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Fronto-parietal and cingulo-opercular network integrity and cognition in health and schizophrenia

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ABSTRACT

Growing evidence suggests that coordinated activity within specific functional brain networks supports cognitive ability, and that abnormalities in brain connectivity may underlie cognitive deficits observed in neuropsychiatric diseases, such as schizophrenia. Two functional networks, the fronto-parietal network (FPN) and cingulo-opercular network (CON), are hypothesized to support top-down control of executive functioning, and have therefore emerged as potential drivers of cognitive impairment in disease-states. Graph theoretic analyses of functional connectivity data can characterize network topology, allowing the relationships between cognitive ability and network integrity to be examined. In the current study we applied graph analysis to pseudo-resting state data in 54 healthy subjects and 46 schizophrenia patients, and measured overall cognitive ability as the shared variance in performance from tasks of episodic memory, verbal memory, processing speed, goal maintenance, and visual integration. We found that, across all participants, cognitive ability was significantly positively associated with the local and global efficiency of the whole brain, FPN, and CON, but not with the efficiency of a comparison network, the auditory network. Additionally, the participation coefficient of the right anterior insula, a major hub within the CON, significantly predicted cognition, and this relationship was independent of CON global efficiency. Surprisingly, we did not observe strong evidence for group differences in any of our network metrics. These data suggest that functionally efficient task control networks support better cognitive ability in both health and schizophrenia, and that the right anterior insula may be a particularly important hub for successful cognitive performance across both health and disease.

1. Introduction

Functional magnetic resonance imaging (fMRI) research has provided evidence of stable, intrinsic functional networks in the human brain (Fox et al., 2005). These functional networks are detectable both during the performance of cognitive tasks (Dosenbach et al., 2006) and while an individual is at rest (Power et al., 2011). These networks appear to support an array of cognitive functions, such as executive functioning, sensory perception, and motor control, and therefore represent important targets for understanding how healthy cognition occurs, and how abnormal cognition can lead to the symptoms observed in clinical populations. One pervasive aspect of mental illness is cognitive deficits (Green et al., 2004). Individuals diagnosed with schizophrenia, bipolar disorder, and major depression all display impairments in a multitude of higher-order cognitive domains, including memory,

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processing speed, and cognitive control (Heinrichs and Zakzanis, 1998; Martinez-Aran et al., 2004; Snyder, 2013). Of all these psychopathologies, patients with schizophrenia consistently exhibit, on average, the most severe cognitive deficits (Hill et al., 2013). These deficits, and the variance shared among them, are associated with impairments in everyday functioning (Sheffield et al., 2014), contributing to the disabling nature of the disorder (Bowie et al., 2008). While researchers have historically attempted to find differential cognitive deficits in schizophrenia, it is increasingly clear that patients are impaired relative to controls on the majority of neuropsychological tasks. This finding has led some to hypothesize that schizophrenia is characterized by a generalized cognitive deficit thought to reflect common psychological or neurobiological mechanisms contributing to performance across cognitive domains (Dickinson and Harvey, 2009). The generalized cognitive deficit makes schizophrenia an ideal population for studying a wide range of individual differences in overall cognitive ability, and this conceptualization of the generalized deficit can be operationalized as the shared variance across tasks that assess different domains of cognition, which we will refer to as global or overall cognition.

Importantly, two functional networks, the fronto-parietal network (FPN) and the cingulo-opercular network (CON), display increased activity during the performance of many complex cognitive tasks (Dosenbach et al., 2006), and the strength of their within-network connectivity predicts cognitive performance (Kelly et al., 2008; Rypma et al., 2006; Seeley et al., 2007; Song et al., 2008), implicating them as part of “task-positive” or “task control” systems that may underlie global cognition. In fact, these networks are hypothesized to represent a dual-system of top-down control that supports cognitive ability, given their pattern of activation and connectivity during task performance (Dosenbach et al., 2008). More specifically, the FPN is thought to be involved in trial-by-trial control during task, facilitating the selective attention of trial-specific information, while the CON is thought to facilitate the maintenance of task-relevant goals and the incorporation of error information to adjust behavior (Cocchi et al., 2013). Therefore, together, these two large-scale networks are globally relevant to wide range of cognitive functions, making them excellent candidates for better understanding individual differences in overall cognitive ability.

Research also suggests that specific brain regions within the FPN and CON play especially important roles in the coordination of information transfer between networks (Dosenbach et al., 2007). In particular, the anterior insula (AI) and dorsal anterior cingulate cortex (DACC) are hypothesized to serve as core hubs within the CON, and the dorsolateral prefrontal cortex (DLPFC) represents a hub within the FPN. Each hub is thought to serve different functions within each network, to support cognitive performance. Given the current conceptualization that multiple brain networks are necessary for higher-order cognition (Cocchi et al., 2013), hub-ness may be an especially important metric for understanding how communication between networks supports cognitive ability. Previous work suggests that the DACC facilitates outcome-monitoring by evaluating the result of an individual's actions, and facilitating the resolution of conflict during task (i.e. conflict-monitoring) (Botvinick et al., 2004). The AI marks information as salient for additional processing and is thought to communicate with multiple large-scale networks to facilitate the utilization of salient information for attention and working memory processes (Menon and Uddin, 2010). The DLPFC maintains task representations and may bias information in line with task-related goals (Miller and Cohen, 2001). Therefore, the putative role of each hub suggests that, together with other regions within the FPN and CON, these hubs facilitate top-down control to support function across many cognitive domains.

Given this conceptualized role of the FPN and CON in global cognition, it has been argued that abnormalities in the control provided by these networks contributes to mental illness (Cole et al., 2014). One piece of evidence supporting this notion is abnormal connectivity within and between these networks in schizophrenia. Studies have found reduced connectivity between the FPN and CON (Repovs et al., 2011) and between the CON and the striatum in patients (Tu et al., 2012), as well as reduced connectivity within the FPN (Woodward et al., 2011). In addition, connectivity between major hubs within these networks is reduced (Meyer-Lindenberg et al., 2001; White et al., 2010). These findings, taken together with the deficits in overall cognition in schizophrenia, make this an excellent population in which to elucidate the relationship between functional networks and global cognition. Therefore, the current study aims to test the hypothesis that FPN and CON abnormalities are associated with shared task variance across many cognitive domains (i.e., global cognition), implicating them as a hypothesized source of the generalized cognitive deficit in schizophrenia.

To date, literature relating cognition and network-specific functional connectivity has largely quantified ‘abnormalities’ as significant differences in the magnitude of average correlation coefficients within and between networks. Recent application of graph theory analysis to functional connectivity data allows for more sophisticated measurement of brain networks, including global and local efficiency of information processing, and the role of hubs (Bullmore and Sporns, 2012; Rubinov and Sporns, 2010). These metrics can be correlated with psychological measures to assess relationships between brain and behavior. In fact, a previous study revealed a significant negative correlation between the characteristic path length of the whole brain network and IQ in a small group of healthy individuals (van den Heuvel et al., 2009), suggesting that more strongly integrated whole brain networks support better cognitive functioning. Efficiency metrics (both global and local) are calculated by taking the inverse of path length between nodes within a network, and therefore quantify how strongly (or efficiently) information can be transferred throughout the network. Given this conceptualization of efficiency metrics, as well as previous findings of a relationship between path length and cognitive ability, these metrics were selected as putatively important for understanding individual differences in overall cognitive functioning in both health and disease. Similarly, the degree to which hub nodes communicate with other networks not only influences the efficiency of a network, but is also a meaningful factor in cognitive functioning, leading us to utilize a metric of hub-ness known as the participation coefficient to quantify the integrity of our *a priori* hubs. Finally, while several studies have reported abnormal graph metrics in schizophrenia (Alexander-Bloch et al., 2010; Liu et al., 2008; Lynall et al., 2010; Rubinov et al., 2009), very few have assessed how the observed abnormalities are related to behavior. Therefore, the current study aims to assess network topology in healthy controls and individuals with schizophrenia, and measure the relationship between functional network metrics and global cognitive ability.

Finally, much of the graph theory literature focuses almost exclusively on the whole-brain. Thus, we extend this research by constructing graphs of specific functional networks: the FPN, the CON, and the auditory network (AUD), which serves as a comparison network hypothesized not to be related to the current measures of cognition. We hypothesized that patients with schizophrenia would show reduced efficiency of the FPN, CON, and whole brain relative to healthy controls. Given our hypothesis that network integrity underlies performance across many cognitive domains, we quantified shared variance from five different cognitive tasks to use as our measure of global cognition. We expected that efficiency of the whole brain, FPN, and CON, but not the AUD,