle,

these data support continued research identifying cognitive mechanisms that may contribute to symptom report and expression (E. K. Moran, Culbreth, & Barch, 2017).

To this end, my colleagues and I recently completed data collection on a project aimed to address the association between cognitive and negative symptoms in patients with schizophrenia. In a study that we developed and conducted during my 4th and 5th years of graduate school, we collected data from negative symptom self-report measures, ecological momentary assessment of motivation and pleasure, functional outcome measurements, and cognitive tasks, from schizophrenia subjects and community controls. From this project, we hope to explore how reward processing abnormalities and higher-order cognitive processes (e.g. working memory ability) contribute to the expression and severity of negative symptoms. Additionally, through this study, I hope to analyze the role of rapid instruction-based task learning (RITL) (Ruge & Wolfensteller, 2010) in the generalized cognitive deficit in schizophrenia. RITL is the process of taking instructions and transferring control of that information into representations that can be implemented to yield task behavior (Cole, Laurent, & Stocco, 2013). RITL is therefore a domain-general cognitive process that is necessary for the completion of cognitive tasks in laboratory studies, which all rely on participants' ability to implement task instructions. Although not specifically CON-dependent, initial learning trials of RITL have been associated with increased anterior insula activity (Ruge & Wolfensteller, 2010). Therefore, I hope to assess whether CON activity and network efficiency predict group differences in performance, to extend our current resting state findings. RITL has not yet been explored in a psychotic disorder population, and therefore I am excited to assess its role in the generalized deficit in schizophrenia. While the imaging data has not yet been analyzed, preliminary behavioral results suggest a robust associations between RITL accuracy during an fMRI task and general cognitive ability as measured during a separate behavioral battery ($r=.596$, $p<.001$). RITL is therefore my next avenue for understanding mechanisms underlying the generalized deficit.

4.2 The Cingulo-Opercular Network

The CON is a functional network that has received significant attention from both the cognitive neuroscience and clinical literatures over the past decade, due primarily to its role in complex cognitive processes (Cocchi et al., 2013) (N. U. Dosenbach et al., 2006) and the hypothesized role of the anterior insula and DACC in psychotic experiences (Palaniyappan & Liddle, 2012). In 2006, Dosenbach and colleagues identified the CON as a "core task" network anchored by the anterior insula and DACC (N. U. Dosenbach et al., 2006). Nodes within this network showed a sustained increase in BOLD activity throughout various cognitive tasks, implicating the CON in domain-general cognitive performance. Since its introduction into the literature, several studies have worked to further elucidate the role of a "core task" network in overall cognitive functioning. Much of that work has focused on the CON as a network that maintains tonic alertness (Coste & Kleinschmidt, 2016; Sadaghiani & D'Esposito, 2015; Sadaghiani et al., 2010). Tonic alertness is described as an effortful, top-down, self-initiated preparedness to process and respond to incoming information (Posner, 2008; Sadaghiani & D'Esposito, 2015). The process of "alerting" serves to "produce and maintain optimal vigilance and performance during tasks", and can be probed as a cognitive function through the use of a warning signal that serves to prioritize sensory input (Petersen & Posner, 2012). Therefore, tonic alertness is an important state for optimizing performance in neurocognitive tasks.

Several studies have worked to establish the role of the CON in the process of tonic alertness (Coste & Kleinschmidt, 2016; Sadaghiani & D'Esposito, 2015). In their paper from 2009, Sadaghiani and colleagues observed that higher pre-stimulus activity in the CON predicted better stimulus detection during a simple continuous detection task that relied on tonic alertness (Sadaghiani, Hesselmann, & Kleinschmidt, 2009). They concluded that this increased CON activity reflected the CON's facilitation of stimulus detection through tonic alertness, and therefore cognitive performance. A follow-up study combining fMRI and EEG methods found a selective association between resting-state BOLD activity in the CON and fluctuations in the

global oscillation power in the alpha frequency band (~10-12 Hz) – a frequency band that is the most consistent EEG marker of tonic alertness (Sadaghiani et al., 2010). Most recently, Sadaghiani & D'Esposito used a factorial fMRI task design to dissociate selective attention and tonic alertness (Sadaghiani & D'Esposito, 2015). Again, they found that CON BOLD activity increased when more tonic alertness was required, but also showed that BOLD activity in the dorsal attention network increased when selective attention was required, dissociating the function of these two networks in task performance. Converging evidence for the CON's role in tonic alertness was observed by Coste and colleagues, who demonstrated that higher BOLD activity in the CON preceded task trials with faster reaction times, for both visual and auditory stimuli (Coste & Kleinschmidt, 2016). Interestingly, Sadaghiani & D'Esposito also looked at functional connectivity on the CON, and found that when tonic alertness demands increased, there was a significant increase in the functional connectivity within the CON. The authors interpreted this as higher within-network communication facilitating the maintenance of tonic alertness by the CON. This finding fits particularly well with our current results showing that greater within-network CON global efficiency predicted better overall cognitive functioning.

Evidence for impaired tonic alertness in psychotic disorders is limited. Although the domain of attention is commonly probed in psychotic disorder subjects, alertness is a cognitive process that is less frequently studied in this population. In schizophrenia patients, most research assessing tonic alertness has used the Test for Attention Performance (TAP; (Zimmermann, 2002)). The TAP measures a subject's reaction time in responding to stimuli when they either have or have not been preempted by an acoustic signal. Using this paradigm, schizophrenia patients have shown significantly impaired tonic alertness when compared to healthy controls (Hofer et al., 2005), for both symptom-remitted and non-remitted patients (Hofer et al., 2011). However in another study, when patients were asked to press a button as quickly as possible in response to a randomly presented stimulus (as a measure of tonic alertness), their performance was statistically similar to controls (Wolf, Hose, Frasch, Walter, & Vasic,

2008). In bipolar disorder patients, a study measuring sustained attention through a rapid visual information processing (RVIP) task found that euthymic bipolar patients had significantly impaired sustained attention, and that sustained attention ability was significantly negatively correlated with duration of illness and number of manic and depressive episodes (Clark, Iversen, & Goodwin, 2002). Although sustained attention is considered a process more focused on a readiness to detect rarely and unpredictably occurring signals over long periods of time (Sarter, Givens, & Bruno, 2001), it is conceptually similar to tonic alertness. While none of the tasks in the current study probed tonic alertness or sustained attention, the ability of an individual to prepare for goal-relevant stimuli is arguably an important component of all neurocognitive tasks. The relationship between CON global efficiency and tonic alertness cannot be directly addressed in the current study, but can and should be further explored in fMRI studies of individuals with psychotic disorders, to assess whether reduced CON global efficiency contributes to impaired tonic alertness, and consequently impaired general cognition.

Independent of questions about tonic alertness, abnormalities in the neurobiology of the CON in psychotic disorders have been validated through the convergence of structural and functional neuroimaging evidence. A recent trans-diagnostic meta-analysis, for instance, revealed reduced gray matter volume of the insula and DACC in a range of psychiatric disorders (Goodkind et al., 2015). Decreased volume of these nodes predicted worse executive functioning ability, providing further support for the CON's role in cognitive dysfunction in mental health disorders. A similar relationship between smaller gray matter volume of the anterior insula and anterior cingulate cortex and worse cognitive functioning was seen in the current dataset, however this relationship was likely driven by total gray matter volume. Nonetheless, the meta-analytic findings point to a behaviorally relevant trans-diagnostic reduction in insula and DACC volume, aggregated across 193 studies.

Functional connectivity studies have also revealed abnormalities in the CON that are related to both psychotic experiences and cognitive ability. These studies have been influenced

by an increasingly prominent theory from Menon and colleagues that the anterior insula and DACC are hubs that facilitate information processing between multiple networks, in particular the default mode network (DMN) and the fronto-parietal network (FPN), to promote processing of goal-relevant information (Menon, 2011). In the current dataset, we worked to address this theory by calculating the global efficiency of graphs of nodes that only comprised the CON, DMN, and FPN. Global efficiency of this graph should estimate how efficiently integrated these three networks are during rest. We also calculated the node degree of the DACC, AI, and DLPFC, which reflects the number of connections each node has with other nodes in the graph. Despite a robust literature suggesting abnormalities in these networks in schizophrenia (discussed below), we observed no significant associations between any of these variables and cognition, or significant group differences. Given the lack of group differences and relationships with cognition for DMN and FPN within-network global efficiency, this is not entirely surprising. However, it suggests at least two possible conclusions: 1) CON within-network resting state global efficiency is specifically abnormal in psychotic disorders and does not extend to abnormalities with the FPN and DMN, or 2) that abnormalities in global efficiency and hub degree with the FPN and DMN are difficult to detect in resting-state data, given the dynamic nature of these networks.

Despite our null findings, it is still important to consider the literature that *has* identified abnormalities in these networks in the context of psychosis. Two independent studies published in 2013 supported Menon's dynamic information processing theory by demonstrating reduced connectivity of the right anterior insula in schizophrenia, using Granger Causality analysis. One study found that patients with schizophrenia had lower effective connectivity between the right anterior insula and the DLPFC (Palaniyappan, Simmonite, White, Liddle, & Liddle, 2013), providing support for the notion of an impaired feedback-mechanism between the CON and FPN in schizophrenia. Moran and colleagues revealed a similarly impaired effective connectivity between the right anterior insula and the FPN, but also observed reduced connectivity between

the insula and DMN. Connectivity values between the insula, DMN, and FPN correlated with performance on an information processing task, suggesting the importance of these systems in cognitive impairment in schizophrenia (L. V. Moran et al., 2013). Interestingly, a third study found that reduced BOLD activity of the right anterior insula in schizophrenia was associated with severity of hallucinations, as was higher connectivity between the DMN and FPN (Manoliu et al., 2014). Together, this literature suggests that abnormal functioning of the CON in schizophrenia impacts modulation of the DMN and FPN, which is in turn associated with cognitive impairment and severity of psychotic symptoms.

The current study adds to this literature by revealing significantly reduced global and local efficiency of the CON in psychotic disorders. Our findings also demonstrate that global efficiency predicts cognitive ability beyond the average strength of functional connectivity, pointing to an important role of the CON's functional organization in supporting cognitive processes. These findings therefore suggest that information transfer within the CON is not optimally integrated in ways that contribute robustly to cognitive function. Given mounting evidence of functional connectivity abnormalities in the context of reduced brain volume in the CON, future work looking at the efficiency of structural connections within and between the CON would help further understanding of the abnormalities present within this network.

4.3 The Subcortical Network

The subcortical network as defined by the Power (2011) atlas includes 13 nodes located primarily within the thalamus and basal ganglia. Both the thalamus and basal ganglia are key nodes comprising a thamalocortical circuit, which is believed to play a critical role in higher order cognition, and to be abnormal in psychotic disorders (Andreasen, Paradiso, & O'Leary, 1998; Anticevic et al., 2015). In 1986, Alexander and colleagues identified five thalamocortical circuits connecting thalamic nuclei with the basal ganglia and distinct cortical targets (Alexander, DeLong, & Strick, 1986). One of these circuits connected the mediodorsal nucleus of the

thalamus and prefrontal cortex (PFC), a pathway of structural connectivity that was later identified in functional connectivity data as well (Zhang et al., 2008).

Given its connectivity with prefrontal targets, this pathway with the mediodorsal (MD) nucleus of the thalamus was hypothesized to be particularly important for supporting higher-order cognition. This was further supported by work in mice, showing that pharmacogenic-induced reductions in MD neuron activity resulted in reduced synchrony between the MD thalamus and PFC (Parnaudeau et al., 2013). In this study, connectivity between the MD thalamus and PFC was highly correlated with working memory and reversal learning ability, revealing impairments in cognition when synchrony between these regions was disrupted. These findings were conceptually linked to abnormalities observed in schizophrenia patients, who demonstrate reduced functional connectivity between the PFC and MD (Woodward et al., 2012). Reduced connectivity between the MD and PFC was observed in an independent dataset that also included patients with bipolar disorder, with and without a history of psychosis (Anticevic et al., 2014). This study found that bipolar disorder subjects with a history of psychosis had significantly reduced connectivity between the MD thalamus and the PFC similar to schizophrenia subjects; however connectivity for the bipolar subjects without a history of psychosis was more similar to healthy controls. These findings suggest that thalamocortical connectivity abnormalities may be related more specifically to psychotic disorders. Providing further support for the importance of thalamic connectivity in psychotic disorders, thalamocortical hypoconnectivity was associated with conversion to a psychotic disorder in a large cohort of individuals who were identified as high risk (Anticevic et al., 2015). Finally, a recent study demonstrated that individuals with schizophrenia who underwent cognitive remediation had a greater increase in thalamocortical functional connectivity when compared to schizophrenia patients in the placebo group. Following this intervention, thalamus-PFC connectivity predicted improvements in overall cognition (Ramsay, 2016). Together, these studies provide strong evidence of reduced thalamocortical functional connectivity in psychotic

disorders that contribute to cognitive impairment.

Our findings of reduced global efficiency of the subcortical network suggest that the functional topology of subcortical nodes is not optimal for supporting efficient information transfer in psychotic disorders. While connectivity between the thalamus and PFC has been well-studied in schizophrenia, our findings suggest the need for further investigation into the connectivity amongst subcortical nodes. In addition, we observed that subcortical network global efficiency significantly mediated the association between psychotic disorder status and cognitive ability, and that this relationship was independent of the association between cognition and CON global efficiency. These findings not only point to the importance of subcortical network efficiency in cognitive impairment, but also suggest that abnormalities within this network are independently contributing to the generalized deficit, beyond the contribution of cortical/frontal structures. Therefore, abnormalities in both networks appear affected in psychotic disorders; however whether these abnormalities develop independently or are the product of a common neurodevelopmental process, remains to be determined.

4.4 Nodal Properties

In addition to investigating network-level abnormalities, we also performed several analyses to assess structural and functional alterations in specific brain regions that comprise our networks of interest. One initial hypothesis was that hub nodes within the FPN and CON would show reduced participation coefficients in psychotic disorders, which would reflect that these hubs were less connected with regions outside of their main network. Participation coefficient was selected to address this question, due to its robustness in controlling for network size, unlike a metric such as node degree (Power et al., 2013). We calculated participation coefficient of the anterior insula, DACC, and DLPFC based on the network structure defined by the Power atlas, as well as by the community structure from a Louvain algorithm designed to increase within-community connectivity and decrease between-community connectivity.

Contrary to our hypothesis, we did not observe any significant group differences in participation coefficients of our *a priori* hubs, for either the Power or Louvain community structures. This indicated that the anterior insula, DACC, and DLPFC had relatively intact distribution of edges with outside networks. We also found no evidence to suggest that participation of these nodes contributed to the generalized cognitive deficit in psychotic disorders. Despite these null findings, we performed additional analyses exploring the role of gray matter volume of the anterior insula, DACC, and DLPFC in psychotic disorders and cognitive ability, as well as relationships with our graph metrics. Conceptually, we wanted to assess whether nodes with smaller gray matter volume, and therefore presumably a lower count of cell bodies, participated less with outside networks. We also wondered whether nodes with smaller gray matter volume were associated with less efficient networks, allowing us to test relationships between gray matter volume of specific regions and both within- and between-network connectivity.

When looking at gray matter volume, we observed significant group differences in our hub nodes, such that psychotic disorder patients had smaller insula, DACC, and DLPFC volumes than healthy controls. We also found significant relationships between gray matter volume and cognitive ability, suggesting that smaller gray matter volume was associated with worse general cognition. Importantly, these relationships were not robust when controlling for total gray matter volume, revealing that it is likely not these hubs in particular that are smaller in psychotic disorders, but that smaller overall gray matter volume is related to worse cognition. Further, relationships between node volume and graph metrics were weak and often difficult to interpret. For instance, larger gray matter volume of the anterior cingulate was correlated with lower participation coefficient of the DACC, and larger gray matter volume of the anterior insula was correlated with lower whole brain efficiency, which was opposite of our prediction.

While the finding of smaller total gray matter volume and its relationship with cognitive deficits in psychotic disorders is well inline with what has been previously reported (Gur et al.,

2000) (Sullivan, Shear, Lim, Zipursky, & Pfefferbaum, 1996), the lack of specificity to our hub nodes, and the negative relationships between node volume and connectivity measures, are somewhat surprising. There is strong evidence of reduced gray matter volume of the anterior insula and DACC in schizophrenia from previous studies (Goodkind et al., 2015), and we expected that smaller gray matter volumes of these major hub nodes would contribute to less functionally efficient networks and lower participation with outside networks. We have also previously shown, in a dataset using pseudo-resting state data, a positive association between right anterior insula participation and overall cognitive ability in healthy controls and patients with schizophrenia (J. M. Sheffield et al., 2015). We were therefore surprised that we failed to replicate this finding in a larger sample of individuals with psychotic disorders.

Regarding the volume associations, it is possible that the regions calculated to determine gray matter volume were not well-matched with the corresponding Power nodes. We utilized the Destrieux atlas (Destrieux et al., 2010) to calculate gray matter volume of distinct brain regions, and identified regions that approximated the location of our Power hubs. The nodes from Power, however, are 6mm spheres, while the Destrieux regions vary in size and shape. While this mismatch does not explain all of our null results, it may contribute to our lack of robust findings between hub volume and hub participation coefficient, which we expected to be positively correlated. In addition, although it makes conceptual sense that larger gray matter volume would be related to higher global efficiency, there is little published data to support this hypothesis. Therefore, it is possible that the mechanisms contributing to stronger or weaker functional connectivity are relatively independent of gray matter volume.

4.5 Synaptic Pruning as a Putative Mechanism

While the presented results cannot directly address the question of how lower network efficiency arises in psychotic disorders, the synaptic pruning hypothesis provides an interesting framework in which to understand our findings. Pruning of synaptic connections amongst both

cortical and subcortical neurons is a process that occurs throughout development, and is necessary for the elimination of extraneous synaptic connections in order to streamline and optimize cognitive functions (A. H. Stephan, Barres, & Stevens, 2012). Following birth, synaptic density increases until approximately 2-3 years of age, at which point it declines sharply into early adolescence, due to a surge of synaptic pruning processes (Rakic, Bourgeois, & Goldman-Rakic, 1994). Abnormally aggressive synaptic pruning was hypothesized as a mechanism underlying schizophrenia by Feinberg in 1982, who aptly noted that schizophrenia's emergence in late adolescence coincides with the end of the developmental pruning process (Feinberg, 1982). He therefore theorized that the reorganization of synaptic connections that occur during development may be abnormal in individuals who ultimately develop schizophrenia. This hypothesis fits well with the neurodevelopmental model of schizophrenia, which suggests that schizophrenia is the result of complex gene and environment interactions that alter the individual's neurodevelopmental course, ultimately leading to cognitive, negative, and psychotic symptoms (Howes & Murray, 2014; Keshavan, Anderson, & Pettegrew, 1994).

The abnormal synaptic pruning hypothesis as a mechanism for schizophrenia was further bolstered by a study published in 2016, which identified a specific genetic variant associated with schizophrenia (Sekar et al., 2016). Using the genome from 65,000 individuals and 700 post-mortem brains, researchers revealed that higher expression of the gene C4A was associated with schizophrenia. Further, the more variants of C4A an individual had, the greater their risk of developing schizophrenia. In mice, C4 expression was associated with synaptic pruning, such that higher C4 expression was related to greater elimination of synaptic connections. Therefore, overexpression of C4 provides a genetic mechanism that may underlie abnormal synaptic pruning in individuals at risk for schizophrenia.

In terms of network efficiency, synaptic connectivity is believed to be a key mechanism that contributes to functional connectivity (Cossell et al., 2015; Zhan et al., 2014), providing an empirically-supported pathway from genetic vulnerability (overexpression of C4A) causing

inappropriate synaptic pruning of cortical and subcortical connections throughout development, coalescing into the brain of individuals with schizophrenia and its associated cognitive deficits. Reductions in global efficiency are potential byproducts of this neurodevelopmental process. The concept of global efficiency in functional connectivity data implies that nodes within a network can be organized in a way that facilitates optimal information processing (Bullmore & Sporns, 2012). Global efficiency specifically, and functional connectivity more broadly, therefore depend on the strength of communication between nodes, with stronger connectivity implying more robust information transfer. If synaptic connections are inappropriately pruned during development, leading to either the elimination of critical connections or the preservation of unnecessary connections, efficiency of that network could be reduced. In their writings about graph theory in the brain, Bullmore & Sporns (2012) theorize that the brain develops to optimize a trade-off between the energy costs of maintaining neural connections and the importance of efficiently transmitting information between brain regions to produce complex behavior. Globally efficient networks may therefore be ones that balance short- and long-distance connections. Elimination of necessary long-distance connections or over-abundance of weak short-distance connections could lead to less efficient networks.

Although speculative, our findings of reduced network efficiency in psychotic disorders may be consistent with the hypothesis of abnormal synaptic pruning throughout neurodevelopment in individuals with psychotic disorders. One important consideration, however, is why the CON and subcortical networks may be more specifically impacted by abnormal pruning throughout development, given that a global reduction in functional efficiency was not observed. One aspect of the CON that is of potential importance is the fact that the insula and anterior cingulate cortex contain von Economo neurons (VENs), which are rare in the brain and related to later evolutionary development (N. U. Dosenbach et al., 2008; Uddin, 2015). Given the large size and location of these neurons, they are hypothesized to relay outputs from the insula and anterior cingulate cortex to frontal and temporal regions, to facilitate rapid

information processing. One study of individuals with schizophrenia found that VEN density was significantly reduced in the right ACC in early onset patients, and that VEN density in the ACC correlated with age of onset and inversely correlated with duration of illness (Brune et al., 2010). These findings suggested that pruning of VENs may be an aspect of the neurodevelopmental process in schizophrenia. Computation modeling work has suggested that increased synaptic pruning may create a noisy system in the brains of individuals with schizophrenia, which influences the depth of attractor-basins, impairing memory and attention (Rolls & Deco, 2011). However this work has focused on modeling dopamine neurotransmission in the DLPFC, not regions specific to the CON or subcortical network.

Finally, research on developmental changes of functional networks has revealed that executive control networks, specifically the FPN and CON, undergo important changes during teenage years (N. U. F. Dosenbach, Petersen, & Schlaggar, 2013). In a study using multivariate pattern analysis of resting-state fMRI data, Dosenbach and colleagues assessed which functional connections predicted brain maturation (N. U. Dosenbach et al., 2010). They found that connections within the CON had the strongest weighting in the model, indicating that CON functional connectivity had the most predictive power for determining brain maturation. In addition, connectivity strength between the insula and anterior cingulate cortex has been found to be greater in adults, as compared to children, suggesting that increased within-network connectivity between these two core CON nodes may be a feature of healthy development (Uddin, Supekar, Ryali, & Menon, 2011). Together, these finding indicate that the CON undergoes significant changes in functional connectivity during later development, and therefore may be more susceptible to synaptic pruning abnormalities. Given the influence of environmental factors on psychosis risk (Varese et al., 2012), CON's development during adolescence may also increase its role in the manifestation of psychotic disorders. Unfortunately none of these findings address reduced efficiency in the subcortical network. Future work in mice with an overexpression of C4, or additional post-mortem studies in

schizophrenia, could better investigate the hypothesis that synaptic pruning affects VENs in the insula and anterior cingulate cortex and/or neurons in the thalamus and basal ganglia, which thereby reduces network efficiency, impairing cognitive ability.

4.6 Limitations

Several limitations are present in the current study. Although it is not clear how much resting-state data is needed to gain reliable network metrics, what is clear is that more data is better (Birn et al., 2013). In the current B-SNIP project, only five minutes of resting-state data was collected, which is in an intermediate range of the time needed for stable resting-state data estimates. Therefore, a limitation of the current study is that the global efficiency values calculated from five minutes of data may be less reliable than the estimates calculated from a longer scan. Despite this relatively small amount of data, we are encouraged that the finding of CON global efficiency positively predicting overall cognitive ability replicates findings from the Human Connectome Project dataset, which included almost two hours of resting state data, and the CNTRACS project, which included approximately one hour of pseudo-resting state data. Although we still hypothesized a relationship between FPN global efficiency and cognitive ability, our null results are also a replication of findings from the two-hour Human Connectome resting state scans, providing further support for the reliability of our findings. Another limitation of the current study is that nearly all subjects were taking antipsychotic medications, and the impact of these medications on our findings cannot be determined. However, generalized cognitive deficits in psychotic disorders are not believed to be secondary to antipsychotics (Keefe et al., 2007). In addition, inclusion of CPZ-equivalent dose as a covariate did not change the relationship between cognition and CON global efficiency, suggesting that antipsychotic dose was not driving our main findings. Finally, data on nicotine use was not available, and therefore we cannot know how nicotine use impacted our results. Rates of smoking are high in schizophrenia patients, and there is evidence that nicotine may increase functional connectivity

and possibly enhance cognitive functioning (Jacobsen et al., 2004) (Janes, Nickerson, Frederick Bde, & Kaufman, 2012). Because schizophrenia patients in our sample had reduced functional connectivity and reduced cognitive ability, nicotine use should have weakened our ability to detect group differences and relationships with cognition. We therefore believe that nicotine use is unlikely to have contributed to a false positive in our findings.

4.7 Conclusions

Distinct categories of psychiatric disorders have persisted for decades in the Diagnostic and Statistical Manual, aiding in the pursuit of treatment development and facilitating communication amongst mental health providers. Despite these benefits, it has become increasingly clear that diagnostic groups are far from independent and discrete. To address this, the National Institute of Mental Health's Research Domain Criteria encourages the exploration of how neural systems contribute to dimensions of behavioral phenotypes – information that can hopefully be applied to the treatment of a range of disorders. To this end, we hypothesized that reduced functional network integrity of the cingulo-opercular and fronto-parietal networks reflect a dimension of abnormality associated with the generalized cognitive deficit in multiple psychotic disorders. These hypotheses were based on work identifying BOLD activity in the cingulo-opercular and fronto-parietal networks as supporting higher-order cognitive processing across multiple cognitive domains. This study is the first to identify significant reductions in the global and local efficiency of the cingulo-opercular network across the psychosis spectrum, and is also the first to observe significantly reduced global efficiency of the subcortical network in psychotic disorders. Further, we demonstrated the behavioral importance of reduced network efficiency, by showing that individuals with lower global efficiency of the cingulo-opercular and subcortical networks have greater impairment in generalized cognitive ability. These relationships with cognition were independent of brain volume and functional connectivity strength, indicating that functional organization of the nodes within the cingulo-opercular network is less efficient in

psychotic disorders, leading to less robust integration of information processing to support cognitive functioning. Given that psychotic disorder patients with greater cognitive impairment demonstrate lower functional outcome, and that current psychiatric medications do not improve cognitive ability, these findings indicate that the cingulo-opercular and subcortical networks may be useful targets for future treatments. In particular, future studies in high-risk patient groups could assess whether cingulo-opercular and subcortical network efficiency is reduced prior to illness onset, which would help elucidate the developmental timing of abnormal network topology. Functional brain networks may be amenable to environmental interventions, as has been shown in research on mindfulness (Gard et al., 2014), exercise (Voss et al., 2010), and cognitive remediation (Ramsay, 2016), and therefore efficient organization of these networks could plausibly be promoted through appropriate intervention in the future.

5. References

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci, 9*, 357-381. doi:10.1146/annurev.ne.09.030186.002041

Andreasen, N. C. (1982). Negative symptoms in schizophrenia. Definition and reliability. *Arch Gen Psychiatry, 39*(7), 784-788.

Andreasen, N. C., Paradiso, S., & O'Leary, D. S. (1998). "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophr Bull, 24*(2), 203-218.

Andrews-Hanna, J. R., Snyder, A. Z., Vincent, J. L., Lustig, C., Head, D., Raichle, M. E., & Buckner, R. L. (2007). Disruption of large-scale brain systems in advanced aging. *Neuron, 56*(5), 924-935. doi:10.1016/j.neuron.2007.10.038

Anticevic, A., Haut, K., Murray, J. D., Repovs, G., Yang, G. J., Diehl, C., . . . Cannon, T. D. (2015). Association of Thalamic Dysconnectivity and Conversion to Psychosis in Youth and Young Adults at Elevated Clinical Risk. *JAMA Psychiatry, 72*(9), 882-891. doi:10.1001/jamapsychiatry.2015.0566

Anticevic, A., Savic, A., Repovs, G., Yang, G., McKay, D. R., Sprooten, E., . . . Glahn, D. C. (2014). Ventral Anterior Cingulate Connectivity Distinguished Nonpsychotic Bipolar Illness from Psychotic Bipolar Disorder and Schizophrenia. *Schizophr Bull*. doi:10.1093/schbul/sbu051

Association, A. P. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5)*: American Psychiatric Pub.

Baker, J. T., Holmes, A. J., Masters, G. A., Yeo, B. T., Krienen, F., Buckner, R. L., & Ongur, D. (2014). Disruption of cortical association networks in schizophrenia and psychotic bipolar disorder. *JAMA Psychiatry, 71*(2), 109-118. doi:10.1001/jamapsychiatry.2013.3469

Barch, D. M., & Sheffield, J. M. (2014). Cognitive impairments in psychotic disorders: common mechanisms and measurement. *World Psychiatry, 13*(3), 224-232. doi:10.1002/wps.20145

Bassett, D. S., Bullmore, E., Verchinski, B. A., Mattay, V. S., Weinberger, D. R., & Meyer-Lindenberg, A. (2008). Hierarchical organization of human cortical networks in health and schizophrenia. *J Neurosci, 28*(37), 9239-9248. doi:10.1523/JNEUROSCI.1929-08.2008

Bassett, D. S., Nelson, B. G., Mueller, B. A., Camchong, J., & Lim, K. O. (2012). Altered resting state complexity in schizophrenia. *Neuroimage, 59*(3), 2196-2207. doi:10.1016/j.neuroimage.2011.10.002

Bearden, C. E., Glahn, D. C., Monkul, E. S., Barrett, J., Najt, P., Villarreal, V., & Soares, J. C. (2006). Patterns of memory impairment in bipolar disorder and unipolar major depression. *Psychiatry Res, 142*(2-3), 139-150. doi:10.1016/j.psychres.2005.08.010

Birn, R. M., Molloy, E. K., Patriat, R., Parker, T., Meier, T. B., Kirk, G. R., . . . Prabhakaran, V. (2013). The effect of scan length on the reliability of resting-state fMRI connectivity estimates. *Neuroimage, 83*, 550-558. doi:10.1016/j.neuroimage.2013.05.099

Bora, E. (2015). Developmental trajectory of cognitive impairment in bipolar disorder: comparison with schizophrenia. *Eur Neuropsychopharmacol, 25*(2), 158-168. doi:10.1016/j.euroneuro.2014.09.007

Bora, E., & Murray, R. M. (2014). Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: do the cognitive deficits progress over, or

after, the onset of psychosis? *Schizophr Bull, 40*(4), 744-755. doi:10.1093/schbul/sbt085
Bora, E., & Pantelis, C. (2015). Meta-analysis of Cognitive Impairment in First-Episode Bipolar Disorder: Comparison With First-Episode Schizophrenia and Healthy Controls. *Schizophr Bull, 41*(5), 1095-1104. doi:10.1093/schbul/sbu198
Bora, E., Yucel, M., & Pantelis, C. (2009). Cognitive functioning in schizophrenia, schizoaffective disorder and affective psychoses: meta-analytic study. *Br J Psychiatry, 195*(6), 475-482. doi:10.1192/bjp.bp.108.055731
Bowie, C. R., Leung, W. W., Reichenberg, A., McClure, M. M., Patterson, T. L., Heaton, R. K., & Harvey, P. D. (2008). Predicting schizophrenia patients' real-world behavior with specific neuropsychological and functional capacity measures. *Biol Psychiatry, 63*(5), 505-511. doi:10.1016/j.biopsych.2007.05.022
Bowie, C. R., Reichenberg, A., Patterson, T. L., Heaton, R. K., & Harvey, P. D. (2006). Determinants of real-world functional performance in schizophrenia subjects: correlations with cognition, functional capacity, and symptoms. *Am J Psychiatry, 163*(3), 418-425. doi:10.1176/appi.ajp.163.3.418
Brune, M., Schobel, A., Karau, R., Benali, A., Faustmann, P. M., Juckel, G., & Petrasch-Parwez, E. (2010). Von Economo neuron density in the anterior cingulate cortex is reduced in early onset schizophrenia. *Acta Neuropathol, 119*(6), 771-778. doi:10.1007/s00401-010-0673-2
Bullmore, E., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci, 10*(3), 186-198. doi:10.1038/nrn2575
Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. *Nat Rev Neurosci, 13*(5), 336-349. doi:10.1038/nrn3214
Burton, H., Sinclair, R. J., Wingert, J. R., & Dierker, D. L. (2008). Multiple parietal operculum subdivisions in humans: tactile activation maps. *Somatosens Mot Res, 25*(3), 149-162. doi:10.1080/08990220802249275
Cavanagh, J. T., Van Beck, M., Muir, W., & Blackwood, D. H. (2002). Case-control study of neurocognitive function in euthymic patients with bipolar disorder: an association with mania. *Br J Psychiatry, 180*, 320-326.
Clark, L., Iversen, S. D., & Goodwin, G. M. (2002). Sustained attention deficit in bipolar disorder. *Br J Psychiatry, 180*, 313-319.
Cocchi, L., Zalesky, A., Fornito, A., & Mattingley, J. B. (2013). Dynamic cooperation and competition between brain systems during cognitive control. *Trends Cogn Sci, 17*(10), 493-501. doi:10.1016/j.tics.2013.08.006
Cole, M. W., Bassett, D. S., Power, J. D., Braver, T. S., & Petersen, S. E. (2014). Intrinsic and task-evoked network architectures of the human brain. *Neuron*.
Cole, M. W., Laurent, P., & Stocco, A. (2013). Rapid instructed task learning: a new window into the human brain's unique capacity for flexible cognitive control. *Cogn Affect Behav Neurosci, 13*(1), 1-22. doi:10.3758/s13415-012-0125-7
Cole, M. W., Repovs, G., & Anticevic, A. (2014). The Frontoparietal Control System: A Central Role in Mental Health. *Neuroscientist*. doi:10.1177/1073858414525995
Cole, M. W., Reynolds, J. R., Power, J. D., Repovs, G., Anticevic, A., & Braver, T. S. (2013). Multi-task connectivity reveals flexible hubs for adaptive task control. *Nat Neurosci, 16*(9), 1348-1355. doi:10.1038/nn.3470

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The reorienting system of the human brain: from environment to theory of mind. *Neuron, 58*(3), 306-324. doi:10.1016/j.neuron.2008.04.017

Cossell, L., Iacaruso, M. F., Muir, D. R., Houlton, R., Sader, E. N., Ko, H., . . . Mrsic-Flogel, T. D. (2015). Functional organization of excitatory synaptic strength in primary visual cortex. *Nature, 518*(7539), 399-403. doi:10.1038/nature14182

Coste, C. P., & Kleinschmidt, A. (2016). Cingulo-opercular network activity maintains alertness. *Neuroimage, 128*, 264-272. doi:10.1016/j.neuroimage.2016.01.026

Daban, C., Martinez-Aran, A., Torrent, C., Tabares-Seisdedos, R., Balanza-Martinez, V., Salazar-Fraile, J., . . . Vieta, E. (2006). Specificity of cognitive deficits in bipolar disorder versus schizophrenia. A systematic review. *Psychother Psychosom, 75*(2), 72-84. doi:10.1159/000090891

Destrieux, C., Fischl, B., Dale, A., & Halgren, E. (2010). Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *Neuroimage, 53*(1), 1-15. doi:10.1016/j.neuroimage.2010.06.010

Dickinson, D., Iannone, V. N., Wilk, C. M., & Gold, J. M. (2004). General and specific cognitive deficits in schizophrenia. *Biol Psychiatry, 55*(8), 826-833. doi:10.1016/j.biopsych.2003.12.010

Dickinson, D., Ragland, J. D., Gold, J. M., & Gur, R. C. (2008). General and specific cognitive deficits in schizophrenia: Goliath defeats David? *Biol Psychiatry, 64*(9), 823-827. doi:10.1016/j.biopsych.2008.04.005

Dosenbach, N. U., Fair, D. A., Cohen, A. L., Schlaggar, B. L., & Petersen, S. E. (2008). A dual-networks architecture of top-down control. *Trends Cogn Sci, 12*(3), 99-105. doi:10.1016/j.tics.2008.01.001

Dosenbach, N. U., Fair, D. A., Miezin, F. M., Cohen, A. L., Wenger, K. K., Dosenbach, R. A., . . . Petersen, S. E. (2007). Distinct brain networks for adaptive and stable task control in humans. *Proc Natl Acad Sci U S A, 104*(26), 11073-11078. doi:10.1073/pnas.0704320104

Dosenbach, N. U., Nardos, B., Cohen, A. L., Fair, D. A., Power, J. D., Church, J. A., . . . Schlaggar, B. L. (2010). Prediction of individual brain maturity using fMRI. *Science, 329*(5997), 1358-1361. doi:10.1126/science.1194144

Dosenbach, N. U., Visscher, K. M., Palmer, E. D., Miezin, F. M., Wenger, K. K., Kang, H. C., . . . Petersen, S. E. (2006). A core system for the implementation of task sets. *Neuron, 50*(5), 799-812. doi:10.1016/j.neuron.2006.04.031

Dosenbach, N. U. F., Petersen, S. E., & Schlaggar, B. L. (2013). The Teenage Brain: Functional Connectivity. *Current Directions in Psychological Science, 22*(2), 101-107. doi:10.1177/0963721412474297

Feinberg, I. (1982). Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J Psychiatr Res, 17*(4), 319-334.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1995). *Structured Clinical Intervew for DSM-IV Axis I Disorders- Non-Patient Edition (SCID-I/NP, Version 2.0)*. New York.

Fischl, B. (2012). FreeSurfer. *Neuroimage, 62*(2), 774-781. doi:10.1016/j.neuroimage.2012.01.021

Fornito, A., Zalesky, A., Pantelis, C., & Bullmore, E. T. (2012). Schizophrenia, neuroimaging and connectomics. *Neuroimage, 62*(4), 2296-2314. doi:10.1016/j.neuroimage.2011.12.090

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A, 102*(27), 9673-9678. doi:10.1073/pnas.0504136102

Gard, T., Taquet, M., Dixit, R., Holzel, B. K., de Montjoye, Y. A., Brach, N., . . . Lazar, S. W. (2014). Fluid intelligence and brain functional organization in aging yoga and meditation practitioners. *Front Aging Neurosci, 6*, 76. doi:10.3389/fnagi.2014.00076

Gold, J. M., & Dickinson, D. (2012). "Generalized Cognitive Deficit" in Schizophrenia: Overused or Underappreciated? *Schizophr Bull*. doi:10.1093/schbul/sbs143

Gold, J. M., Hahn, B., Strauss, G. P., & Waltz, J. A. (2009). Turning it upside down: areas of preserved cognitive function in schizophrenia. *Neuropsychol Rev, 19*(3), 294-311. doi:10.1007/s11065-009-9098-x

Goodkind, M., Eickhoff, S. B., Oathes, D. J., Jiang, Y., Chang, A., Jones-Hagata, L. B., . . . Etkin, A. (2015). Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry, 72*(4), 305-315. doi:10.1001/jamapsychiatry.2014.2206

Goodwin, G. M., Martinez-Aran, A., Glahn, D. C., & Vieta, E. (2008). Cognitive impairment in bipolar disorder: neurodevelopment or neurodegeneration? An ECNP expert meeting report. *Eur Neuropsychopharmacol, 18*(11), 787-793. doi:10.1016/j.euroneuro.2008.07.005

Green, M. F. (2006). Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *J Clin Psychiatry, 67*(10), e12.

Green, M. F., Horan, W. P., & Sugar, C. A. (2013). Has the generalized deficit become the generalized criticism? *Schizophr Bull, 39*(2), 257-262. doi:10.1093/schbul/sbs146

Green, M. F., Kern, R. S., & Heaton, R. K. (2004). Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophr Res, 72*(1), 41-51. doi:10.1016/j.schres.2004.09.009

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A, 100*(1), 253-258. doi:10.1073/pnas.0135058100

Guimera, R., & Amaral, L. A. (2005). Cartography of complex networks: modules and universal roles. *J Stat Mech, 2005*(P02001), nihpa35573. doi:10.1088/1742-5468/2005/02/P02001

Gur, R. E., Cowell, P. E., Latshaw, A., Turetsky, B. I., Grossman, R. I., Arnold, S. E., . . . Gur, R. C. (2000). Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. *Arch Gen Psychiatry, 57*(8), 761-768.

Heckers, S. (2009). Is schizoaffective disorder a useful diagnosis? *Curr Psychiatry Rep, 11*(4), 332-337.

Heinrichs, R. W., Ammari, N., McDermid Vaz, S., & Miles, A. A. (2008). Are schizophrenia and schizoaffective disorder neuropsychologically distinguishable? *Schizophr Res, 99*(1-3), 149-154. doi:10.1016/j.schres.2007.10.007

Heinrichs, R. W., & Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology, 12*(3), 426-445.

Hill, S. K., Reilly, J. L., Keefe, R. S., Gold, J. M., Bishop, J. R., Gershon, E. S., . . . Sweeney, J. A. (2013). Neuropsychological impairments in schizophrenia and psychotic bipolar disorder: findings from the Bipolar-Schizophrenia Network on Intermediate

Phenotypes (B-SNIP) study. *Am J Psychiatry, 170*(11), 1275-1284. doi:10.1176/appi.ajp.2013.12101298
Hochberger, W. C., Hill, S. K., Nelson, C. L., Reilly, J. L., Keefe, R. S., Pearlson, G. D., . . . Sweeney, J. A. (2016). Unitary construct of generalized cognitive ability underlying BACS performance across psychotic disorders and in their first-degree relatives. *Schizophr Res, 170*(1), 156-161. doi:10.1016/j.schres.2015.11.022
Hofer, A., Baumgartner, S., Bodner, T., Edlinger, M., Hummer, M., Kemmler, G., . . . Fleischhacker, W. W. (2005). Patient outcomes in schizophrenia II: the impact of cognition. *Eur Psychiatry, 20*(5-6), 395-402. doi:10.1016/j.eurpsy.2005.02.006
Hofer, A., Bodner, T., Kaufmann, A., Kemmler, G., Mattarei, U., Pfaffenberger, N. M., . . . Fleischhacker, W. W. (2011). Symptomatic remission and neurocognitive functioning in patients with schizophrenia. *Psychol Med, 41*(10), 2131-2139. doi:10.1017/S0033291711000353
Horner, M. D., & Hamner, M. B. (2002). Neurocognitive functioning in posttraumatic stress disorder. *Neuropsychol Rev, 12*(1), 15-30.
Howes, O. D., & Murray, R. M. (2014). Schizophrenia: an integrated sociodevelopmental-cognitive model. *Lancet, 383*(9929), 1677-1687. doi:10.1016/S0140-6736(13)62036-X
Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., . . . Wang, P. (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry, 167*(7), 748-751. doi:10.1176/appi.ajp.2010.09091379
Jacobsen, L. K., D'Souza, D. C., Mencl, W. E., Pugh, K. R., Skudlarski, P., & Krystal, J. H. (2004). Nicotine effects on brain function and functional connectivity in schizophrenia. *Biol Psychiatry, 55*(8), 850-858. doi:10.1016/j.biopsych.2003.12.023
Janes, A. C., Nickerson, L. D., Frederick Bde, B., & Kaufman, M. J. (2012). Prefrontal and limbic resting state brain network functional connectivity differs between nicotine-dependent smokers and non-smoking controls. *Drug Alcohol Depend, 125*(3), 252-259. doi:10.1016/j.drugalcdep.2012.02.020
Karbasforoushan, H., & Woodward, N. D. (2012). Resting-state networks in schizophrenia. *Curr Top Med Chem, 12*(21), 2404-2414.
Kay, S. R., Opler, L. A., & Lindenmayer, J. P. (1989). The Positive and Negative Syndrome Scale (PANSS): rationale and standardisation. *Br J Psychiatry Suppl*(7), 59-67.
Keefe, R. S., Bilder, R. M., Davis, S. M., Harvey, P. D., Palmer, B. W., Gold, J. M., . . . Lieberman, J. A. (2007). Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Arch Gen Psychiatry, 64*(6), 633-647. doi:10.1001/archpsyc.64.6.633
Keefe, R. S., Bilder, R. M., Harvey, P. D., Davis, S. M., Palmer, B. W., Gold, J. M., . . . Lieberman, J. A. (2006). Baseline neurocognitive deficits in the CATIE schizophrenia trial. *Neuropsychopharmacology, 31*(9), 2033-2046. doi:10.1038/sj.npp.1301072
Keefe, R. S., Goldberg, T. E., Harvey, P. D., Gold, J. M., Poe, M. P., & Coughenour, L. (2004). The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophr Res, 68*(2-3), 283-297. doi:10.1016/j.schres.2003.09.011
Keefe, R. S., Harvey, P. D., Goldberg, T. E., Gold, J. M., Walker, T. M., Kennel, C., & Hawkins, K. (2008). Norms and standardization of the Brief Assessment of Cognition in

Schizophrenia (BACS). *Schizophr Res, 102*(1-3), 108-115. doi:10.1016/j.schres.2008.03.024
Keshavan, M. S., Anderson, S., & Pettegrew, J. W. (1994). Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? The Feinberg hypothesis revisited. *J Psychiatr Res, 28*(3), 239-265.
Kochunov, P., Glahn, D. C., Rowland, L. M., Olvera, R. L., Winkler, A., Yang, Y. H., . . . Hong, L. E. (2013). Testing the hypothesis of accelerated cerebral white matter aging in schizophrenia and major depression. *Biol Psychiatry, 73*(5), 482-491. doi:10.1016/j.biopsych.2012.10.002
Kumar, C. T., & Frangou, S. (2010). Clinical implications of cognitive function in bipolar disorder. *Ther Adv Chronic Dis, 1*(3), 85-93. doi:10.1177/2040622310374678
Lee, R. S., Hermens, D. F., Scott, J., Redoblado-Hodge, M. A., Naismith, S. L., Lagopoulos, J., . . . Hickie, I. B. (2014). A meta-analysis of neuropsychological functioning in first-episode bipolar disorders. *J Psychiatr Res, 57*, 1-11. doi:10.1016/j.jpsychires.2014.06.019
Light, G., Greenwood, T. A., Swerdlow, N. R., Calkins, M. E., Freedman, R., Green, M. F., . . . Braff, D. L. (2014). Comparison of the heritability of schizophrenia and endophenotypes in the COGS-1 family study. *Schizophr Bull, 40*(6), 1404-1411. doi:10.1093/schbul/sbu064
Light, G. A., Hsu, J. L., Hsieh, M. H., Meyer-Gomes, K., Sprock, J., Swerdlow, N. R., & Braff, D. L. (2006). Gamma band oscillations reveal neural network cortical coherence dysfunction in schizophrenia patients. *Biol Psychiatry, 60*(11), 1231-1240. doi:10.1016/j.biopsych.2006.03.055
Lowe, M. J., Mock, B. J., & Sorenson, J. A. (1998). Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. *Neuroimage, 7*(2), 119-132. doi:10.1006/nimg.1997.0315
Lynall, M. E., Bassett, D. S., Kerwin, R., McKenna, P. J., Kitzbichler, M., Muller, U., & Bullmore, E. (2010). Functional connectivity and brain networks in schizophrenia. *J Neurosci, 30*(28), 9477-9487. doi:10.1523/JNEUROSCI.0333-10.2010
Mamah, D., Barch, D. M., & Repovs, G. (2013). Resting state functional connectivity of five neural networks in bipolar disorder and schizophrenia. *J Affect Disord, 150*(2), 601-609. doi:10.1016/j.jad.2013.01.051
Manoliu, A., Riedl, V., Zherdin, A., Muhlau, M., Schwerthoffer, D., Scherr, M., . . . Sorg, C. (2014). Aberrant dependence of default mode/central executive network interactions on anterior insular salience network activity in schizophrenia. *Schizophr Bull, 40*(2), 428-437. doi:10.1093/schbul/sbt037
Martinez-Aran, A., Vieta, E., Colom, F., Torrent, C., Sanchez-Moreno, J., Reinares, M., . . . Salamero, M. (2004). Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. *Bipolar Disord, 6*(3), 224-232. doi:10.1111/j.1399-5618.2004.00111.x
Meda, S. A., Ruano, G., Windemuth, A., O'Neil, K., Berwise, C., Dunn, S. M., . . . Pearlson, G. D. (2014). Multivariate analysis reveals genetic associations of the resting default mode network in psychotic bipolar disorder and schizophrenia. *Proc Natl Acad Sci U S A, 111*(19), E2066-2075. doi:10.1073/pnas.1313093111
Meda, S. A., Wang, Z., Ivleva, E. I., Poudyal, G., Keshavan, M. S., Tamminga, C. A., . . . Pearlson, G. D. (2015). Frequency-Specific Neural Signatures of Spontaneous Low-Frequency

Resting State Fluctuations in Psychosis: Evidence From Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) Consortium. *Schizophr Bull, 41*(6), 1336-1348. doi:10.1093/schbul/sbv064

Medaglia, J. D., Lynall, M. E., & Bassett, D. S. (2015). Cognitive network neuroscience. *J Cogn Neurosci, 27*(8), 1471-1491. doi:10.1162/jocn_a_00810

Medalia, A., & Saperstein, A. M. (2013). Does cognitive remediation for schizophrenia improve functional outcomes? *Curr Opin Psychiatry, 26*(2), 151-157. doi:10.1097/YCO.0b013e32835dcbd4

Meng, X. L., Rosenthal, R., & Rubin, D. B. (1992). Comparing Correlated Correlation-Coefficients. *Psychological Bulletin, 111*(1), 172-175. doi:Doi 10.1037/0033-2909.111.1.172

Menon, V. (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci, 15*(10), 483-506. doi:10.1016/j.tics.2011.08.003

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct, 214*(5-6), 655-667. doi:10.1007/s00429-010-0262-0

Millier, A., Schmidt, U., Angermeyer, M. C., Chauhan, D., Murthy, V., Toumi, M., & Cadi-Soussi, N. (2014). Humanistic burden in schizophrenia: a literature review. *J Psychiatr Res, 54*, 85-93. doi:10.1016/j.jpsychires.2014.03.021

Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *Br J Psychiatry, 134*, 382-389.

Moran, E. K., Culbreth, A. J., & Barch, D. M. (2017). Ecological momentary assessment of negative symptoms in schizophrenia: Relationships to effort-based decision making and reinforcement learning. *J Abnorm Psychol, 126*(1), 96-105. doi:10.1037/abn0000240

Moran, L. V., Tagamets, M. A., Sampath, H., O'Donnell, A., Stein, E. A., Kochunov, P., & Hong, L. E. (2013). Disruption of anterior insula modulation of large-scale brain networks in schizophrenia. *Biol Psychiatry, 74*(6), 467-474. doi:10.1016/j.biopsych.2013.02.029

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, 37*(1), 17-27. doi:10.1503/jpn.100176

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*(4), 814-828. doi:10.1016/j.neuron.2013.06.027

Parnaudeau, S., O'Neill, P. K., Bolkan, S. S., Ward, R. D., Abbas, A. I., Roth, B. L., . . . Kellendonk, C. (2013). Inhibition of mediodorsal thalamus disrupts thalamofrontal connectivity and cognition. *Neuron, 77*(6), 1151-1162. doi:10.1016/j.neuron.2013.01.038

Petersen, S. E., & Posner, M. I. (2012). The attention system of the human brain: 20 years after. *Annu Rev Neurosci, 35*, 73-89. doi:10.1146/annurev-neuro-062111-150525

Posner, M. I. (2008). Measuring alertness. *Ann N Y Acad Sci, 1129*, 193-199. doi:10.1196/annals.1417.011

Power, J. D., Cohen, A. L., Nelson, S. M., Wig, G. S., Barnes, K. A., Church, J. A., . . . Petersen, S. E. (2011). Functional network organization of the human brain. *Neuron, 72*(4), 665-678. doi:10.1016/j.neuron.2011.09.006

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. doi:10.1016/j.neuroimage.2013.08.048

Power, J. D., Schlaggar, B. L., Lessov-Schlaggar, C. N., & Petersen, S. E. (2013). Evidence for hubs in human functional brain networks. *Neuron, 79*(4), 798-813. doi:10.1016/j.neuron.2013.07.035

Preacher, K. J., & Hayes, A. F. (2004). SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behav Res Methods Instrum Comput, 36*(4), 717-731.

Rakic, P., Bourgeois, J. P., & Goldman-Rakic, P. S. (1994). Synaptic development of the cerebral cortex: implications for learning, memory, and mental illness. *Prog Brain Res, 102*, 227-243. doi:10.1016/S0079-6123(08)60543-9

Ramsay, I. S., Nienow, T.M., MacDonald III, A.W. (2016). Increases in intrinsic thalamocortical connectivity and overall cognition following cognitive remediation in chronic schizophrenia. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, In Press*.

Reilly, J. L., & Sweeney, J. A. (2014). Generalized and specific neurocognitive deficits in psychotic disorders: utility for evaluating pharmacological treatment effects and as intermediate phenotypes for gene discovery. *Schizophr Bull, 40*(3), 516-522. doi:10.1093/schbul/sbu013

Repovs, G., Csernansky, J. G., & Barch, D. M. (2011). Brain network connectivity in individuals with schizophrenia and their siblings. *Biol Psychiatry, 69*(10), 967-973. doi:10.1016/j.biopsych.2010.11.009

Robinson, L. J., Thompson, J. M., Gallagher, P., Goswami, U., Young, A. H., Ferrier, I. N., & Moore, P. B. (2006). A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J Affect Disord, 93*(1-3), 105-115. doi:10.1016/j.jad.2006.02.016

Rolls, E. T., & Deco, G. (2011). A computational neuroscience approach to schizophrenia and its onset. *Neurosci Biobehav Rev, 35*(8), 1644-1653. doi:10.1016/j.neubiorev.2010.09.001

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: uses and interpretations. *Neuroimage, 52*(3), 1059-1069. doi:10.1016/j.neuroimage.2009.10.003

Ruge, H., & Wolfensteller, U. (2010). Rapid formation of pragmatic rule representations in the human brain during instruction-based learning. *Cereb Cortex, 20*(7), 1656-1667. doi:10.1093/cercor/bhp228

Sadaghiani, S., & D'Esposito, M. (2015). Functional Characterization of the Cingulo-Opercular Network in the Maintenance of Tonic Alertness. *Cereb Cortex, 25*(9), 2763-2773. doi:10.1093/cercor/bhu072

Sadaghiani, S., Hesselmann, G., & Kleinschmidt, A. (2009). Distributed and antagonistic contributions of ongoing activity fluctuations to auditory stimulus detection. *J Neurosci, 29*(42), 13410-13417. doi:10.1523/JNEUROSCI.2592-09.2009

Sadaghiani, S., Scheeringa, R., Lehongre, K., Morillon, B., Giraud, A. L., & Kleinschmidt, A. (2010). Intrinsic connectivity networks, alpha oscillations, and tonic alertness: a simultaneous electroencephalography/functional magnetic resonance imaging study. *J Neurosci, 30*(30), 10243-10250. doi:10.1523/JNEUROSCI.1004-10.2010

Sarter, M., Givens, B., & Bruno, J. P. (2001). The cognitive neuroscience of sustained attention: where top-down meets bottom-up. *Brain Res Brain Res Rev, 35*(2), 146-160.
Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., . . . Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci, 27*(9), 2349-2356. doi:10.1523/JNEUROSCI.5587-06.2007
Sekar, A., Bialas, A. R., de Rivera, H., Davis, A., Hammond, T. R., Kamitaki, N., . . . McCarroll, S. A. (2016). Schizophrenia risk from complex variation of complement component 4. *Nature, 530*(7589), 177-183. doi:10.1038/nature16549
Sheffield, J. M., & Barch, D. M. (2016). Cognition and resting-state functional connectivity in schizophrenia. *Neurosci Biobehav Rev, 61*, 108-120. doi:10.1016/j.neubiorev.2015.12.007
Sheffield, J. M., Gold, J. M., Strauss, M. E., Carter, C. S., MacDonald, A. W., 3rd, Ragland, J. D., . . . Barch, D. M. (2014). Common and specific cognitive deficits in schizophrenia: relationships to function. *Cogn Affect Behav Neurosci, 14*(1), 161-174. doi:10.3758/s13415-013-0211-5
Sheffield, J. M., Kandala, S., Burgess, G. C., Harms, M. P., & Barch, D. M. (2016). Cingulo-opercular network efficiency mediates the association between psychotic-like experiences and cognitive ability in the general population. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, In Press*.
Sheffield, J. M., Repovs, G., Harms, M. P., Carter, C. S., Gold, J. M., MacDonald, A. W., 3rd, . . . Barch, D. M. (2016). Evidence for Accelerated Decline of Functional Brain Network Efficiency in Schizophrenia. *Schizophr Bull, 42*(3), 753-761. doi:10.1093/schbul/sbv148
Sheffield, J. M., Repovs, G., Harms, M. P., Carter, C. S., Gold, J. M., MacDonald Iii, A. W., . . . Barch, D. M. (2015). Fronto-parietal and cingulo-opercular network integrity and cognition in health and schizophrenia. *Neuropsychologia, 73*, 82-93. doi:10.1016/j.neuropsychologia.2015.05.006
Sheffield, J. M., Williams, L. E., Cohen, N., & Heckers, S. (2012). Relational memory in psychotic bipolar disorder. *Bipolar Disord, 14*(5), 537-546. doi:10.1111/j.1399-5618.2012.01036.x
Sitskoorn, M. M., Aleman, A., Ebisch, S. J., Appels, M. C., & Kahn, R. S. (2004). Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. *Schizophr Res, 71*(2-3), 285-295. doi:10.1016/j.schres.2004.03.007
Smith, S. M., Vidaurre, D., Beckmann, C. F., Glasser, M. F., Jenkinson, M., Miller, K. L., . . . Van Essen, D. C. (2013). Functional connectomics from resting-state fMRI. *Trends Cogn Sci, 17*(12), 666-682. doi:10.1016/j.tics.2013.09.016
Snitz, B. E., Macdonald, A. W., 3rd, & Carter, C. S. (2006). Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. *Schizophr Bull, 32*(1), 179-194. doi:10.1093/schbul/sbi048
Stephan, A. H., Barres, B. A., & Stevens, B. (2012). The complement system: an unexpected role in synaptic pruning during development and disease. *Annu Rev Neurosci, 35*, 369-389. doi:10.1146/annurev-neuro-061010-113810

Stephan, K. E., Friston, K. J., & Frith, C. D. (2009). Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. *Schizophr Bull, 35*(3), 509-527. doi:10.1093/schbul/sbn176

Sullivan, E. V., Shear, P. K., Lim, K. O., Zipursky, R. B., & Pfefferbaum, A. (1996). Cognitive and motor impairments are related to gray matter volume deficits in schizophrenia. *Biol Psychiatry, 39*(4), 234-240. doi:10.1016/0006-3223(95)00135-2

Tamminga, C. A., Ivleva, E. I., Keshavan, M. S., Pearlson, G. D., Clementz, B. A., Witte, B., . . . Sweeney, J. A. (2013). Clinical phenotypes of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). *Am J Psychiatry, 170*(11), 1263-1274. doi:10.1176/appi.ajp.2013.12101339

Tiihonen, J., Haukka, J., Henriksson, M., Cannon, M., Kieseppa, T., Laaksonen, I., . . . Lonnqvist, J. (2005). Premorbid intellectual functioning in bipolar disorder and schizophrenia: results from a cohort study of male conscripts. *Am J Psychiatry, 162*(10), 1904-1910. doi:10.1176/appi.ajp.162.10.1904

Torres, I. J., Boudreau, V. G., & Yatham, L. N. (2007). Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. *Acta Psychiatr Scand Suppl*(434), 17-26. doi:10.1111/j.1600-0447.2007.01055.x

Tu, P. C., Hsieh, J. C., Li, C. T., Bai, Y. M., & Su, T. P. (2012). Cortico-striatal disconnection within the cingulo-opercular network in schizophrenia revealed by intrinsic functional connectivity analysis: a resting fMRI study. *Neuroimage, 59*(1), 238-247. doi:10.1016/j.neuroimage.2011.07.086

Uddin, L. Q. (2015). Salience processing and insular cortical function and dysfunction. *Nat Rev Neurosci, 16*(1), 55-61. doi:10.1038/nrn3857

Uddin, L. Q., Supekar, K. S., Ryali, S., & Menon, V. (2011). Dynamic reconfiguration of structural and functional connectivity across core neurocognitive brain networks with development. *J Neurosci, 31*(50), 18578-18589. doi:10.1523/JNEUROSCI.4465-11.2011

van den Heuvel, M. P., Mandl, R. C., Stam, C. J., Kahn, R. S., & Hulshoff Pol, H. E. (2010). Aberrant frontal and temporal complex network structure in schizophrenia: a graph theoretical analysis. *J Neurosci, 30*(47), 15915-15926. doi:10.1523/JNEUROSCI.2874-10.2010

van den Heuvel, M. P., Stam, C. J., Kahn, R. S., & Hulshoff Pol, H. E. (2009). Efficiency of functional brain networks and intellectual performance. *J Neurosci, 29*(23), 7619-7624. doi:10.1523/JNEUROSCI.1443-09.2009

Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., . . . Bentall, R. P. (2012). Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophr Bull, 38*(4), 661-671. doi:10.1093/schbul/sbs050

Voss, M. W., Prakash, R. S., Erickson, K. I., Basak, C., Chaddock, L., Kim, J. S., . . . Kramer, A. F. (2010). Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Front Aging Neurosci, 2*. doi:10.3389/fnagi.2010.00032

Wang, L., Li, Y., Metzak, P., He, Y., & Woodward, T. S. (2010). Age-related changes in topological patterns of large-scale brain functional networks during memory encoding and recognition. *Neuroimage, 50*(3), 862-872. doi:10.1016/j.neuroimage.2010.01.044

Warren, D. E., Power, J. D., Bruss, J., Denburg, N. L., Waldron, E. J., Sun, H., . . . Tranel, D. (2014). Network measures predict neuropsychological outcome after brain injury. *Proc Natl Acad Sci U S A, 111*(39), 14247-14252. doi:10.1073/pnas.1322173111

White, T. P., Joseph, V., Francis, S. T., & Liddle, P. F. (2010). Aberrant salience network (bilateral insula and anterior cingulate cortex) connectivity during information processing in schizophrenia. *Schizophr Res, 123*(2-3), 105-115. doi:10.1016/j.schres.2010.07.020

Willcutt, E. G., Doyle, A. E., Nigg, J. T., Faraone, S. V., & Pennington, B. F. (2005). Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. *Biol Psychiatry, 57*(11), 1336-1346. doi:10.1016/j.biopsych.2005.02.006

Wolf, R. C., Hose, A., Frasch, K., Walter, H., & Vasic, N. (2008). Volumetric abnormalities associated with cognitive deficits in patients with schizophrenia. *Eur Psychiatry, 23*(8), 541-548. doi:10.1016/j.eurpsy.2008.02.002

Woodward, N. D., Karbasforoushan, H., & Heckers, S. (2012). Thalamocortical dysconnectivity in schizophrenia. *Am J Psychiatry, 169*(10), 1092-1099. doi:10.1176/appi.ajp.2012.12010056

Woodward, N. D., Rogers, B., & Heckers, S. (2011). Functional resting-state networks are differentially affected in schizophrenia. *Schizophr Res, 130*(1-3), 86-93. doi:10.1016/j.schres.2011.03.010

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry, 133*, 429-435.

Zhan, Y., Paolicelli, R. C., Sforazzini, F., Weinhard, L., Bolasco, G., Pagani, F., . . . Gross, C. T. (2014). Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. *Nat Neurosci, 17*(3), 400-406. doi:10.1038/nn.3641

Zhang, D., Snyder, A. Z., Fox, M. D., Sansbury, M. W., Shimony, J. S., & Raichle, M. E. (2008). Intrinsic functional relations between human cerebral cortex and thalamus. *J Neurophysiol, 100*(4), 1740-1748. doi:10.1152/jn.90463.2008

Zimmermann, P. a. F., B. (2002). Testbatterie zur Aufmerksamkeitspruefung (TAP). *Psytest, Verson 1.7*.