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Investigating Brain Networks Associated with Insight in Adolescents at Ultra High-Risk for Schizophrenia

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INVESTIGATING BRAIN NETWORKS ASSOCIATED WITH INSIGHT IN ADOLESCENTS AT ULTRA HIGH-RISK FOR SCHIZOPHRENIA

By

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ABSTRACT

Background. Impaired insight, or unawareness of illness, is a common symptom of schizophrenia. Clinical insight is awareness of having a mental disorder; cognitive insight is ability to self-reflect (self-reflectiveness) and certainty in cognitions (self-certainty). In schizophrenia insight is associated with brain function and improving insight is a potential early intervention point. This study investigated whether insight is impaired in youth at ultra high-risk (UHR) for psychosis, and if it is related to major brain networks. **Methods.** Data from a larger UHR study was used, including 55 UHR adolescents and 55 controls assessed with the Structured Interview of Prodromal Symptoms, MATRICS Consensus Cognitive Battery, Scale to Assess Unawareness of Mental Disorder, and Beck Cognitive Insight Scale, as well as resting state functional MRI scans. UHR and control groups were tested for differences in self-reflectiveness and self-certainty, and correlations between insight dimensions and clinical and cognitive measures. Functional connectivity was calculated for the default mode, the cingulo-opercular, and central executive networks and regressed on participants' reported clinical and

cognitive insight, while covarying for head motion. **Results.** Self-reflectiveness was higher in the UHR group (d = 1.28), but the groups did not differ in self-certainty (d = 0.28). Among UHR, poorer clinical insight was related to greater symptom severity. Default mode connectivity was negatively correlated with self-reflectiveness (R^2 = .091) and clinical insight (R^2 = .399) in UHR, but no such correlations were found in controls. Cerebello-prefrontal cortex connectivity was negatively associated with self-certainty in the UHR group (R^2 = .089 - .138). **Conclusions.** Default mode connectivity appears to be associated with the facets of insight concerning self-awareness, whereas cerebello-prefrontal connectivity appears to be associated specifically with self-certainty. This is the first study to relate major brain networks to insight before the onset of psychosis, and is consistent with models proposing that different facets of insight are related to self-awareness and executive functioning through networks associated with these processes.

INDEX WORDS: Insight, Schizophrenia, Ultra high-risk, Psychosis, Functional connectivity

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DEDICATION

This thesis is dedicated to my incredibly supportive family, and my fiancé Conor who has been here with me every step of the way. You all inspire me and give me more support than you know.

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1 INTRODUCTION

1.1 Ultra High-Risk

Schizophrenia is a devastating mental illness which incurs large costs to society (Mcevoy, 2007). It is characterized by psychotic symptoms, including positive symptoms (e.g., hallucinations, delusions), negative symptoms (e.g., anhedonia, flattened affect), disorganized symptoms (e.g., disorganized thought processes), and cognitive deficits (e.g., processing speed, working memory) (Kay, Fiszbein, & Opler, 1987). The process of developing schizophrenia likely begins well before the first psychotic episode; the diathesis-stress model of schizophrenia posits that people are born with vulnerability to psychosis and that biological, social, environmental, and cognitive factors work together throughout development to eventually cause psychotic symptoms (Howes & Murray, 2014). Symptoms typically begin to manifest during adolescence, while the brain is going through many changes (Menon, 2013; Yung & McGorry, 1996).

Because schizophrenia has a neurodevelopmental component, many studies now focus on a population of individuals at ultra high-risk (UHR) for psychosis, the putative prodromal phase of schizophrenia (Nelson, Thompson, & Yung, 2012). This stage of psychosis is characterized by cognitive deficits accompanied by either presence of attenuated psychotic symptoms or genetic risk/schizotypy and a decline in functioning (McGlashan et al., 2001). See Figure 1 for a description of how adolescents are classified as UHR. The UHR criteria help to identify people at high risk for developing psychosis, but since only approximately 35% go on to transition to a psychotic disorder (Cannon et al., 2008), there is still low positive predictive value (Fusar-Poli et al., 2013). Therefore, it is beneficial to investigate clinical and neurobiological factors that can identify who is most at risk and most likely to benefit from treatment. Insight into illness may be

one such factor, as there is evidence insight is related to treatment adherence and outcome in schizophrenia (Lincoln, Lüllmann, & Rief, 2007). Further, adolescence may be an optimal time to provide primary interventions, with aims of reducing duration of untreated psychosis or preventing psychosis onset.

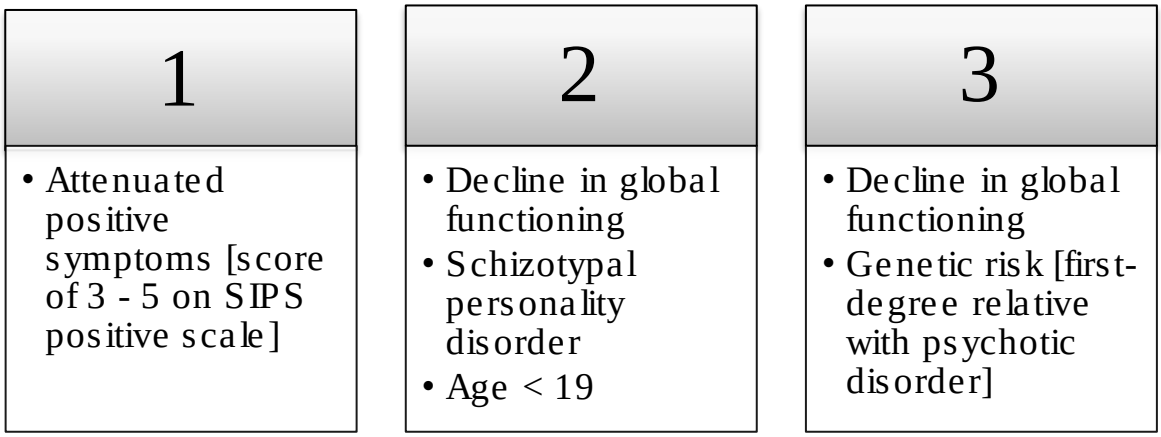

Figure 1 Three (not mutually exclusive) ways of categorizing individuals as ultra high-risk (UHR).
Positive symptoms refer to unusual thought content (delusions), suspiciousness, grandiosity, perceptual abnormalities (hallucinations), and disorganized behavior. A decline in global functioning refers to a 30% decline on the Global Assessment of Functioning compared to baseline. SIPS, Structured Interview of Prodromal Syndromes.

1.2 Insight

Insight broadly refers to a person's awareness of having an illness or disorder (Amador & Kronengold, 2004). It is estimated that approximately 50% of those diagnosed with schizophrenia are unaware of their illness, and that this is relatively stable (Arango & Amador, 2011), but may fluctuate with symptom severity along the course of the illness (Parellada et al., 2011; Quee et al., 2011). Impaired insight can impact prognosis and treatment adherence in schizophrenia, and may predict functioning (Lincoln et al., 2007). However, Lincoln et al. (2007)

noted that there is a complex relationship between insight and symptoms. People with lower insight tend to have greater symptom severity (Mintz, Dobson, & Romney, 2003), but symptoms only account for a small amount of variance and do not always predict insight, indicating other factors are involved (van der Meer et al., 2013). In addition, different dimensions of insight may be associated with different symptom profiles or other factors (Mintz et al., 2003).

Insight is considered to be on a continuum and to consist of multiple dimensions on which a person with schizophrenia may be impaired. Dimensions proposed to comprise insight include clinical insight: awareness of illness, awareness of need for treatment, awareness of social consequences, awareness and attribution of symptoms; and cognitive insight: self-reflectiveness and self-certainty (Amador et al., 1993; Beck, Baruch, Balter, Steer, & Warman, 2004; Birchwood et al., 1994; David, 1990; Gerretsen, Remington, et al., 2014; Marková et al., 2003; McEvoy, Aland, Wilson, Guy, & Hawkins, 1981). A number of measures have been developed to investigate clinical insight, and the Beck Cognitive Insight Scale (BCIS) is currently the only insight scale developed explicitly to assess cognitions related to insight, which includes ability to reflect on unusual thoughts and experiences, ability to correct incorrect judgments, certainty in those judgments, and jumping to conclusions (Beck et al., 2004).

Clinical and cognitive insight appear to be separate but related constructs (McCormack, Tierney, Brennan, Lawlor, & Clarke, 2014). Indeed, clinical insight scales demonstrate moderate to high correlations with each other, and low to moderate correlations with the BCIS, suggesting that clinical and cognitive insight share some variance, but tap into different facets of insight (Lincoln, et al., 2007; Riggs, Grant, Perivoliotis, & Beck, 2012). As such, clinical and cognitive insight may be related to different cognitive processes.

1.3 Insight in UHR

A few studies of insight in the UHR population have recently emerged, but none provide definitive conclusions considering the nature of insight in these individuals. Lappin et al. (2007) found individuals with at-risk mental state (ARMS; similar criteria to UHR) to have overall impaired clinical insight, but with considerable variability. The ARMS group also had greater insight than a first episode psychosis (FEP) group (67% versus 49% of total insight), which the authors pointed out is consistent with cognitive models of psychosis that implicate impaired symptom reappraisal in the development of psychosis (Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001). A review revealed that degree of clinical insight appears to follow a U-shaped curve along the lifespan of individuals with schizophrenia, with people most impaired at the first psychotic episode and late in the disease and improvement with treatment in-between (Philip Gerretsen, Plitman, Rajji, & Graff-Guerrero, 2014). This evidence suggests that insight impairment may be a factor contributing to transition to psychosis, although more research is required in the prodromal phase to support this hypothesis.

With the limited amount of cognitive insight research in UHR adolescents, it is also unclear whether cognitive insight is impaired in this population or not, but it may be related to delusion-like symptoms. In one of three studies to date, Kimhy et al. (2014) found that scores on self-reflectiveness, self-certainty, and the cognitive insight composite did not differentiate UHR and control groups and cognitive insight did not predict transition to psychosis. “Near threshold” (rating of 5 on the SOPS) delusional symptoms were related so low self-reflectiveness and high self-certainty in a subset of participants. Uchida et al. (2014) found individuals with ARMS to have higher self-certainty than controls, and also found the composite to be negatively correlated and self-certainty to be positively correlated with sub-threshold delusional symptoms. Similar

results were observed in a sample of patients with chronic schizophrenia, in which patients with delusions were more self-certain and less self-reflective than patients without delusions (Engh et al., 2010). Delusions are characterized by inflexible, strongly held beliefs, which goes hand in hand with self-certainty (Garety et al., 2001). Another study of UHR adolescents found self-certainty to be associated with hallucinatory symptoms and self-reflectiveness and cognitive insight to be associated with avolition (Lyngberg, Buchy, & Addington, 2015).

Based on disparate results of these few studies, it is still not clear if cognitive insight is actually impaired prior to the onset of psychosis, associated with particular symptoms, or if it is a risk factor for transition. However, based on the evidence thus far, there may be some association between delusions and self-certainty prior to psychosis on set, and therefore perhaps those individuals with higher self-certainty are more at risk.

1.4 Self-awareness and executive function as components of insight

1.4.1 Self-awareness

Studies of cognitive mechanisms related to impaired insight have increased understanding of mechanisms involved in developing schizophrenia. One group proposed a neurobiological model of insight in schizophrenia in which impaired insight is a function of executive dysfunction and impaired self-awareness (Shad, Keshavan, Tamminga, Cullum, & David, 2007). Self-awareness refers to an ability to distinguish self from other and make decisions in regards to oneself, and deficits in self-awareness may underlie both impaired insight and symptoms of psychosis (Shad, Brent, & Keshavan, 2011). For example, some people with schizophrenia are able to label psychotic symptoms in others as pathological but not in themselves, and may be unable to distinguish between self and other, monitor one's own or others' internal states, or make meaningful social relationships (David, 1990; David, Bedford,

Wiffen, & Gilleen, 2012; Nekovarova, Fajnerova, Horacek, & Spaniel, 2014; Shad et al., 2011; van der Meer, Costafreda, Aleman, & David, 2010). Further, people with schizophrenia tend to misestimate their abilities, a characteristic which predicts worse functioning.

1.4.2 Executive function

In addition to impaired self-awareness, executive dysfunction may contribute to poor insight. Executive functions are a set of complex effortful processes generally comprised of ability to flexibly adapt to one's surroundings, inhibit inappropriate behavioral responses, and monitor internal and external processes; they are largely controlled by prefrontal cortex (PFC) systems (Diamond, 2013; Niendam et al., 2012). Executive functions are impaired in many disorders, including schizophrenia, and Diamond (2013) noted that they are like a "canary in a coal mine"—executive functions are often the first to suffer when something is physically or mentally wrong. Thus, it is likely executive functions impact ability to recognize mental illness. For instance, deficits in working memory or inflexible thinking may make it difficult to re-appraise anomalous perceptual experiences or delusional beliefs and compare one's own functioning to others' (Gilleen, Greenwood, & David, 2011; Shad et al., 2007).

Demonstrating these relationships, two meta-analyses have been conducted on relationships between insight and cognitive measures. The first found clinical insight in 2,354 individuals (from 35 studies) with psychosis to be significantly associated with overall cognition (r = .17), IQ (r = .14), executive function (r = .19), and Wisconsin Card Sort Test score (WCST; a measure of mental flexibility; r = .23; (Aleman, Agrawal, Morgan, & David, 2006). The correlations between clinical insight and WCST were significantly stronger than correlations between clinical insight and IQ (medium effect size). More recently, Nair, Palmer, Aleman, and David (2014) replicated Aleman et al. (2006) with added cognitive insight studies and found

similar results. In 5429 individuals with psychosis from 72 studies, clinical insight was significantly associated with total cognition (r = .16), memory (r = .13), working memory (r = .13), executive function (r = .14), and WCST (r = .14). In 466 patients from 7 studies, cognitive insight was significantly associated with total cognition (r = .18) and memory (r = .21), and self-certainty was significantly associated with total cognition (r = -.14), IQ (r = -.19) and memory (r = -.23).

While these effect sizes are small, they do indicate that executive function consistently accounts for a significant amount of variance in insight. These meta-analyses do not, however, dissociate different facets of clinical insight and executive functions and their relationships. There are many tests of executive functions used in these studies that all tap into slightly different processes, and working memory, inhibition, and flexibility all influence each other (Diamond, 2013). Many different insight measures were used, as well, which each tap into different dimensions of insight. Relationships between clinical insight and the WCST in the meta-analyses suggest that poor mental flexibility is associated with inability to recognize one's illness, and relationships with memory indicate insight involves reflecting on past events or self-perceptions. However, the lack of relationships between neuropsychological variables and self-reflectiveness on the BCIS suggests that self-reflectiveness may be more closely related to self-awareness than cognition (Nair et al., 2014). It is also possible that these different aspects of cognitive function interact with each other and insight.

1.4.3 Self-awareness and executive function in UHR

Self-related processes appear to be impaired in UHR populations, and may even be an early indicator of psychosis risk (Brent et al., 2014). Nelson et al. (2012) found significantly more self-disturbance in UHR adolescents than controls, and that self-disturbance predicted later

transition to psychosis. However, another study found that clinical high risk adolescents' self-ratings of functioning significantly correlated with clinician ratings, which contrasts with the tendency of people with chronic schizophrenia to misestimate their functioning (Olvet, Carrión, Auther, & Cornblatt, 2013). Perhaps when individuals are UHR they are aware of functional difficulties and strange experiences, but are less aware of the cause of these difficulties. Self-disturbance may be a core deficit underlying transition to psychosis; individuals with psychosis may either be predisposed to self-awareness difficulties that become apparent in adolescence, or may experience a decline in self-awareness. Either way, self-awareness deficits may contribute to symptom development and maintenance (Garety et al., 2001).

Cognitive impairments including executive dysfunction are also present before the first episode of psychosis (Bang et al., 2014; Üçok et al., 2013). In fact, a decline in functioning is one of the criteria for a UHR classification, which may be due to executive dysfunction in activities of daily living, consistent with Diamond's (2013) assertion that executive functions are a sensitive early indication. Bang et al. (2014) found UHR cognitive test scores to be intermediate to controls and FEP; attention/working memory and verbal memory differentiated UHR from both FEP and controls. Additionally, Üçok et al. (2013) found cognitive function to be lower than controls and similar among UHR, familial high risk, and first episode groups, suggesting a genetic component. Generally, UHR and familial high-risk groups demonstrated intermediate cognitive function relative to controls and FEP; compared to controls, the UHR group performed significantly worse on learning/memory, executive function, attention, and global cognition measures. Further, a large study of cognition in prodromal psychosis demonstrated that in the early prodromal phase (before sub-threshold symptoms) there were deficits in executive function and verbal memory, and even greater deficits in UHR individuals.

The authors argued that their results are line with the neurodevelopmental model in which some cognitive functions are already impaired before symptom onset and continue to decline (Frommann et al., 2011).

Because of the cross-sectional nature of these studies, it cannot be concluded whether UHR adolescence lose these skills or fail to keep up with their peers in skill development. However, they do appear to have self-awareness and executive functioning difficulties prior to symptom onset, suggesting early vulnerability. Overall, the evidence suggests that insight, self-awareness, and executive function are impaired prior to the onset of psychosis, but further study in this area is warranted in order to disentangle these relationships because the literature is mixed. Currently, there are no studies of insight and brain function in UHR individuals, but neuroimaging studies of insight in schizophrenia are shedding light on the structures and networks involved, including networks related to self-awareness and executive function. .

1.5 Neural Correlates of Insight

It is unlikely that focal brain abnormalities predispose people to psychosis—vulnerability likely arises from disrupted function in distributed networks (Andreasen, Paradiso, & O'Leary, 1998; Friston, 1998; Fusar-Poli et al., 2007). Further, most researchers agree that insight deficits are likely due, at least in part, to neurological dysfunction (Larøi, Barr, & Keefe, 2004). Menon (2011) proposed a triple network dysfunction model of psychopathology in which hyperconnectivity of the default mode network (DMN) and hypoconnectivity of the central executive network (CEN), facilitated by aberrant switching between the two by the salience network, underlie a variety of psychopathological symptoms. Nekovarova et al. (2014) postulated that in schizophrenia specifically, hyperconnectivity of the DMN may underlie positive symptoms and deficient self-awareness; in addition, hypoconnectivity of the CEN may

underlie general cognitive and executive function impairment. These deficits may, in turn, contribute to deficits in insight, in line with Shad's (2007) model.

1.5.1 Networks hypothesized to be associated with insight

The DMN may be particularly relevant to insight, because parts of the DMN appear to underlie self-referential thought (Northoff et al., 2006; Northoff & Bermpohl, 2004; Northoff & Qin, 2011). Brain areas involved in the DMN include the posterior cingulate cortex (PCC), anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), precuneus/angular gyrus, and lateral temporal lobes; these brain regions are active when a person is at rest, and deactivate during tasks (Buckner, Andrews-Hanna, & Schacter, 2008). Medial areas of the DMN also overlap with the cortical midline structures (CMS), which are active during self-referential tasks (Northoff et al., 2006; Schneider et al., 2008).

The mPFC and PCC appear to be especially important for self-reflection, and are active during both self-reflection and rest (David et al., 2012; van der Meer et al., 2010; Whitfield-Gabrieli et al., 2011). Whitfield-Gabrieli et al. (2011) discovered that the dorsomedial prefrontal cortex (dmPFC) was active exclusively during a self-reflection task, whereas the PCC and ventromedial prefrontal cortex (vmPFC; nodes of the DMN) were active both during rest and self-reflection. Additionally, a meta-analysis revealed that the ventral ACC was specifically activated both at rest and during self-related tasks (Qin & Northoff, 2011). PCC activity also coincided with the DMN and self-related tasks, but was active during other-related tasks as well so was less specific, possibly indicating comparison of self with others. This evidence suggests that nodes of networks active during self-reflection are able to be investigated during resting-state studies as well, and it is likely that self-reflection is occurring during rest.

While midline structures may be more involved in self-referential processing, the lateral prefrontal regions including the dorsolateral prefrontal cortex (dlPFC) and ventrolateral prefrontal cortex (vlPFC) are thought to be more involved in higher-order cognitive processing that interacts with and regulates self-referential processing (Northoff et al., 2006; Qin & Northoff, 2011). In line with this hypothesis, functional neuroimaging studies of insight and self-reflection tasks have implicated cortical midline regions as well as lateral prefrontal regions (discussed below).

The CEN (also known as the task-positive or fronto-parietal network) consists of the dlPFC and posterior parietal lobes and may be important for insight because it is associated with goal-directed activities and executive functions, particularly attention and working memory (Dutt et al., 2015; Niendam et al., 2012) . The CEN is normally anti-correlated with the DMN; once a person begins performing an activity, the DMN switches off and the CEN switches on (Menon, 2011). Another cognitive control network affected in schizophrenia and possibly relevant to insight is the cingulo-opercular network (CON), which overlaps with the salience network and is comprised of the anterior insula/frontal inferior operculum (part of the vlPFC) and dorsal ACC (Dosenbach et al., 2007). Whereas the CEN is more associated with flexibly adapting to task demands, the CON is associated with sustained attention and attention to internal processes (Dosenbach et al., 2006; van der Meer et al., 2010). It also appears that the anterior insula facilitates switching between the DMN and CEN (Manoliu et al., 2014; Menon, 2011), and is involved in general awareness and especially self-awareness (Craig, 2009). Additionally, the cerebellum is functionally connected to all of these networks as an error detector and modulator through cortico-cerebellar-thalamo-cortical loops, allowing cognition to be flexible and automatic (discussed below) (Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011).

These three networks are hypothesized to be abnormal in many disorders, and have particularly been associated with schizophrenia and UHR. Neuroimaging studies have also demonstrated relationships between these networks and different facets of insight.

1.5.2 Insight and functional neuroimaging

Functional neuroimaging, and particularly functional connectivity (FC) can reveal how these large scale networks are organized in relation to certain behavioral phenotypes. It is thought that FC reveals organization of large-scale networks through correlating low frequency oscillations of spatially distinct brain regions (Whitfield-Gabrieli & Ford, 2012). Few resting-state FC studies of clinical and cognitive insight have been conducted. First, Liemburg et al. (2012) used independent components analysis (ICA), which linked lower connectivity within an anterior DMN component and within a posterior DMN component to lower clinical insight. However, they did not test connectivity between anterior and posterior DMN, which may be more informative, as these regions likely work together as a network in self-reflection (Qin & Northoff, 2011; Whitfield-Gabrieli et al., 2011).

In the second resting-state study of insight in schizophrenia, Gerretsen et al. (2014) performed seed-based connectivity analyses with five networks of interest and found poorer clinical insight to be associated with greater DMN connectivity between the PCC/precuneus and left angular gyrus. ROI-to-ROI analysis revealed greater connectivity between the dmPFC ("self-referential network") and left insula with poorer clinical insight. They also found greater self-certainty to be associated with reduced connectivity between the right inferior parietal lobule (IPL; "dorsal attention network") and left frontal inferior operculum. People with schizophrenia tend to have higher self-certainty scores than healthy controls (Riggs et al., 2012), so this may be associated with lower connectivity between cognitive control networks. Gerretsen et al.'s (2014)

results suggest a role of cognitive control in cognitive insight and a role of self-referential processing in clinical insight. They also attributed higher connectivity in the left hemisphere to left hemisphere dominance and thus right hemisphere deficit, in line with one of their structural MRI studies (Gerretsen et al., 2013). Right hemisphere lesions are associated with anosognosia (Lehrer & Lorenz, 2014), so left hemisphere dominance supports the theory of insight deficits as anosognosia. These resting-state studies suggest deficient processing in intrinsic networks in those with impaired insight, but it is unclear in which direction these differences are and more research is required to tease apart the networks' relationships with each other and with clinical and cognitive insight.

Task-based studies of insight and self-reflection in schizophrenia have implicated both midline and left lateral prefrontal regions, as well. For instance, one study demonstrated hyperconnectivity from the IPL, PCC, and dmPFC toward the vmPFC in schizophrenia patients with impaired clinical insight; they also showed hyperconnectivity between the PCC and vmPFC particularly when patients with poor clinical insight were making judgments about themselves (Ćurčić-Blake, van der Meer, Pijnenborg, David, & Aleman, 2015). Shad et al. (2012) also found greater posterior DMN and cerebellum activation in people with chronic schizophrenia compared to controls during self-versus other reflection; further, using the same task, Shad and Keshavan (2015) found unawareness of symptoms in individuals diagnosed with schizophrenia to be associated with activation during self-versus other reflection in the left frontal inferior operculum, left lingual gyrus, and left inferior parietal lobule. van der Meer et al. (2013) found that greater activation during self-reflection in the ventromedial prefrontal cortex (vmPFC) was associated with greater self-reflectiveness, suggesting the vmPFC underlies both the act of self-reflection and self-reflectiveness measured by the BCIS. A recent study also implicated the

vlPFC in self-reflectiveness in healthy controls and in first episode psychosis during source memory retrieval (Buchy et al., 2014; Buchy, Hawco, Joober, Malla, & Lepage, 2015).

Again, the DMN is most often associated with self-reflection tasks, and this relationship seems to hold for resting-state studies as well. Lateral hemispheric regions involved in the CEN and CON are active during self-reflection, as well as executive function. van der Meer (2013) suggested that vlPFC deficits may indicate impairment in cognitive control of self-related processes such as integrating internal and external stimuli; therefore if the vlPFC is not functioning properly, individuals with schizophrenia may have difficulties integrating a personal narrative.

1.6 Aberrant Brain Function in Ultra High-Risk Adolescents

These networks that are likely associated with different facets of insight have been identified as potentially dysfunctional in UHR adolescents. Though still in its infancy, investigating brain connectivity in adolescents at UHR for schizophrenia has enabled researchers to understand schizophrenia as a neurodevelopmental disconnection disorder (Satterthwaite & Baker, 2015). During adolescence, the brain goes through many changes in network organization (Menon, 2013). Menon (2013) posited principles of functional brain network development: strengthening of long-range connections, reconfiguration of cortical-subcortical connections, dynamic pruning of over-connected pathways, and reconfiguration of functional connections within and between large-scale networks. Developmental changes may make the adolescent brain particularly vulnerable to psychosis if any of these processes are compromised. Brent et al. (2014) also argued that self-related deficits in the prodromal phase of schizophrenia are related to these structural and functional changes, especially in the prefrontal cortex, since this is the last brain area to fully develop.

1.6.1 Default mode network

Aberrant DMN function has been implicated in neuroimaging studies of schizophrenia (Garrity et al., 2007; Whitfield-Gabrieli et al., 2009; Whitfield-Gabrieli & Ford, 2012), and more recent studies have found the DMN to be dysfunctional in the prodromal phase of psychosis as well. One resting-state fMRI study of connectivity in a UHR sample found hyperconnectivity in the DMN compared to controls, which is consistent with the majority of research in schizophrenia (Shim et al., 2010). In addition, Shim and colleagues (2010) and Wotruba et al. (2013) found reduced anti-correlations between the DMN and CEN, suggesting that the DMN and CEN are not efficiently activating and deactivating during rest, respectively. Wotruba and colleagues (2013) also found the lack of anticorrelations between these networks to be related to reality distortions, and higher inter-network connectivity to be related to worse cognitive performance. Similar to UHR studies, Satterthwaite et al. (2015) observed DMN hyperconnectivity during resting-state in youth from the general population with psychosis spectrum symptoms, suggesting that DMN hyperconnectivity may predispose people to psychotic symptoms, whether or not these individuals are help-seeking. However, a different group observed DMN hypoconnectivity in a similar sample (Orr, Turner, & Mittal, 2014), and a recent study utilizing some of the same participants as the current study found no connectivity differences within the DMN but increased connectivity between the salience network and DMN (Pelletier-Baldelli, Bernard, & Mittal, 2015). These studies suggest potential major network connectivity abnormalities across the psychosis spectrum, but as methods and study samples vary, it is not entirely clear in which direction the abnormalities are.

1.6.2 Cognitive control networks

Many task-based fMRI studies show abnormal CEN activity in UHR individuals, but findings have been mixed (Dutt et al., 2015; Fusar-Poli et al., 2007). Dutt and colleagues (2015) integrated studies in an ALE analysis and found regions of the CEN to be hypoactivated during cognitive tasks (mainly working memory and verbal fluency) compared to controls. In particular, the right inferior parietal lobule showed lower activation across all cognitive tasks studied, illustrating that this region may be particularly vulnerable during the development of psychosis. The left dmPFC was another common area of decreased activation during cognitive tasks. As previously mentioned, both of these areas are parts of networks hypothesized to be involved in insight and the right parietal lobe is associated with anosognosia in other disorders (Prigatano, 2010).

Functional connectivity studies of the CEN and CON are less common in UHR, but Schmidt et al. (2014) found both decreased fronto-parietal connectivity, especially in the right hemisphere, and impaired working memory performance in individuals with ARMS. Greater right hemisphere differences between ARMS and healthy controls echo the left hemisphere dominance theory of insight impairment, Further, Schmidt et al. (2015) discovered in their review that the fronto-parietal network is disrupted throughout different stages of psychosis, though it is unclear what the pattern of disruption looks like.

Two studies have also observed decreased cingulo-opercular connectivity in community samples of adolescents with psychosis spectrum symptoms (Orr et al., 2014; Satterthwaite et al., 2015), providing evidence for hypoconnectivity in cognitive control networks during rest along the psychosis continuum. Orr et al. (2014) also observed that connectivity within the CEN was stronger in their non-clinical psychosis group compared to healthy controls, which contrasts with

UHR studies. This could indicate a compensatory mechanism in non-help-seeking individuals that is not present once sub-threshold symptoms develop (Schmidt et al. 2015). Orr et al. (2014) also observed reduced connectivity in cerebellar networks.

1.6.3 Cerebellar networks

While most studies of functional connectivity are cortically-focused, Bernard and colleagues (2014) recently found adolescents at risk for psychosis to have decreased cerebello-cortical connectivity compared to healthy controls. The cerebellum is anatomically and intrinsically connected to the cortex, and particularly to regions in the DMN, CEN, and CON, both in healthy individuals (Buckner, 2013; Buckner et al., 2011; Krienen & Buckner, 2009), and in schizophrenia (Chen et al., 2013). It is hypothesized to create "internal models" that predict and then help modulate and coordinate behavior (Ito, 2008). The cerebellum may be an important node involved in functional dysconnectivity in psychosis, but it remains underinvestigated (Andreassen et al., 1998). According to an ALE analysis, cerebellar regions that appear to be most hypoconnected to the cortex in schizophrenia are crus I and lobule VI, which are involved in diverse cognitive processes, including executive function and self-reflection (Bernard & Mittal, 2015; Buckner et al., 2011).

The cerebellum is involved in many complex cognitive processes, including executive function and working memory; the posterior regions of the cerebellum (crus I/II, lobules VI/VII) appear to be especially important for these types of tasks (Keren-Happuch, Chen, Ho, & Desmond, 2014). Because it is involved in these complex cognitions, the cognitive dysmetria hypothesis posits that in disorders such as schizophrenia, the cerebellum is not properly coordinating and refining thought based on the situation, resulting in disorganized thought processes (Andreasen et al., 1998). These deficits could have consequences for insight and

development of psychotic symptoms if cerebellar dysfunction impairs integrating and updating one's personal narrative and cognitive control. In fact, preliminary evidence from the author's lab suggests weaker crus I – prefrontal cortex connectivity in individuals with low insight. Further, the posterior cerebellum, including crus I, was associated with error detection when activated with the CEN and CON (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008), suggesting that when these circuits are not functioning properly, individuals may be prone to errors in judgment.

Cerebellar abnormalities have been observed in UHR adolescents. Structurally, Dean et al. (2013) demonstrated that cerebellar volumes of both motor and cognitive regions were smaller in UHR compared to controls, and that left crus I volume correlated with procedural learning rate, which was slower in UHR. In addition, Mittal and colleagues (2013) found cerebellar-thalamic white matter tract integrity to decrease over a year in UHR, but increase in controls; the white matter tract integrity was predicted by presence of neurological soft signs and negative symptoms, which were increased in UHR. The posterior cerebellum is connected to the cortex through the thalamus (Barch, 2014), so integrity of these tracts may be crucial for correct modulation of cognitive and motor processes. Bernard and colleagues (2014) also demonstrated decreased cerbello-cortical connectivity in UHR adolescents compared to controls. Because studies have found parts of the cerebellum to be associated with psychotic symptoms, cognition, and insight, it is worth investigating it in its own right. The posterior cerebellum appears to be especially important for diverse cognitive functions, and crus I in particular appears to be associated with multiple cortical networks and cognitive processes. Therefore, crus I may be related to insight through organizing and coordinating thoughts about the self.

1.7 Aims of This Study

The literature reviewed thus far provides evidence that insight in schizophrenia is related to self-awareness and executive functions, which are associated with distributed brain networks. These networks appear to be dysfunctional in schizophrenia as well as the prodromal phase of schizophrenia, and there is limited evidence for insight deficits in prodromal psychosis as well. Both insight and functional connectivity remain understudied in this population, but may be risk factors for developing psychosis and may even help predict transition. Therefore, this study aims to investigate brain networks involved in clinical and cognitive insight in UHR adolescents. Regions of interest (ROIs) will be defined in the DMN, CEN, CON, and cerebellum crus I to calculate connectivity within and between these networks and relate it to insight dimensions.

Aim 1: The first aim is to characterize the nature of cognitive insight dimensions in UHR adolescents compared to healthy controls, thus adding to the extant literature on cognitive insight in UHR.

Hypothesis 1a: UHR adolescents will display higher self-certainty than healthy controls.

Hypothesis 1b: UHR adolescents will display lower self-reflectiveness than healthy controls.

Hypothesis 1c: UHR adolescents will display lower cognitive insight than healthy controls.

Aim 2: The second aim is to investigate how cognitive insight dimensions are associated with connectivity in default mode and cognitive control networks. Because cognitive insight does not directly measure experiences related mental illness, it was assessed in both UHR and control groups, therefore relationships between cognitive insight dimensions and connectivity

will be calculated for all participants. I will also investigate a Group × Cognitive Insight Dimension interaction.

Hypothesis 2a: Greater self-reflectiveness will be associated with greater connectivity between the PCC and vmPFC, and between right crus I and the PCC.

Hypothesis 2b: Greater self-certainty will be associated with lower connectivity between the right dlPFC and right posterior parietal lobe, between the right dlPFC and left crus I, and between left crus I and the right anterior insula/frontal operculum.

Hypothesis 2c: Greater cognitive insight will be associated with greater connectivity between the PCC and vmPFC, between right crus I and the PCC, between left crus I and the right dlPFC, between left crus I and the right anterior insula/frontal operculum, and between the right dlPFC and right posterior parietal lobe.

Hypothesis 2d: There will be a significant Group × Cognitive Insight Dimension interaction for all analyses.

Aim 3: The third aim is to investigate how clinical insight is associated with connectivity in default mode and cognitive control networks. The clinical insight scores were only assessed in the UHR group. The two resting-state studies of insight and the DMN thus far oppose each other and utilized different methods, so it may be premature to propose directional hypotheses in relation to the DMN (Gerretsen et al., 2014; Liemburg et al., 2012), but previous research from our lab indicates lower connectivity in the DMN is associated with lower insight. Because the proposed analyses are similar to Gerretsen and colleagues' (2014) analyses and are using some of the same ROIs, a comparison between our UHR results and their chronic schizophrenia results may be possible.

Hypothesis 3a: Greater clinical insight will be associated with greater connectivity between the PCC and vmPFC, between right crus I and the PCC, between left crus I and the right dlPFC, between left crus I and the right anterior insula/frontal operculum, and between the right dlPFC and right posterior parietal lobe.

Hypothesis 3b: Greater clinical insight will be associated with greater anticorrelations between the right dlPFC and PCC.

Exploring dimensions of insight and their neurofunctional correlates in adolescents at UHR for psychosis will broaden knowledge of psychosis development. If insight is related to brain networks in this population, this may enable clinicians to identify who is most at risk of psychosis and develop more effective interventions to prevent psychosis.

2 METHODS

2.1 Procedures

The data used for this project were obtained from an ongoing study at the University of Colorado Boulder. Obtainment of data and analyses were approved by the Georgia State University institutional review board (IRB #H15274).

2.1.1 Participants

Participants were recruited from the University of Colorado Boulder's Adolescent Development and Preventative Treatment (ADAPT) research program, through Vijay Mittal, PhD and colleagues. Control participants were recruited from the community. All participants gave informed consent, and all procedures were reviewed and approved by the University of Colorado Boulder institutional review board. Participants consisted of 130 adolescents, ages 12-23.

The UHR group was screened with the Structured Interview for Prodromal Syndromes (SIPS) by an advanced doctoral student or clinical psychologist (Miller et al., 1999), and those who met criteria for a prodromal syndrome were included. All interviewers received reliability training, and reliability was assessed periodically for drift; all raters had inter-rater reliabilities that exceeded the minimum study criterion of Kappa ≥ 80. Help-seeking individuals who did not meet criteria were referred to community resources. The SIPS contains the Scale of Psychosis-Risk Symptoms (SOPS), which contains items on a scale of 0 – 6 for severity of positive, negative, and disorganized symptoms. Scores of 3 – 5 are considered prodromal. It also contains a family history worksheet, Global Assessment of Functioning Scale, and Schizotypal Personality Disorder Checklist. As per the SIPS, adolescents were considered UHR if they had moderate positive symptoms and/or a decline in functioning accompanied by schizotypal traits and/or a family history of schizophrenia (Figure 1).

Exclusion criteria for the UHR group included history of head injury, diagnosis of an Axis I psychotic disorder, neurological disorder, or MRI contraindication. Exclusion criteria for the control group further included any Axis I diagnosis and psychotic disorder in a first-degree relative (this confers genetic risk). To assess these criteria, a trained advanced doctoral student or clinical psychologist administered the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID) (First, Spitzer, Gibbon, & Williams, 1997)

Eight participants were excluded from these analyses because they did not meet criteria for UHR or control groups, ten because they were under age 14 and behavioral measures were not normed for younger children, and two had previously been diagnosed with a psychotic disorder. This left a total of 110 participants for behavioral analyses (55 UHR and 55 controls). Participants were excluded from imaging analyses for the following reasons: six were under age

16, seven had current substance dependence, three were not scanned, six did not have sufficient scan quality, and five moved in the scanner more than the 3 mm voxel size (see below for image preprocessing pipeline). Due to further missing data, final imaging analyses included 35 UHR in clinical insight analyses and 24 UHR and 33 controls in cognitive insight analyses. Table 2 presents participant characteristics for the entire sample. Tables 24 and 25 in Appendix E show demographic information for subsets of participants with imaging data.

2.1.2 Insight measures

Insight was assessed with the abbreviated version of the Scale to Assess Unawareness of Mental Disorder (SUMD) (David, 1990; Michel et al., 2013) and the Beck Cognitive Insight Scale (BCIS) (Beck et al., 2004). The SUMD was used to assess the UHR group because they are help-seeking individuals who have had experiences similar to psychosis; the BCIS was used to assess both the UHR and control group for comparison because it does not directly assess psychotic experiences and has been normed in healthy individuals (Martin, Warman, & Lysaker, 2010).

The SUMD is a clinician-rated measure of insight. It includes three general items: awareness of having a mental disorder, awareness of the need for treatment, and awareness of social consequences of the disorder. These items are rated on a scale of 0 – 5 for current awareness and past awareness: 0) the item cannot be assessed, 1) aware, 3) somewhat aware/unaware, and 5) completely unaware. The SUMD also includes items related to specific symptoms—both awareness of symptoms and attribution in the past and present. (Michel et al., 2013) assessed the psychometric properties of the abbreviated SUMD in 531 patients with schizophrenia. They confirmed that awareness of disease, need for treatment, and consequences loaded on a single factor. Internal consistency was above .7 and convergent validity was

established with relationship with the PANSS insight item. SUMD scores did not significantly correlate with depression, quality of life, or demographic factors, indicating discriminant validity. The SUMD items assessed in this study include the three general items and the items for awareness and attribution of thought disorder.

The BCIS is a self-report measure of cognitive insight. It includes two subscales: self-reflectiveness (SR; 9 items) and self-certainty (SC; 6 items). Each item is rated by the patient as 0) do not agree at all, 1) agree slightly, 2) agree a lot, or 3) agree completely. The self-reflectiveness subscale items all assess the patient's ability to reflect on their cognitive processes and perceptual experiences. The self-certainty subscale items assess beliefs around cognitions being correct and accepting corrective feedback from others.

In studies of cognitive insight, each subscale is typically used separately as well as a composite score derived from subtracting self-certainty from self-reflectiveness. Beck's original study assessed psychometrics in 150 inpatients (75 with schizophrenia and 75 with depression). Varimax-rotated principal components analysis revealed two factors: SC and SR. Internal consistency values ranged from .59 to .67, which are acceptable for research according to the authors, but low. The BCIS composite correlated with the SUMD awareness of mental disorder, indicating convergent validity. However, the BCIS did not correlate as highly with clinical insight measures as clinical insight measures correlated with each other, which indicates that cognitive insight appears to be a separate, but related construct to clinical insight (Lincoln et al., 2007). Beck et al. (2004) also found support for significant differences in BCIS scores between the patients with and without psychosis. In addition, Martin et al. (2010) assessed psychometrics of the BCIS in a healthy sample, finding the same two factors. Internal consistency values were

above .70, and there were significant differences between patients and healthy controls (patients reported higher self-certainty, lower self-reflectiveness, and lower composite scores).

To get scores for current clinical insight, responses to the three current general items were summed. Cronbach's alpha in the current sample for this scale was 0.36, which is low, however it was higher when only including subjects with imaging data (0.52). BCIS responses for self-reflectiveness and self-certainty items were summed, and self-certainty was subtracted from self-reflectiveness in order to get the cognitive insight composite score. Cronbach's Alpha in the current sample for the self-reflectiveness scale was 0.72, and for self-certainty was 0.57. For the group included in imaging analysis, Cronbach's alpha for self-reflectiveness was 0.73, and for self-certainty it was 0.41. Three participants did not answer the last BCIS question, so their scores were imputed in the following way: their scores on other items were inspected and compared to their nearest neighbor, then they were given the same score on item 15 that their nearest neighbor reported. Excluding these three imputed data points did not impact results.

2.1.3 Scanning

Participants underwent both structural and functional magnetic resonance imaging (MRI) scans on a 3T Siemens Magnetom TrioTim scanner. Structural images were acquired with a T1-weighted 3D magnetization prepared rapid gradient multi-echo sequence (MPRAGE; sagittal plane; repetition time [TR] = 2,530 ms; echo times [TE] = 1.64 ms, 3.5 ms, 5.36 ms, 7.22 ms, 9.08 ms; GRAPPA parallel imaging factor of 2; 1 mm^3 isomorphic voxels, 192 interleaved slices; FOV = 256 mm; flip angle 57°). A 5 min 34 s functional resting state blood-oxygen-level-dependent scan was acquired with a T2*-weighted echo-planar functional protocol (number of volumes = 165; TR = 2,000 ms; TE = 29 ms; matrix size = 64 x 64 x 33; FA = 75°; 3.8 x 3.x 3 3.5 mm^3 voxels; 33 interleaved slices; FOV = 240 mm). During the resting state scan,

participants were instructed to relax and close their eyes. A turbo spin echo proton density (PD)/T2-weighted acquisition (TSE; axial oblique aligned with anterior commissure–posterior commissure line; TR = 3,720 ms; TE = 89 ms; GRAPPA parallel imaging factor of 2; FOV = 240 mm; flip angle: 120 ; 0.9 x 0.9 mm^2 voxels; 77 interleaved 1.5 mm slices) was acquired to check for incidental pathology.

2.1.4 Preprocessing

Data were preprocessed using the Data Processing Assistant for Resting State fMRI, Advanced Edition (DPARSFA) (Yan & Zang, 2010). The first four time points were removed, and then scans were slice-timing corrected, motion corrected, and co-registered to the T1 image. The images were then normalized to MNI space, smoothed with a 6 mm Gaussian kernel. After smoothing, nuisance covariates were regressed out: white matter, cerebrospinal fluid, head motion scrubbing regressors (framewise displacement (FD) > 0.5, two volumes before, and one volume after the bad time point), and 12 motion parameters. Finally, images were temporally filtered (0.01 – 0.08 Hz).

2.2 Analyses

2.2.1 Aim 1: Cognitive Insight dimensions

First, independent samples *t*-tests and chi-square tests were calculated to compare the UHR and control groups on demographic measures using the Statistical Package for the Social Sciences (SPSS; version 21). Then, independent samples *t*-tests were calculated to compare cognitive insight between the UHR and control groups. Tests were carried out with group as the independent variable and self-reflectiveness, self-certainty, and cognitive insight as dependent variables. The Bonferroni method was used to correct for multiple comparisons, and group

comparisons were considered significant if they passed a threshold of $p < .017$. Pearson's bivariate correlations were also performed between insight measures and clinical and cognitive measures in the UHR group to investigate potential covariates in regression analyses. Significant correlations were plotted to examine scatter and potential leverage points that influenced correlations, and measures were tested as covariates if they correlated strongly with both the independent and dependent variables.

2.2.2 Aims 2 and 3: Functional connectivity

Functional connectivity (FC) analyses investigate how low frequency fluctuations in blood-oxygen level dependent (BOLD) signal in two spatially distinct regions are functionally related by calculating a bivariate correlation (Biswal, Yetkin, Haughton, & Hyde, 1995). One method for calculating FC, seed-based connectivity, involves choosing a seed region of interest (ROI) in the brain and correlating its BOLD signal to other voxels in the brain. Seed-based connectivity was calculated in DPARSFA using seeds in the DMN, CEN, CON, and a cerebellar seed related to these networks. Table 1 demonstrates the seeds of interest within each network, which were defined by 10 mm spheres centered on coordinates used in Orr et al.'s (2014) study.

Seeds in the cerebellum were defined by masks created with the Spatially Unbiased Infratentorial Template (SUIT) atlas (Diedrichson, 2006) in order to improve spatial alignment (Bernard et al., 2014). As identified by previous research (Buckner et al., 2011; Chen et al., 2013; Dosenbach et al., 2008), crus I was defined as an ROI because it appears to be connected to all networks of interest and associated with both cognition and self-reflection.

Table 1 Seeds of interest, defined by Orr et al. (2014). Seeds in bold will be used for seed-to-voxel analyses.

Network	Region of Interest	MNI Coordinates
Default Mode Network	**PCC**	-11, -57, 13
	vmPFC	1, 31, -2
Central Executive Network	**R dlPFC**	43, 22, 34
	R inferior parietal lobule	51, -47, 42
Cingulo-Opercular Network	R anterior insula/frontal operculum	36, 16, 4
Cerebellum	**L/R Crus I**	Defined by SUIT atlas
Control seed	L Primary Visual Cortex	-7, -83, 2

Additionally, a control seed was included in order to specify that any results obtained are indeed related to insight and not just a generally dysfunctional brain. The control seed was located in the primary visual cortex because it is not functionally connected to the DMN or CEN and the participants had their eyes closed during the scan. It was expected that the activity of this ROI was not significantly correlated with the other ROIs.

DPARSFA calculates correlations between seed regions of interest (ROIs) and all of the voxels in the brain (seed-to-voxel approach) and between ROIs (ROI-to-ROI approach). For seed-to-voxel calculations, the correlations are converted into *z* maps with Fisher's *r* to *z* transformation. For ROI-to-ROI calculations, DPARSFA creates a matrix of FC *z* scores for each participant. Similar to Gerrestsen et al. (2014), I investigated both seed-to-voxel and ROI-to-ROI connectivity. While ROI-to-ROI analyses were hypothesis driven (see hypotheses), seed-to-voxel analyses were more exploratory and included the PCC, right dlPFC, and right and left crus I. In keeping with Gerretsen's theory that insight is right hemisphere related, and to reduce multiple comparisons, I focused on right hemisphere cortical ROIs and left crus I.

2.2.3 General Linear Model analyses

For ROI-to-ROI analyses, SPSS was used to perform multiple linear regression analyses on connectivity values between ROIs. Insight dimensions (and group, for cognitive insight analyses) were entered as predictor variables and FC correlations were the outcome variables. Framewise displacement (FD), a measure of mean head motion, was included as a covariate in regression analyses, in order to control for effects of head motion on FC (Power et al., 2014). For those covariates that correlated with both the dependent and independent variables, analyses were re-run with covariates included as a post-hoc analysis.

Because the clinical insight measures are only available for the UHR group, analyses with clinical insight items were only performed within this group. Cognitive insight analyses were performed with all participants for whom cognitive insight scores were available, and a group × cognitive insight dimension interaction term was included. Results were considered significant if they passed a threshold of $p < .05$, Bonferroni corrected for multiple comparisons for each hypothesis.

For seed-to-voxel analyses, SPM8 (http//www.fil.ion.ucl.ac.uk/spm) was used to perform voxel-wise multiple linear regression analyses on the FC maps. When investigating interaction effects, the flexible factorial model was used, with group as a factor, FD as a covariate, and self-reflectiveness or self-certainty as a covariate of interest. When investigating main effects, multiple linear regression was used, with FD as a covariate and cognitive or clinical insight dimension as a covariate of interest. A cluster-forming threshold of $p < .001$, extent threshold 10 voxels was set, and resulting clusters were considered significant if they passed a cluster-level threshold of $p < .05$, familywise error (FWE) corrected for multiple comparisons.

3 RESULTS

3.1 Participants

Participants did not differ in age ($t(108) = -0.10$, $p = .921$), handedness ($\chi^2 = 0.25$, $p = .673$), race ($\chi^2 = 4.73$, $p > .05$), IQ ($t(83) = 1.50$, $p = .138$), mother's ($t(97.18) = -0.53$, $p = .597$) or father's ($t(104) = 0.97$, $p = .334$) education, or framewise displacement (FD) ($t(68) = -0.23$, $p = .817$). The UHR group contained significantly more males than the control group ($\chi^2 = 5.28$, $p = .022$), consistent with the schizophrenia literature. However, for imaging analyses, the subset included did not differ in gender between groups. UHR had significantly lower general functioning ($M = 60.06$, $SD = 16.41$) than controls ($M = 86.19$, $SD = 5.60$; $t(65.18) = -11.07$ $p < .001$). Within the subset of participants used in imaging analyses, there was a significant difference in IQ, with the UHR group ($M = 111.31$, $SD = 12.55$) performing better than the control group ($M = 104.92$, $SD = 10.26$; $t(53) = 2.05$, $p = .045$. IQ was not included as a covariate because it is not recommended to do so in neurodevelopmental studies (Dennis et al., 2009), and it did not significantly predict connectivity. Table 2 illustrates group differences for the entire sample, and Table 24 illustrates group differences for the imaging subset.

In regards to symptomatology, the UHR group displayed average SIPS scores of 11.69 ± 5.82 for positive symptoms, 9.69 ± 6.72 for negative symptoms, 5.05 ± 3.86 for disorganized symptoms, and 6.60 ± 4.54 for general symptoms. UHR displayed a range of clinical insight, with mean awareness of mental disorder of 2.10 ($SD = 1.42$), mean awareness of effects of medication of 1.10 ($SD = 1.56$), and mean awareness of consequences of 1.73 ($SD = 1.55$). According to the awareness of mental disorder item, 30 participants were considered "aware" (score of 2 or below), and 22 were considered "somewhat aware" to "unaware". Mean sum

clinical insight scores ranged from 0 – 12, with a mean of 4.92 and standard deviation of 3.00. Higher scores on this measure indicate more impaired insight.

Table 2 Participant Characteristics.

	Healthy Control (N = 55)	UHR (N = 55)	Tests	Significance
Age	19.31 ± 2.13	19.27 ± 1.66	t = -0.10	.921
Gender (M/F)	**24/31**	**36/19**	**χ^2 = 5.28**	**.022**
Handedness (R/L)	31/3	33/2	χ^2 = 0.25	.673
Race (White/Non-White)	25/19	31/13	χ^2 = 1.77	.268
WRAT Sum IQ	104.95 ± 10.28	108.70 ± 12.63	t = 1.50	.138
Framewise Displacement (N = 33/37)	0.200 ± 0.071	0.195 ± 0.092	t = -0.23	.815
Mother's Education	16.02 ± 2.78	15.77 ± 1.96	t = -0.53	.597
Father's Education	15.20 ± 3.73	15.85 ± 3.05	t = 0.97	.334
GAF Current	**86.19 ± 5.60**	**60.06 ± 16.41**	**t = -11.07**	**< .001**
Positive Symptoms		11.69 ± 5.82		
Negative Symptoms		9.69 ± 6.72		
Disorganized Symptoms		5.05 ± 3.856		
General Symptoms		6.60 ± 4.54		
Awareness of Mental Disorder		2.10 ± 1.42		
Awareness of Medication Effects		1.10 ± 1.56		
Awareness of Social Consequences		1.73 ± 1.55		
Total Clinical Insight		4.92 ± 3.00		

Note, GAF, General Assessment of Functioning

3.2 Cognitive Insight

UHR (M = 13.66, SD = 4.05) displayed greater self-reflectiveness than controls (M = 9.00, SD = 3.15; $t(73) = 5.61$, $p < .001$). They also displayed greater cognitive insight than controls (UHR M = 5.67 SD = 5.59, control M = 2.14, SD = 4.04; $t(73) = 3.50$, $p = .001$). The two groups did not differ in self-certainty ($t(73) = 1.58$, $p = .224$). When three items asking about "unusual experience" were removed from the self-reflectiveness scale, the group difference was

still significant $t(73) = 4.29$, $p < .001$. Acording to Cohen's *d*, the effect size for the self-reflectiveness difference is large (1.28), as is the effect size for cognitive insight (0.797). The effect size for the self-certainty difference is small (0.286).

In regards to correlation analyses, within the UHR group the cognitive insight composite significantly correlated with self-reflectiveness ($r(32) = .853$, $p < .001$) and self-certainty ($r(32) = -.681$, $p < .001$). Cognitive insight did not significantly correlate with any other clinical or cognitive measures. Clinical insight significantly correlated with positive ($r(52) = .465$, $p = .001$) and negative symptoms ($r(52) = .318$, $p = .022$). Self-reflectiveness significantly correlated with social cognition ($r(27) = .424$, $p = .027$), and IQ ($r(25) = .426$, $p = .034$). Self-certainty significantly correlated with working memory ($r(27) = .382$, $p = .049$) and negative symptoms ($r(32) = -.432$, p = .014). All correlations did not survive correction for multiple comparisons ($p < .001$), and many were influenced by leverage points that made correlations nonsignificant when removed. See Appendix A for all correlations.

Table 3 Cognitive Insight differences.

	Control (N = 43)	UHR (N = 32)	Test	Significance
Self-Reflectiveness	**9.00 ± 3.15**	**13.66 ± 4.05**	**t = 5.61**	**< .001**
Self-Certainty	6.86 ± 2.98	7.70 ± 2.89	t = 1.22	.224
Cognitive Insight	**2.14 ± 4.04**	**5.95 ± 5.42**	**t = 3.50**	**.001**

Note, UHR, ultra high-risk

3.3 ROI-to-ROI Connectivity

3.3.1 Self-reflectiveness and DMN

ROI – ROI regression results indicated a significant group × self-reflectiveness interaction within the DMN, adjusted $R^2 = .182$, $F(4, 52) = 4.12$, p = .006; interaction $B = -.228$, $t = -2.5$, $p = .016$. The interaction accounted for 9.1% of the variance in DMN connectivity.

Simple slopes analysis indicated that the slope of the regression line for the UHR group significantly differed from zero (B = -.176, t = -2.93, p = .005), but the slope of the regression line for the control group did not (B = .052, t = .768, p = .446). Table 4 and Figure 2 illustrate the significant results. Because positive symptoms and depressive symptoms correlated with both self-reflectiveness and DMN connectivity, the regression was tested with symptoms as covariates and the regression remained significant, adjusted R^2 = .170, F(6, 50) = 2.91, p = .016. The model investigating connectivity between right crus I and PCC/precuneus was not significant. All nonsignificant regression models are reported in Appendix A.

Table 4 Hierarchical regression for self-reflectiveness (SR) and group predicting default mode network connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.074	4.38	.041
FD	.080	2.09	.041			
Step 2				.076	3.10	0.34
FD	.076	2.03	.047			
SR	-.076	-1.62	.111			
Group	.201	2.13	.038			
Step 3				.091	4.12	.006
FD	**.090**	**2.49**	**.016**			
SR	.052	.768	.446			
Group	**.205**	**2.27**	**.027**			
Group × SR	**-.228**	**-2.50**	**.016**			

Note, FD, framewise displacement; SR, self-reflectiveness

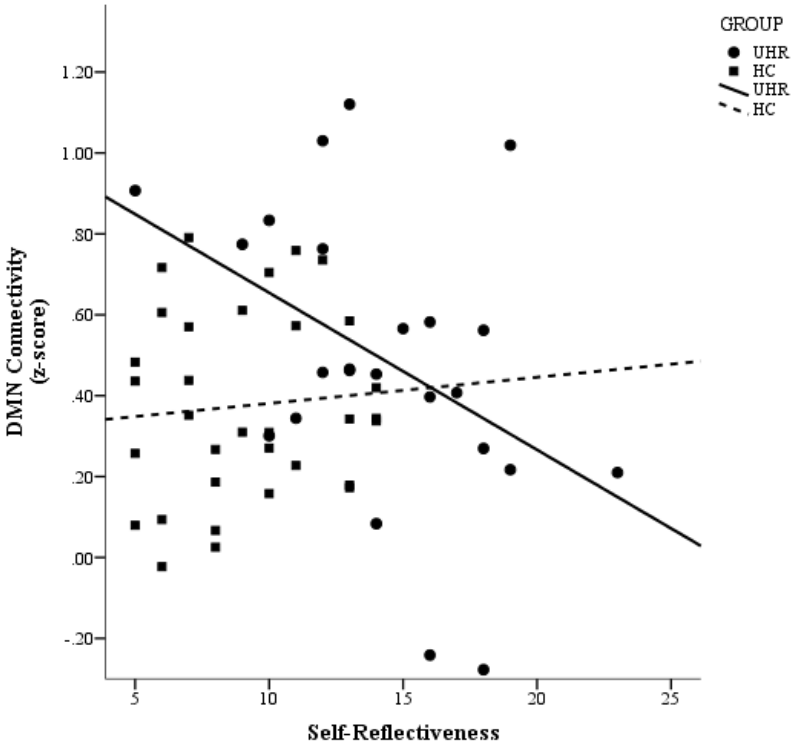

Figure 2 Scatterplot of connectivity values and self-reflectiveness by group, illustrating the significant group × self-reflectiveness interaction for ROI-to-ROI connectivity between the posterior cingulate and ventromedial prefrontal cortex.

3.3.2 Self-certainty and CEN, CON

The model for self-certainty predicting left crus I – right dlPFC connectivity was significant, adjusted R^2 = .27, $F(4, 52) = 6.23$, $p < .001$. The group × self-certainty interaction accounted for 8.9% of the variance in connectivity, $B = -.171$, $t = 2.62$, $p = .011$. Simple slopes analysis indicated that the slope of the regression line for the UHR group significantly differed from zero ($B = -.111$, $t = -2.00$, $p = .05$), but the slope of the regression line for the control group did not ($B = .059$, $t = 1.73$, $p = .089$). Table 5 and Figure 3 illustrate the significant results.

Table 5 Hierarchical regression for self-certainty (SC) and group predicting left crus I – right dorsolateral prefrontal cortex connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.223	15.79	.000
FD	-.119	-3.97	.000			
Step 2				.012	5.42	.003
FD	-.120	-3.92	.000			
SC	.013	.413	.681			
Group	-.052	-.848	.400			
Step 3				.089	6.24	.000
FD	**-.121**	**-4.17**	**.000**			
SC	.059	1.73	.089			
Group	-.039	-.672	.505			
Group × SC	**-.171**	**-2.62**	**.011**			

Note, FD, framewise displacement; SC, self-certainty

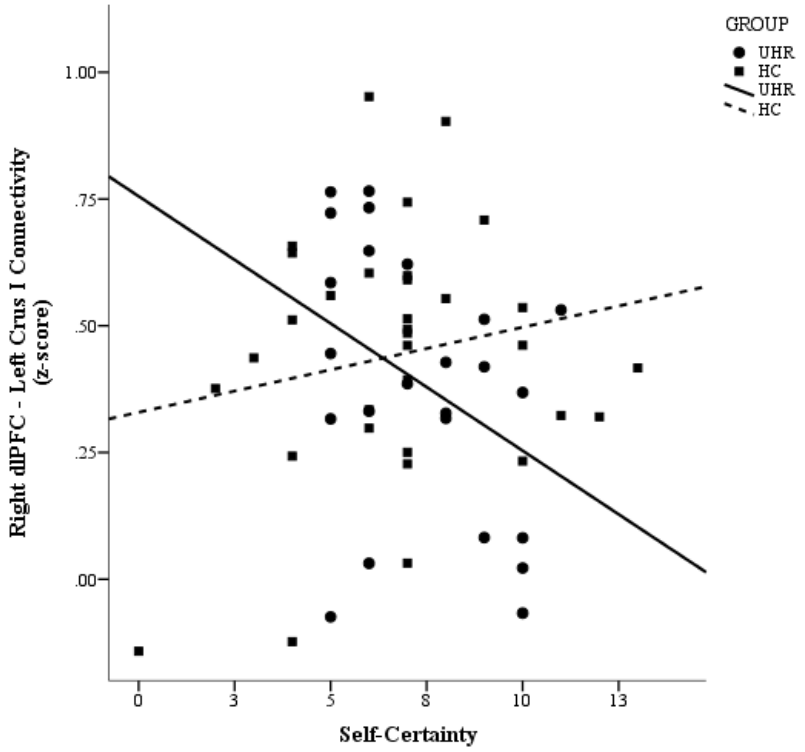

Figure 3 Scatterplot of connectivity values and self-certainty by group, illustrating the significant group × self-certainty interaction for ROI-to-ROI connectivity between the left crus I and right dorsolateral prefrontal cortex (dlPFC).

The model for self-certainty predicting left crus I – right anterior insula/frontal operculum connectivity was significant, adjusted R^2 = .17, $F(4, 52) = 3.87$, p = .008. The group × SC interaction accounted for 13.8% of the variance in connectivity, B = -.196, t = -3.06, p = .004.

Simple slopes analysis indicated that the slope of the regression line for the UHR group significantly differed from zero (B = -.168, t = -3.07, p = .003), but the slope of the regression line for the control group did not (B = .028, t = .821, p = .416). Table 6 and Figure 4 illustrate the significant results. Because negative symptoms correlated with both self-certainty and connectivity, the regression was tested with negative symptoms as a covariate and the regression remained significant, adjusted R^2 = .172, F(5, 51) = 3.33, p = .011.

No other regression models significantly predicted connectivity within the CEN.

Table 6 Hierarchical regression for self-certainty (SC) and group predicting left crus I – right anterior insula/frontal operculum connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.054	3.15	.082
FD	-.054	-1.77	.082			
Step 2				.037	1.77	.165
FD	-.052	-1.68	.099			
SC	-.026	-.831	.410			
Group	.080	1.30	.201			
Step 3				.138	3.87	.008
FD	-.053	-1.84	.071			
SC	.028	.821	.416			
Group	.094	1.64	.106			
Group × SC	**-.196**	**-3.06**	**.004**			

Note, FD, framewise displacement; SC, self-certainty

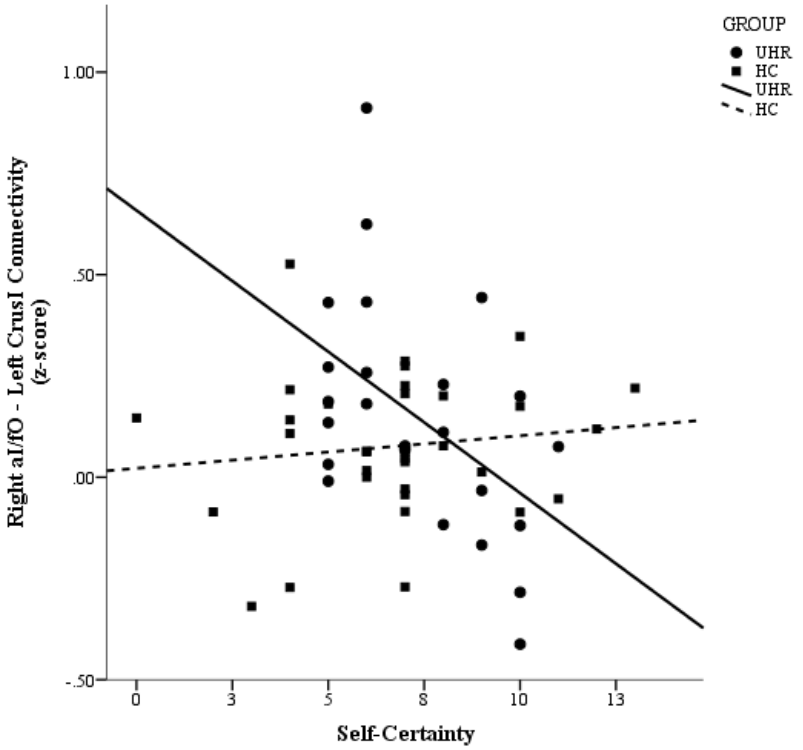

Figure 4 Scatterplot of connectivity values and self-certainty by group, illustrating the significant group × self-certainty interaction for ROI-to-ROI connectivity between the left crus I and right anterior insula/frontal operculum.

3.3.3 Cognitive insight and DMN, CEN, CON

The regression model predicting DMN connectivity showed main effects of head motion (B = .086, t = 2.32, p = .024) group (B = .199, t = 2.32, p = .024), and a significant interaction (B = -.195, t = -2.27, p = .027). The model was not significant when correcting for multiple comparisons (adjusted R^2 = .160, $F(4, 52) = 3.66$, p = .011). Regression models predicting CEN, CON, and cerebellar connectivity were not significant.

3.3.4 Clinical insight and DMN, CEN, CON

Hierarchical regression indicated a significant main effect of clinical insight on DMN connectivity (adjusted R^2 = .379, $F(2, 32) = 11.38$, $p < .001$; see Table 7 and Figure 5). Poorer clinical insight predicted significantly higher connectivity within the DMN (B = .058, t = 4.68, p

< .001). Clinical insight accounted for 40% of the variance in DMN connectivity. When this regression model was run with symptom severity as a covariate, the relationship remained significant (adjusted R^2 = .364, $F(3, 31) = 7.50$, p = .001). There was a significant main effect of head motion on right crus I – PCC connectivity (B = .852, t = 2.44, p = .020), but the model was not significant after multiple comparisons correction (adjusted R^2 = .152, $F(2, 32) = 4.06$, p = .027). Similarly, there was a significant main effect of head motion on DMN – CEN connectivity (B = 1.10, t = 2.13, p = .040), though the model was not significant after multiple comparisons correction (adjusted R^2 = .128, $F(2, 32) = 3.50$, p = .042). No other regression models significantly predicted connectivity within the CEN or CON, or between right crus I and left dlPFC or anterior insula/frontal operculum.

Table 7 Hierarchical regression for clinical insight impairment predicting default mode network connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.016	.554	.462
FD	.399	.744	.462			
Step 2				.399	11.38	.000
FD	.515	1.23	.229			
Impaired Clinical Insight	**.058**	**4.68**	**.000**			

Note, FD, framewise displacement

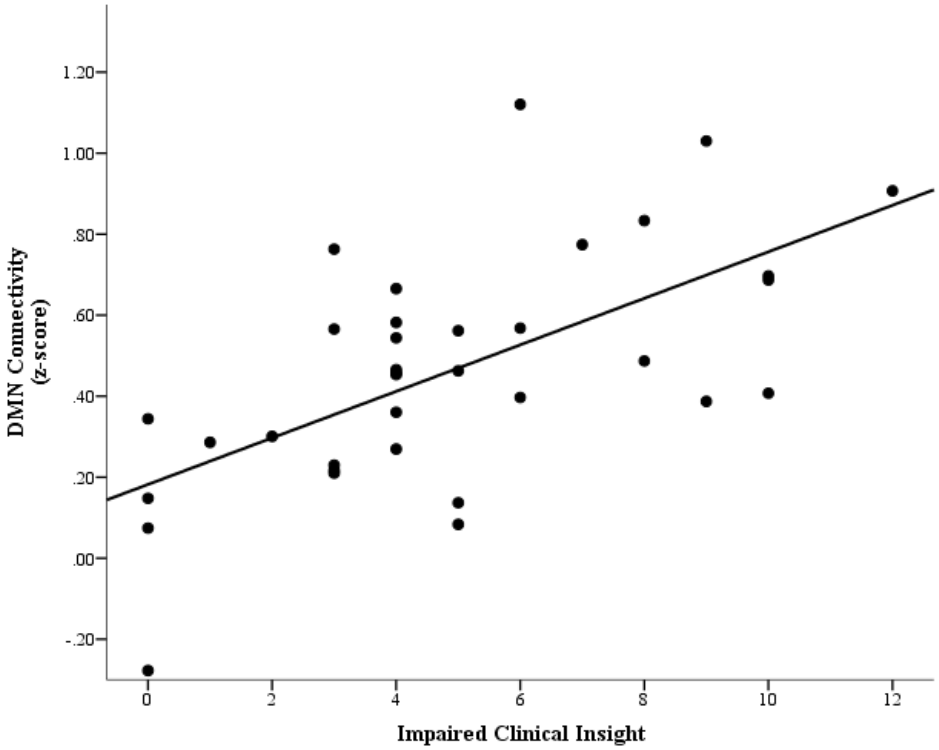

Figure 5 Scatterplot of default mode network (DMN) connectivity and clinical insight impairment,
illustrating the main effect of impaired clinical insight on DMN connectivity.

3.3.5 Clinical and cognitive insight and primary visual cortex

Hierarchical regression models predicting connectivity between the primary visual cortex and PCC and right dlPFC showed a main effect of head motion, but regression models were not significant after correction for multiple comparisons (see Tables 20 – 23 in Appendix B).

3.4 Seed-to-Voxel Connectivity

Significant results are reported based on the proposed method of analysis, though it was recently revealed that clusterwise correction for multiple comparisons is susceptible to false positives (Eklund, Nichols, & Knutsson, 2016). Therefore, these exploratory results should be

viewed as trends that should be replicated in a larger sample with more power. Connectivity maps for each seed ROI are presented in Appendix B.

The strongest seed-to-voxel result was a group × self-certainty interaction for connectivity between the left crus I seed and right middle frontal gyrus. The significant cluster was centered at MNI coordinates (45, 48, 15), with a peak T value of 4.82, $p_{FWE\text{-}corr} = .007$ (see Figure 6 and Table 24 in Appendix D). In this analysis, there was also a significant cluster in the anterior cingulate gyrus, centered at MNI coordinates (6, 33, 42), with a peak T value of 4.40, $p_{FWE\text{-}corr} = .035$.

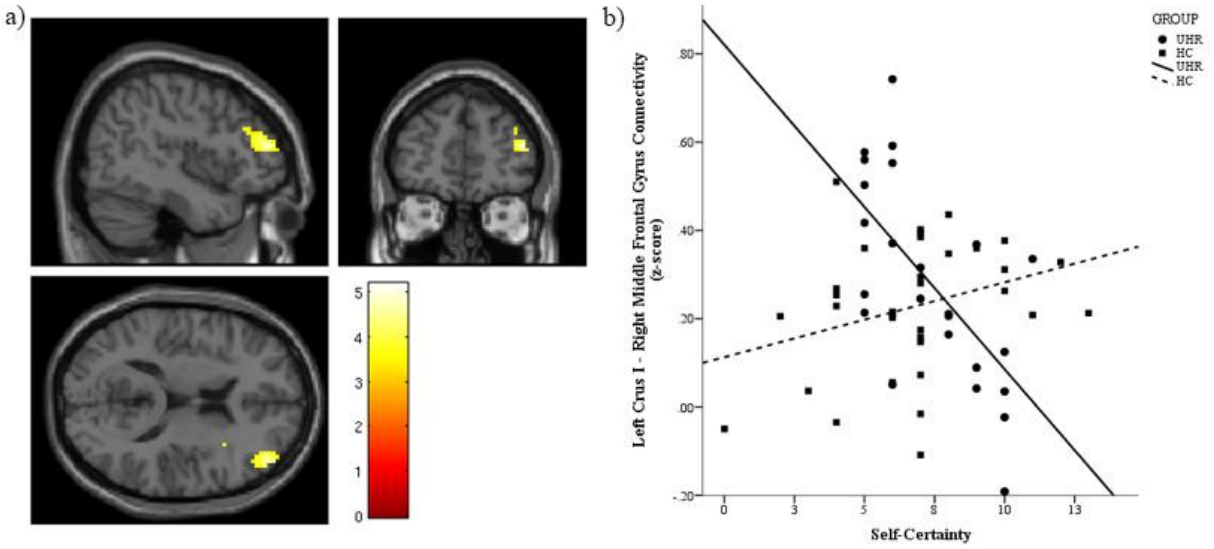

Figure 6 Significant interaction for self-certainty predicting connectivity between the left crus I and right middle frontal gyrus (dlPFC).
a) Significant cluster centered at MNI coordinates (45, 48, 15), with a cluster extent of 116 voxels. A cluster forming threshold of $p < .001$ was applied, and this cluster was significant at the cluster level with a familywise-corrected significance of $p = .007$. The color bar shows T values. b) Scatterplot of individual connectivity values (Fisher's *z* scores) extracted from the significant cluster displayed in a), plotted against self-certainty.

Further seed-to-voxel results that are more likely to be false positives are illustrated in Appendix D. There was a significant group × self-reflectiveness interaction for connectivity between the right crus I and left ventrolateral prefrontal cortex (vlPFC). The significant cluster

was centered at MNI coordinates (-33, 51, -6), with a peak T value of 4.88, $p_{FWE\text{-}corr}$ = .021 (Table 24, Figure 9). There was also a significant group × self-certainty interaction for connectivity between the right crus I seed and right middle frontal gyrus, centered at MNI coordinates (42, 48, 15) with a peak T value of 4.11, $p_{FWE\text{-}corr}$ = .038 (See Table 24, Figure 11). Similarly, there was a significant group × self-certainty interaction for connectivity between the right dlPFC seed and right crus I/II. The significant cluster was centered at MNI coordinates (30, -81, -33) with a peak T value of 4.47, $p_{FWE\text{-}corr}$ = .049 (see Table 24, Figure 11).

Seed-to-voxel analysis for clinical insight showed a significant main effect of clinical insight on connectivity between the PCC and vmPFC. The significant cluster was centered at MNI coordinates (-6, 30 0) with a peak T value of 4.78, $p_{FWE\text{-}corr}$ = .011 (see Figure 7).

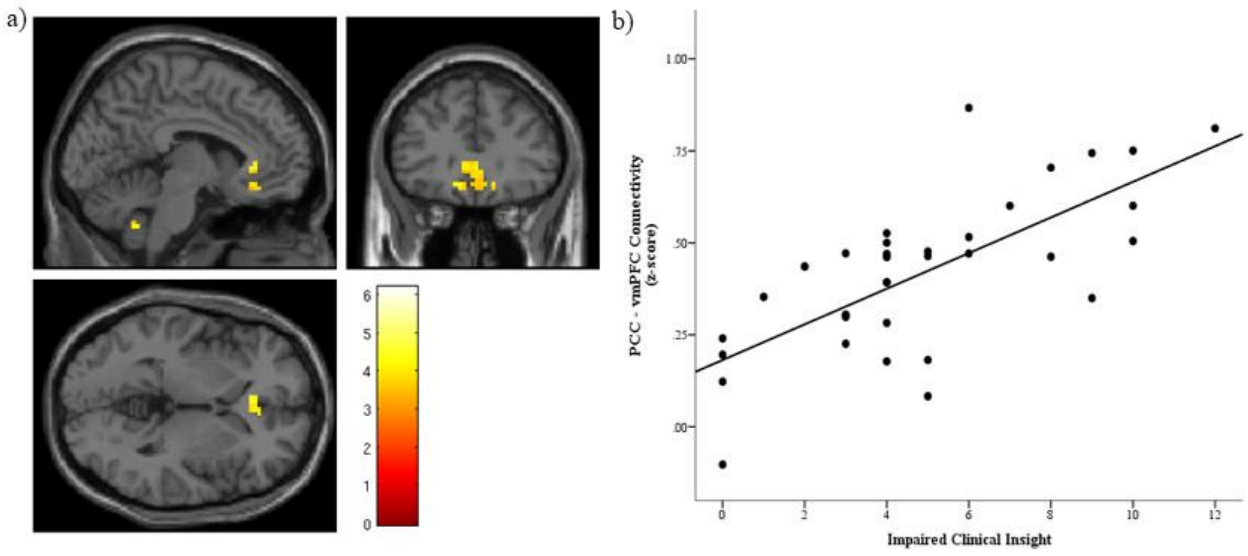

Figure 7 Significant main effect of clinical insight predicting connectivity between the posterior cingulate cortex (PCC) and ventromedial prefrontal cortex (vmPFC).
a) Significant cluster centered at MNI coordinates (-6, 30, 0), with a cluster extent of 113 voxels. A cluster forming threshold of $p < .001$ was applied, and this cluster was significant at the cluster level with a familywise-corrected significance of $p = .011$. The color bar shows T values. b) Scatterplot of individual connectivity values (Fisher's *z* scores) extracted from the significant cluster displayed in a), plotted against impaired clinical insight.

4 DISCUSSION

The strongest result of this study was that poorer clinical insight in UHR was related to stronger DMN connectivity, which was corroborated by exploratory analyses. In addition, this UHR sample reported higher self-reflectiveness than controls, and high self-reflectiveness was associated with stronger DMN connectivity in UHR but not in controls. Greater self-certainty in UHR was associated with lower connectivity between the left crus I and right prefrontal cortex. Exploratory findings also suggested that weaker posterior cerebellum – PFC connectivity was associated with greater self-reflectiveness and self-certainty in UHR adolescents. Two patterns emerged: first, in UHR adolescents, the default mode network (DMN) appears to be associated with self-reflective processes including clinical insight; second, connectivity between the cerebellum and lateral prefrontal cortex (PFC) appears to be related to cognitive insight subscales, especially self-certainty. These findings are broadly aligned with Shad et al.'s (2007) hypothesis of neurobiological underpinnings of insight, as different networks appear to be associated with self-reflective and cognitive aspects of insight.

4.1 Insight in UHR

4.1.1 Cognitive Insight

UHR reported higher self-reflectiveness and cognitive insight than controls, contrary to hypotheses. One explanation for this finding is that UHR adolescents' high self-reflectiveness may indicate "hyper-reflexivity" described by Sass (2014). Hyper-reflexivity includes both passive phenomena such as spontaneous auditory hallucinations, and (over)active self-reflection, so these adolescents may be thinking about their inner mental life more than others and also may be thinking differently to the average adolescent. UHR youths may be unsure what their

attenuated symptoms are and trying to make sense of them, so their confusion may be reported as high self-reflectiveness on the BCIS.

Sass and Parnas (Sass, 2014; Sass & Parnas, 2003) argued that the central disturbance in schizophrenia is a disordered sense of self, and that this disturbance can be linked to positive, negative, and cognitive symptoms. In addition, Nelson et al. (2012) found self-disturbance to be greater in UHR than controls, and found that a self-disturbance measure predicted transition to psychosis above and beyond other factors. Therefore, distorted self-reflection may be a core deficit in psychosis that begins early in the disease process and may be a way of identifying who is most at risk. Similar to the current study, Warman and Martin (2006) reported that delusion-proneness in non-psychotic college students was associated with both high self-reflectiveness and self-certainty, and Lyngberg et al. (2015) found a positive correlation between hallucinatory behavior and self-reflectiveness. These previous studies, and the evidence reported in this study, suggest that while individuals who are not psychotic but have psychotic-like experiences or attenuated positive symptoms may report *more* self-reflection, it appears that those who actually develop psychosis are less self-reflective (Riggs et al., 2012). Longitudinal research over several years would be the best way to confirm if the BCIS has good positive predictive value for UHR individuals, and whether UHR adolescents lose ability to self-reflect.

Alternatively, the relatively high parental education and IQ of our sample may indicate that despite being at-risk, these adolescents are relatively high-functioning and more able to self-reflect than other samples. It may be that within the UHR group, those individuals who demonstrate higher self-certainty and lower self-reflectiveness are more at-risk than others (Warman & Martin, 2006), but there was not enough power to investigate these subsets of

participants. As it is expected that approximately two-thirds of our sample will not develop psychosis, it is possible that high self-reflectiveness is a protective factor for some individuals.

The difference between UHR and control groups in cognitive insight, and the direction of the difference, appears to be driven by self-reflectiveness, as self-reflectiveness and cognitive insight were highly correlated. Further, because self-reflectiveness and self-certainty were not significantly correlated, it appears that self-reflectiveness and self-certainty are more informative as separate measures than the composite cognitive insight score, at least in individuals who have not been diagnosed with a psychotic disorder (Engh et al., 2007; Warman & Martin, 2006). Similarly, Winton-Brown et al. (2015) found that individuals with at-risk mental state (ARMS's) performance on tasks measuring jumping to conclusions (similar to self-certainty) and verbal self-monitoring (similar to self-reflectiveness) were not correlated, and reasoned that they are related to different cognitive processes.

The two previous studies of cognitive insight in UHR indicated only higher self-certainty than controls (Uchida et al., 2014), and no differences between controls and UHR (Kimhy et al., 2014). Our UHR group did report somewhat higher self-certainty than controls, which was also higher than Uchida's UHR and controls, but the difference was not significant. Thus, it is possible that high self-certainty is specific to psychosis or there was not enough power to detect a difference. It should be noted that the controls in this study reported lower self-reflectiveness than other studies of healthy participants (approximately one standard deviation lower than Martin et al. (2010)), so caution must be exercised in interpreting results in relation to controls. One explanation for this finding is that the controls may appear less self-reflective in comparison to UHR because they do not feel the three items referring to "unusual experiences" apply to them, and thus have a different reference point for these items (David et al., 2012; Engh et al.,

2007). While the two groups significantly differed in their responses to these items, when the items were removed from the self-reflectiveness subscale, there was still a significant group difference. Thus, it is unlikely that responses on these three items influenced the control group's low self-reflectiveness. Although a large study indicated that the BCIS is appropriate for control participants (Martin et al., 2010), the current sample appears to have responded differently and makes it difficult to draw conclusions about cognitive insight in UHR.

Investigations of cognitive insight and its relationship to clinical and cognitive measures in UHR revealed that higher self-certainty was related to better working memory and fewer negative symptoms, contrary to what was expected based on the limited schizophrenia literature (Nair et al., 2014). Concordantly, working memory and negative symptoms were positively correlated in this group. Thus, it appears that greater rigidity and tendency to jump to conclusions is actually associated with better working memory and a lower tendency for behaviors such as avolition and anhedonia in this UHR sample. A similar relationship was observed between working memory and self-certainty in the control group, which may indicate that these processes are not yet impaired in our sample, and potentially even protective. In addition, higher self-reflectiveness was associated with better social cognition, suggesting that ability to reflect on one's own mental states may be associated with understanding others' mental states and interacting socially. Self-reflectiveness was further correlated with higher IQ. Importantly, when potential leverage points were removed from the self-reflectiveness correlations, they became nonsignificant, and no correlations survived correction for multiple comparisons, indicating that these relationships are tenuous and require investigation in a larger sample. These correlations suggest that the UHR group demonstrated expected relationships between cognitive measures and self-reflectiveness, but unexpected relationships between

cognitive measures and self-certainty. As mentioned previously, these cognitive insight dimensions may be more useful separately, and self-certainty may be less informative in a UHR population than in a psychosis population.

Overall, it is difficult to make inferences about the nature of cognitive insight in our sample compared to control participants. UHR may be hyper-reflexive as suggested by Sass (2014), but it remains a possibility that self-reflectiveness and self-certainty are not impaired until the onset of psychosis. It also appears that the samples of UHR adolescents and controls under investigation can greatly influence group differences, as each study of cognitive insight in UHR has yielded different results. Further, it is possible that the BCIS is not tapping into the same phenomena in adolescents as it is in adults, as brain development and social processes are likely to affect self-reflectiveness and self-certainty (Brent et al., 2014). Investigating longitudinal properties of the BCIS in prodromal youth would be important in determining whether it is an informative measure during this period. Thus far, cognitive insight dimensions appear to be stable for one month in UHR (Lyngberg et al., 2015), but longer periods and larger samples are necessary.

4.1.2 Clinical Insight

UHR adolescents showed a range of clinical insight, though not as severely impaired as in schizophrenia, and most participants were considered by clinicians to be aware of their mental health difficulties (Amador et al., 1993; Michel et al., 2013; Parellada et al., 2011). In the only other UHR clinical insight study, Lappin et al. (2007) used a different clinical insight scale, but found clinical insight to be impaired in ARMS (as a percentage of total insight), and not as impaired as in first-episode psychosis (FEP). Their study also indicated that within the ARMS group, clinical insight was not significantly correlated with symptom severity, but when ARMS

and FEP were pooled (increasing degrees of freedom), there was a significant correlation, suggesting a relationship between clinical insight and symptom severity across the psychosis continuum and a potential neurodevelopmental course. Within the current UHR sample, poorer clinical insight was associated with more severe positive and negative symptoms, in line with the schizophrenia literature (Mintz et al., 2003), and suggesting that this relationship may indeed exist prior to onset of a psychotic disorder. Thus, clinical insight may be a potential point of early intervention when adolescents begin experiencing sub-threshold psychotic symptoms. There is limited evidence for insight improving with targeted therapy in schizophrenia (Pijnenborg, van Donkersgoed, David, & Aleman, 2013), so it may be worth investigating if this helps improve symptoms in UHR and even potentially prevents psychosis onset.

An important caveat with measuring clinical insight in UHR is that the range may be somewhat restricted in this sample compared to individuals with diagnosed psychotic disorders by the nature of the UHR definition. Specifically, if UHR adolescents are too unaware of their symptoms, they are likely to meet criteria for a psychotic disorder diagnosis and thus would be excluded from this study. Also, because the SUMD was developed for use with individuals with a psychotic disorder diagnosis, it may not be measuring the same construct in adolescents who have not been diagnosed yet, even though clinicians did report a range of awareness.

4.2 DMN and Insight

The strongest imaging result of this study was that greater DMN connectivity was associated with poorer clinical insight in UHR. Concomitantly, greater DMN connectivity was associated with lower self-reflectiveness in this group. However, self-reflectiveness was not associated with DMN connectivity in controls, contrary to hypotheses and previous literature linking the DMN with self-reflection in healthy individuals (Northoff et al., 2006; van der Meer

et al., 2010). Thus, perhaps those UHR youth that are not particularly self-reflective have hyper-connected DMN, or perhaps our control participants were not interpreting the BCIS in the same way as UHR participants, as suggested above. Therefore, the focus will be more on individual differences within UHR than on UHR compared to controls.

Results suggest that poorer insight is associated with DMN hyperconnectivity, in line with past research indicating hyperconnectivity and hyperactivity within the DMN in UHR (Shim et al., 2010) and schizophrenia (Whitfield-Gabrieli & Ford, 2012) compared to healthy controls. In addition, a previous study linked stronger DMN connectivity to poorer clinical insight in schizophrenia (Gerretsen et al., 2014), though between the PCC/precuneus and left angular gyrus and not between PCC/precuneus and vmPFC. However, the other connectivity and clinical insight study in schizophrenia indicated lower connectivity in the PCC and ACC in those with impaired clinical insight, but these researchers did not measure connectivity *between* PCC and ACC, and dichotomized clinical insight, in contrast to Gerretsen's and the current methods (Liemburg et al., 2012).

Further, studies employing self-reflection tasks implicated DMN structures in both self-reflection and insight (Ćurčić-Blake et al., 2015; Modinos, Renken, Ormel, & Aleman, 2011; van der Meer et al., 2013). One implicated the PCC and vmPFC during a clinical insight task that asked mental-illness related questions (Raij et al., 2012). Another associated self-reflectiveness with vmPFC activity during a self-reflection task in individuals with schizophrenia (van der Meer et al., 2013), and Ćurčić-Blake et al. (2015) found hyperconnectivity between the PCC and vmPFC during self-reflection in schizophrenia patients with poor clinical insight. In addition, another study indicated that a higher psychosis score was associated with higher activity of the vmPFC in healthy individuals with psychosis-prone traits (Modinos et al., 2011). Taken together,

these studies indicate that an overactive DMN may reflect an inability to disengage from internally-focused thought or overactive "tagging" of stimuli for self-relevance (Ćurčić-Blake et al., 2015), as well as difficulty in retrieving autobiographical memories (van der Meer et al., 2010). Disruption of these processes may result in a distorted view of the self in relation to others and illness, and it appears that they may be disrupted across the psychosis continuum.

This study is the first to find that higher DMN connectivity is associated with poorer clinical insight prior to psychosis onset, and it was shown in both ROI-to-ROI and seed-to-voxel analysis, strengthening confidence in the results. Thus, it appears that DMN hyperconnectivity is associated with poor illness awareness, and that this relationship is present in the high-risk state. This study is also the first to associate self-reflectiveness measured by the BCIS with DMN connectivity, and thus results support the dominant view that the DMN is associated with self-reflection generally (Northoff et al., 2006; van der Meer et al., 2010). As UHR adolescents who reported lower self-reflectiveness also demonstrated stronger DMN connectivity, a hyper-connected DMN may lead to an impaired ability to reflect on one's own thoughts generally and reflect on one's illness. If UHR adolescents are experiencing a breakdown in self-monitoring as one of the first signs of psychosis (Garety et al., 2001; Nelson et al., 2012; Sass, 2014), it is possible that this breakdown is associated with a hyperconnected DMN. Further research is required to determine if self-disturbance is associated with insight and the DMN, ideally combining clinical and cognitive insight measures, a self-disturbance measure, and neuroimaging.

While the current study presents compelling evidence that the DMN is associated with self-reflectiveness and clinical insight in UHR, hypotheses involving the CEN were not supported, suggesting that clinical insight in UHR is more closely related to self-awareness than

executive function. It may be the case that executive functioning has a greater impact on the ability to recognize one's illness after psychosis onset, or that insight is not directly associated with executive function networks, and rather, executive functioning may influence clinical insight through self-monitoring (Shad et al., 2007).

4.3 Cerebellum – Prefrontal Cortex Circuits and Insight

While clinical insight and self-reflectiveness were related to the DMN and thus self-related processing, self-certainty was associated with connectivity between the posterior cerebellum (crus I) and PFC, suggesting a relationship with executive function. However, as hypotheses involving the CEN were not supported, there may be a specific relationship between self-certainty and cerebello-cortical loops. Greater self-certainty in UHR was associated with lower connectivity between the left crus I and right anterior insula/frontal operculum (a node of the CON), as well as lower connectivity between the left crus I and right dlPFC (a node of the CEN). Because the cerebellum is thought to aid in efficiency of cognition and help free up prefrontal cognitive resources for complex tasks (Ramnani, 2006), it is possible that a disturbance in this system makes it more difficult for individuals to perform complex cognitive tasks, such as analyzing one's own thoughts and resisting jumping to conclusions.

Relatedly, Dosenbach and colleagues associated the posterior cerebellum – CON/CEN relationship with error detection (Dosenbach et al., 2006, 2008), and Klein et al. (2007) observed that the bilateral anterior insula was active during error processing as well. The anterior insula has consistently been implicated as an important region for sense of self, including introspection, salience, and interoception (Craig, 2009; Manoliu et al., 2014; Palaniyappan & Liddle, 2012; Sridharan, Levitin, & Menon, 2008). It is also postulated to be involved in schizophrenia, and particularly delusion, pathogenesis (Palaniyappan & Liddle, 2012; Raij, Mäntylä, Mantere,

Kieseppä, & Suvisaari, 2016). Craig (2009) suggested that the right anterior insula integrates emotional and interoceptive states, which may affect ability to recognize one's internal states as pathological. He also speculated that the junction of the anterior insula/frontal operculum is responsible for generating a representation of the self in the current moment. Therefore, reduced connectivity between crus I and anterior insula/frontal operculum in those with high self-certainty suggests that a failure of error detection in relation to self-perception may be associated with rigid overconfidence in one's cognitions, and inability to recognize incorrect cognitions.

Recent meta-analysis revealed that left crus I is consistently associated with executive functions broadly, as well as working memory, language, and emotion (Keren-Happuch et al., 2014). Low connectivity between crus I and the dlPFC was also found in schizophrenia, which may indicate that those individuals with high self-certainty and low crus I – dlPFC connectivity are more at-risk for schizophrenia. Koziol et al. (2009) posited that the cerebellum's role in executive function is specifying how to perform behavior—it helps with smoothly manipulating ideas for problem-solving. In addition, Küper et al. (2015) observed increasing cerebellar activation (including crus I) as a working memory task became more difficult, suggesting that the cerebellum offers "online" support to the cortex during more complex processes. Perhaps reduced connectivity in the current study reflects inability for the cerebellum to take over and automate self-certainty-related cognitions (Ramnani, 2006), and those UHR individuals with lower connectivity therefore make more errors in judgment.

Koziol and colleagues (2011) also argued that the cerebellum is sending "bad data" to the cortex in schizophrenia, resulting in impaired executive functions. Similar to crus I's relationship with the CON, poor error detection and less modulation of cognitive control via the dlPFC may result in more rigidity and unwillingness to reconsider one's cognitions, though more behavioral

data is needed to confirm this idea, particularly because UHR in this study with high self-certainty showed better working memory and there was no relationship with executive function measures. Notably, Gerretsen and colleagues (2014) also found their cognitive control ROIs in the dlPFC to be more weakly connected to cerebellar regions in individuals with greater self-certainty, though their results did not pass multiple comparisons correction. As these may be subtle effects, a larger sample than Gerretsen's and the current study may be necessary to test for specificity of these relationships.

Voxelwise analyses also suggested that posterior cerebellum – lateral PFC connectivity is related to self-reflectiveness and self-certainty in UHR adolescents, and there was overlap with the ROI-to-ROI results. While the seed-to-voxel results suggest potentially interesting cerebellar – PFC relationships, a recent paper highlighted that the threshold method used is susceptible to false positives (Eklund et al., 2016), and significant results are not particularly strong. Therefore, before firm conclusions can be drawn it would be necessary to replicate these findings with a more detailed study of sufficient power to detect voxelwise correction for multiple comparisons.

The group × self-certainty interaction in connectivity between the right dlPFC and the right crus I/II and between left crus I and the right middle frontal gyrus indicated a positive relationship in controls and a negative relationship in UHR. Both of these results echo what was found in ROI-to-ROI analyses, suggesting that the posterior cerebellum and right dlPFC may comprise an important network in the development of psychosis. The relationship between the left crus I and right dlPFC is particularly interesting, as it is the strongest seed-to-voxel result and is located near the effect observed between left crus I and right dlPFC in ROI-to-ROI analysis.

The group × self-reflectiveness interaction in connectivity between the right crus I and the left vlPFC revealed a positive relationship with self-reflectiveness in controls, but a negative

relationship in UHR. These results overlap with previous studies of insight implicating the inferior frontal gyrus in self-reflectiveness, self-reflection tasks, and clinical insight (Bedford et al., 2012; Buchy et al., 2014, 2015; van der Meer et al., 2013). As the result in this study was not particularly strong and potentially a false positive, replication is necessary.

Results from this study add to the increasing literature illustrating diverse functions of the cerebellum beyond motor functions, and suggest that the cerebellum should be incorporated into network models of psychosis (Bernard et al., 2014; Bernard & Mittal, 2015; Dean et al., 2013; Mittal et al., 2013). Many neuroimaging studies do not include the cerebellum, despite its potential importance for many cognitive processes. In fact, Nekovarova et al.'s (2014) triple network argument alludes to the cerebellum in self-disturbance because they describe self-disturbance as a disconnect between predicted and perceived consequences, through efference copies and forward and inverse models (activities ascribed to the cerebellum; Ramnani, 2006). A recent theoretical article argued that the cerebellum may even be centrally involved in the development of self, so abnormal development of the cerebellum may lead to disorders in which self-awareness is impaired, such as schizophrenia (Ceylan, Dönmez, & Ülsalver, 2015). In relation to insight, the cerebellum may help to maintain a stable sense of self during retrieval of autobiographical memories and self-projection into future or others' mental states. Thus, if the internal models of the cerebellum are not functioning optimally, the individual may not have the correct self-reference point and make errors in judgment, possibly reflected in high self-certainty.

4.4 Limitations

This study does not come without limitations. First, the sample size was small, limiting power to detect subtle differences and generalizability. In addition, although previous research has demonstrated that the BCIS is useful for studying healthy controls (Buchy et al., 2014;

Martin et al., 2010), it is possible that in an adolescent population such as this one, the scale is not as relevant or is not measuring the same construct. This study highlights the importance of a BCIS validation study in adolescents—both healthy controls and UHR. By nature of this sample, there was also a limited range of clinical insight compared to studies of schizophrenia because adolescents with severely impaired clinical insight would be diagnosed with schizophrenia. Again, it may be more informative to use a clinical insight scale more tailored to the UHR population.

The nature of neuroimaging also introduces potential confounds, as MRI signals can be contaminated with noise, even when controlled for using recommended methods. Nuisance signals were regressed out using recommended methods, and head motion was entered as a covariate in our second-level analyses, but it is always possible that signals are arising from unknown sources (Weinberger & Radulescu, 2015). However, as results do broadly align with other studies of insight in psychosis, they do likely represent consistent brain networks associated with clinical and cognitive insight. Further, the methods used in this study cannot infer causation or directionality of connectivity, as it was a cross-sectional study. In the future, it may be useful to use methods such as dynamic causal modeling or Granger causality to infer which network nodes are influencing each other and to what degree.

4.5 Future Directions

The original study for which these data were collected at the University of Colorado, Boulder is still ongoing, with follow-up data for many participants. Therefore, in the future it will be possible to see who developed psychosis and who did not, and investigate whether insight and/or connectivity have good positive predictive value. It would also be informative to examine subsets of the UHR group who have high self-certainty and low self-reflectiveness compared to

previous literature, to see if they differ from the rest of the group in symptoms or other cognitive measures or if they have a different neurodevelopmental trajectory. Because the control group in this study may not have had the most reliable BCIS scores, it may be more valuable to compare cognitive insight dimensions in those who transition versus those who do not. Ultimately, it would be most useful to understand whether clinical and/or cognitive insight can predict who will develop a psychotic disorder and who will benefit from psychosocial or treatments targeting self-reflection or self-certainty, or even neurostimulation treatments.

4.6 Summary

In summary, these results lend some support to the triple network-inspired model of psychosis symptoms that proposed impaired coordination within and between large-scale networks may underlie self-disturbance that precedes and then contributes to the wide array of symptoms seen in psychosis (Nekovarova et al., 2014). It also partially supports Shad et al.'s (2007) theoretical model implicating executive function and self-awareness in different dimensions of insight. Specifically, the DMN appears to be particularly important, as evidenced by previous work and the current study. In this UHR sample, poorer clinical insight was associated with more positive and negative symptoms and a hyperconnected DMN. Low self-reflectiveness also appears to also be associated with a hyperconnected DMN, suggesting that a hyperconnected DMN in UHR, as observed in previous literature, may reduce the ability to self-reflect and recognize one's mental problems. The differences between controls and UHR in reported self-reflectiveness appear to be tenuous, but may suggest hyper-reflexivity in UHR proposed by Sass and Nekovarova, which may also be supported by the DMN connectivity results (Nekovarova et al., 2014; Sass, 2014).

Greater self-certainty in UHR appears to be associated with weaker connectivity between the cerebellum and prefrontal cognitive control regions, which may indicate poor coordination of self-related cognition and poor control over cognition. Despite not finding differences in self-certainty between controls and UHR, reduced connectivity between crus I and the lateral PFC in individuals with high levels of self-certainty suggests a potential neural basis for errors in judgment or jumping to conclusions that can be studied longitudinally across the psychosis continuum. If the cerebellum is not efficiently modulating cognitive processes in concert with major intrinsic networks (Buckner et al., 2011; Koziol et al., 2009; Ramnani, 2006), consequences may include judgment errors and an impaired sense of self, and it is possible that this dysregulation leads to psychosis (Andreasen & Pierson, 2008). With further research, clinical and cognitive insight and associated brain networks may indicate potential risk factors and psychosocial, cognitive, or brain stimulation interventions to prevent psychosis.

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APPENDICES

Appendix A Correlations among insight, clinical, and cognitive measures.

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
1. Self-Reflectiveness												
2. Self-Certainty	-.198 N=32											
3. Cognitive Insight	.853** N=32	-.681** N=32										
4. Clinical Insight	-.230 N=29	-.269 N=29	-.025 N=29									
5. Positive Symptoms	.111 N=32	-.295 N=32	.240 N=32	.465** N=52								
6. Negative Symptoms	.073 N=32	-.432* N=32	.285 N=32	.318* N=52	.422** N=55							
7. Processing Speed	.217 N=26	.309 N=26	-.001 N=26	-.241 N=44	-.113 N=45	-.187 N=45						
8. Working Memory	.272 N=27	.382* N=27	.000 N=27	-.166 N=46	-.004 N=47	.358* N=47	.536** N=45					
9. Problem Solving	.216 N=27	.022 N=27	.158 N=27	-.068 N=46	-.160 N=47	-.145 N=47	.406** N=45	.343* N=47				
10. Social Cognition	.424* N=27	.362 N=27	.080 N=27	-.030 N=46	.125 N=47	.045 N=47	.416** N=45	.271 N=47	.315* N=47			
11. Executive Function (Trails B – Trails A)	-.127 N=19	-.300 N=19	-.264 N=19	.105 N=19	-.115 N=19	.287 N=19	-.049 N=19	.011 N=19	.251 N=19	.446 N=19		
12. IQ (WRAT)	.426* N=25	.033 N=25	.289 N=25	-.008 N=42	.399** N=43	-.091 N=43	.035 N=41	.201 N=43	-.120 N=43	.050 N=43	-.492* N=27	

* correlation is significant at the .05 level; ** correlation is significant at the .01 level

Appendix B Results of nonsignificant ROI-to-ROI regression analyses

Table 8 Hierarchical regression for group and self-certainty (SC) predicting right CEN connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.000	.023	.879
FD	-.007	-.153	.879			
Step 2				.097	1.90	.141
FD	-.017	-.387	.700			
SC	.060	1.36	.180			
Group	.155	1.78	.081			
Step 3				.000	1.40	.248
FD	-.017	-.384	.702			
SC	.061	1.17	.247			
Group	.156	1.76	.084			
Group × SC	-.004	-.040	.968			

Table 9 Hierarchical regression for group and self-reflectiveness (SR) predicting right crus I – PCC connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.038	2.18	.146
FD	.046	1.48	.146			
Step 2				.025	1.18	.326
FD	.046	1.47	.147			
SR	.026	.664	.510			
Group	.029	.372	.711			
Step 3				.010	1.02	.404
FD	.050	1.57	.123			
SR	.061	1.01	.317			
Group	.030	.382	.704			
Group × SR	-.061	-.763	.449			

Table 10 Hierarchical regression for group and cognitive insight (CI) predicting DMN connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.074	4.38	.041
FD	.080	2.09	.041			
Step 2				.069	2.93	.042
FD	.072	1.89	.064			
CI	-.065	-1.47	.146			
Group	.177	2.00	.051			
Step 3				.077	3.66	.011
FD	**.086**	**2.32**	**.024**			
CI	.026	.438	.663			
Group	**.199**	**2.32**	**.024**			
Group × CI	**-.195**	**-2.26**	**.027**			

Table 11 Hierarchical regression for group and cognitive insight (CI) predicting right crus I – PCC connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.038	2.18	.146
FD	.046	1.48	.146			
Step 2				.017	1.03	.387
FD	.045	1.44	.156			
CI	.004	-.121	.904			
Group	.056	.762	.449			
Step 3				.000	.760	.556
FD	.046	1.42	.161			
CI	.008	.152	.880			
Group	.057	.761	.450			
Group × CI	-.007	-.095	.925			

Table 12 Hierarchical regression for group and cognitive insight (CI) predicting left crus I – right dlPFC connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.223	15.79	.000
FD	-.119	-3.97	.000			
Step 2				.016	5.55	.002
FD	-.116	-3.79	.000			
CI	.024	.675	.502			
Group	-.074	-1.04	.303			
Step 3				.004	4.17	.005
FD	**-.118**	**-3.81**	**.000**			
CI	.007	.136	.892			
Group	-.078	-1.09	.283			
Group × CI	.037	.515	.609			

Table 13 Hierarchical regression for group and cognitive insight (CI) predicting right CEN connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.000	.023	.879
FD	-.007	-.153	.879			
Step 2				.71	1.36	.265
FD	-.012	-.279	.782			
CI	-.030	-.587	.560			
Group	.201	1.95	.057			
Step 3				.007	1.11	.360
FD	-.007	-.162	.872			
CI	.001	.018	.986			
Group	.209	2.00	.051			
Group × CI	-.068	-.647	.520			

Table 14 Hierarchical regression for group and cognitive insight (CI) predicting left crus I – right anterior insula/frontal operculum connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.054	3.15	.082
FD	-.054	-1.77	.082			
Step 2						
FD	-.055	-1.78	.080	.025	1.52	.221
CI	-.001	-.036	.971			
Group	.075	1.04	.303			
Step 3				.000	1.12	.357
FD	-.056	-1.76	.084			
CI	-.006	-.117	.908			
Group	.074	1.01	.318			
Group × CI	.010	.132	.895			

Table 15 Hierarchical regression for clinical insight impairment predicting right crus I – PCC connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.138	5.27	.028
FD	.818	2.30	.028			
Step 2				.065	4.06	.027
FD	**.852**	**2.44**	**.020**			
Impaired Clinical Insight	.017	1.61	.118			

Table16 Hierarchical regression for clinical insight impairment predicting right CEN connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.000	.002	.962
FD	-.030	-.047	.962			
Step 2				.033	.552	.581
FD	-.070	-.110	.913			
Impaired Clinical Insight	-.020	-1.05	.302			

Table 17 Hierarchical regression for clinical insight impairment predicting left crus I – right anterior insula/frontal operculum connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.008	.257	.615
FD	-.254	-.507	.615			
Step 2				.008	.256	.776
FD	-.238	-.470	.641			
Impaired Clinical Insight	.008	.509	.614			

Table 18 Hierarchical regression for clinical insight impairment predicting left crus I – right dlPFC connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.131	4.991	.032
FD	-.943	-2.23	.032			
Step 2				.006	2.55	.094
FD	-.931	-2.18	.037			
Impaired Clinical Insight	.006	.477	.637			

Table 19 Hierarchical regression for clinical insight impairment predicting connectivity between the DMN and CEN.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.107	3.95	.055
FD	1.05	1.99	.055			
Step 2				.073	3.50	.042
FD	**1.10**	**2.13**	**.040**			
Impaired Clinical Insight	.026	1.68	.102			

Table 20 Hierarchical regression for group and self-reflectiveness (SR) predicting primary visual cortex – PCC connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.153	11.13	.002
FD	.127	3.34	.002			
Step 2				.020	4.11	.011
FD	.129	3.35	.001			
SR	.053	1.10	.276			
Group	-.039	-.399	.692			
Step 3				.000	3.02	.026
FD	**.128**	**3.27**	**.002**			
SR	.049	.667	.508			
Group	-.039	-.396	.694			
Group × SR	.006	.065	.948			

Table 21 Hierarchical regression for clinical insight impairment predicting primary visual cortex – PCC connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.170	6.77	.014
FD	1.33	2.60	.014			
Step 2				.004	3.37	.047
FD	**1.32**	**2.54**	**.016**			
Impaired Clinical Insight	-.006	-.390	.699			

Table 22 Hierarchical regression for group and self-certainty predicting primary visual cortex – right dlPFC connectivity.

Predictor	*B*	*t*	*p*	ΔR^2	*F*	*p*
Step 1				.213	14.91	.000
FD	.111	3.86	.000			
Step 2				.001	4.83	.005
FD	.112	3.76	.000			
SC	-.002	-.078	.938			
Group	.019	.313	.756			
Step 3				.012	3.81	.009
FD	**.111**	**3.74**	**.000**			
SC	.014	.401	.690			
Group	.023	.386	.701			
Group × SC	-.060	-.902	.371			

Appendix C Connectivity maps of seeds of interest

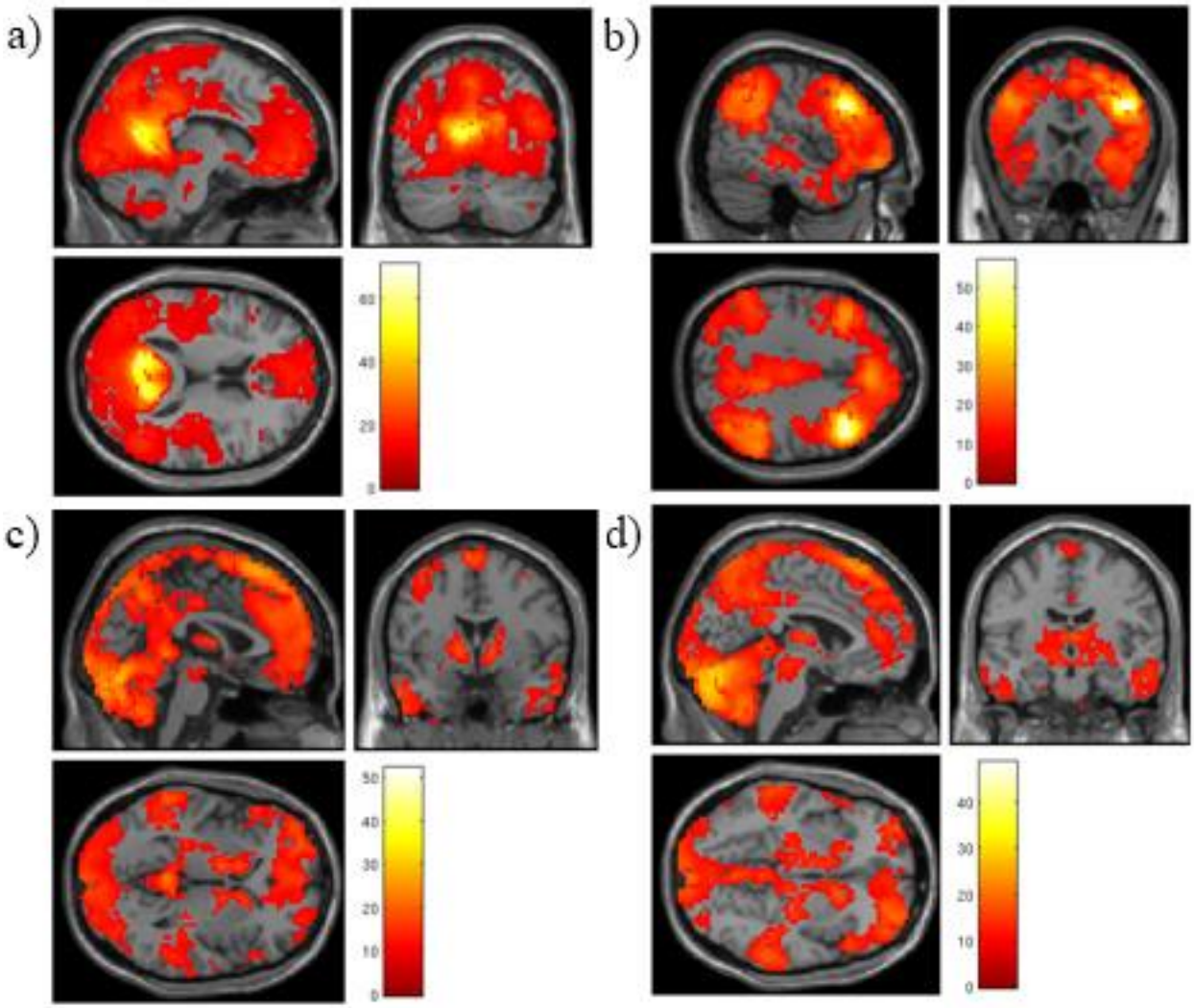

Figure 8 Connectivity maps of seeds of interest used for seed-to-voxel analysis. a) PCC, b) right dorsolateral prefrontal cortex (dlPFC), c) right crus I, d) left crus I. Maps were created by running a one sample t test in SPM8, with all subjects combined. Results were (arbitrarily) thresholded with a minimum T value of 10 in order to demonstrate areas of maximal connectivity. The color bar shows T values.

Appendix D Seed-to-voxel Connectivity Results

Table 23 Significant seed – voxel clusters for Group × self-reflectiveness (SR) or self-certainty (SC) interactions (indicated in the table as SR or SC). Models were specified in Statistical Parametric Mapping (SPM) using the flexible factorial approach, including framewise displacement (FD) as a covariate of no interest. A cluster-forming threshold of $p < .001$ was applied, and clusters were considered significant if they passed cluster FWE-corrected $p < .05$.

Region	Number of Voxels	MNI Coordinates (x, y, z)	Brodmann Area	T value	$p_{FWE\text{-}corrected}$
Right Crus I Seed (SR)					
L Middle Frontal Gyrus (Orbital)	85	-33, 51, -6	47	4.88	.021
L Frontal Inferior Triangle		-51, 42, 0	45	4.24	
L Middle Frontal Gyrus		-42, 51, 3	46	4.14	
Right Crus I Seed (SC)					
R Middle Frontal Gyrus	72	42, 48, 15	46	4.11	.038
R Middle Frontal Gyrus		48, 36, 21	45	4.06	
Left Crus I Seed (SC)					
R Middle Frontal Gyrus	116	45, 48, 15	46	4.82	.007
R Middle Frontal Gyrus		42, 42, 21	45	4.45	
R Frontal Inferior Triangle		51, 30, 27	45	4.25	
R Superior Frontal Gyrus	76	6, 33, 42	8	4.40	.035
R Anterior Cingulate		9, 42, 24	32	3.74	
R Supplementary Motor Area		6, 24, 48	8	3.59	
Right dlPFC Seed (SC)					.049
R Crus I	73	30, -81, -33	NA	4.47	
R Crus II		21, -72, -39	NA	4.06	
R Crus I		12, -87, -24	NA	3.55	

Note, R, right; L, left; SR, self-reflectiveness; SC, self-certainty

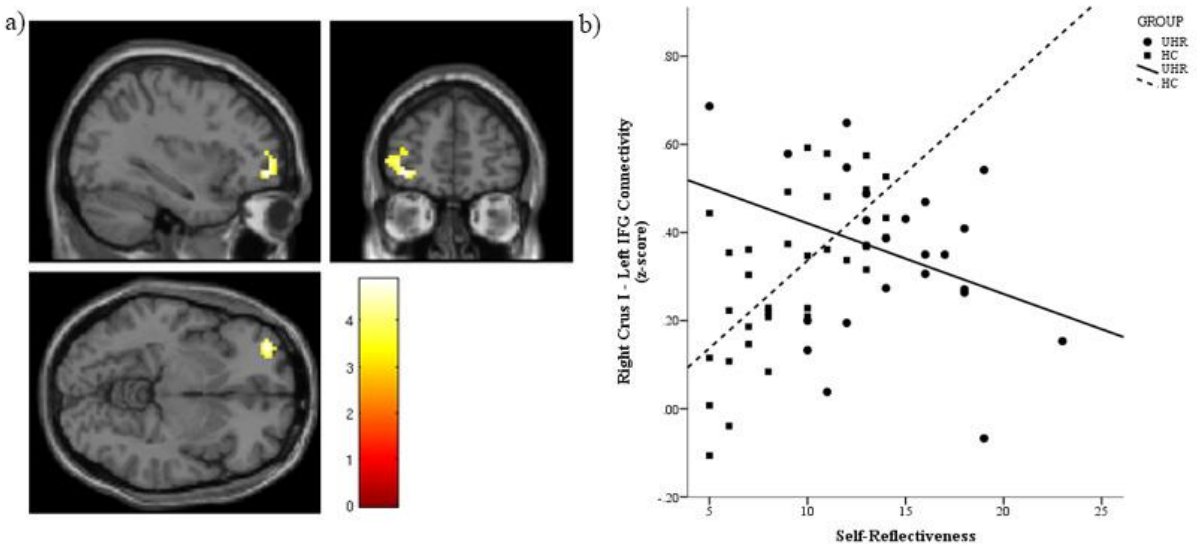

Figure 9 Significant interaction for self-reflectiveness predicting connectivity between the right crus I seed and left ventrolateral prefrontal cortex (vlPFC). a) Significant cluster centered at MNI coordinates (-33, 51, -6), with a cluster extent of 85 voxels. A cluster forming threshold of $p <$ .001 was applied, and this cluster was significant at the cluster level with a familywise-corrected significance of $p = .021$. The color bar shows T values. b) Scatterplot of individual connectivity values (Fisher's *z* scores) extracted from the significant cluster displayed in a), plotted against self-certainty.

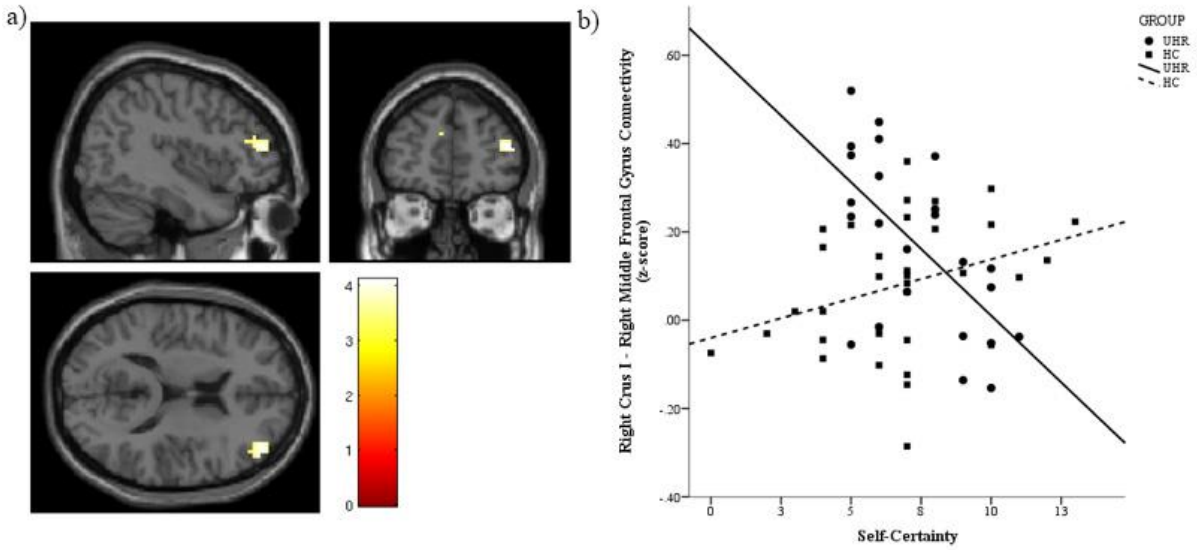

Figure 10 Significant interaction for self-certainty predicting connectivity between the right crus I seed and right middle frontal gyrus. a) Significant cluster centered at MNI coordinates (42, 48, 15), with a cluster extent of 46 voxels. A cluster forming threshold of $p <$ .001 was applied, and this cluster was significant at the cluster level with a familywise-corrected significance of $p =$ .038. The color bar shows T values. b) Scatterplot of individual connectivity values (Fisher's *z* scores) extracted from the significant cluster displayed in a), plotted against self-certainty.

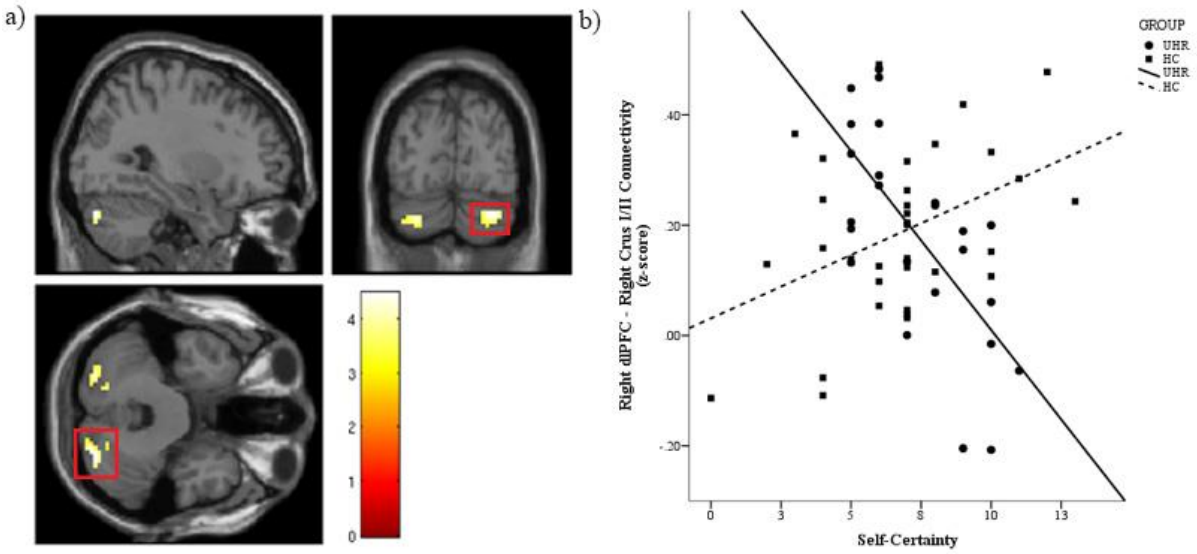

Figure 11 Significant interaction for self-certainty predicting connectivity between the right dorsolateral prefrontal cortex (dlPFC) seed and right crus I/II. a) Significant cluster centered at MNI coordinates (30, -81, -33), with a cluster extent of 116 voxels. A cluster forming threshold of $p < .001$ was applied, and this cluster was significant at the cluster level with a familywise-corrected significance of $p = .049$. The significant cluster has a red box around it and the color bar shows T values. b) Scatterplot of individual connectivity values (Fisher's *z* scores) extracted from the significant cluster displayed in a), plotted against self-certainty.

Appendix E Participant Demographics for Subsets in Imaging Analyses

Table 24 Demographic characteristics of sample with imaging data for cognitive insight analyses.

	Healthy Control (N = 33)	UHR (N = 24)	Tests	Significance
Age	19.70 ± 1.78	19.17 ± 1.52	t = -1.18	.243
Gender (M/F)	14/19	14/10	χ^2 = 1.41	.289
Handedness (R/L)	24/3	19/1	χ^2 = .551	.626
Race (White/Non-White)	24/12	17/16	χ^2 = 1.64	.228
WRAT Sum IQ (N = 26/19)	**104.92 ± 10.26**	**113.63 ± 12.92**	***t* = 2.52**	**.016**
Framewise Displacement	0.200 ± 0.071	0.204 ± 0.096	t = 0.186	.853
Mother's Education	15.70 ± 3.00	15.30 ± 1.55	t = -0.640	.525
Father's Education	15.12 ± 4.27	15.22 ± 3.55	t = .089	.930
GAF Current	**86.45 ± 5.52**	**65.09 ± 15.34**	***t* = -6.40**	**< .001**
Positive Symptoms		11.54 ± 4.88		
Negative Symptoms		8.87 ± 6.85		
Disorganized Symptoms		5.13 ± 3.76		
General Symptoms		6.71 ± 4.39		

Table 25 Demographic characteristics of the sample with imaging data for clinical insight analyses.

	UHR (N = 35)
Age	18.80 ± 1.72
Gender (M/F)	23/12
Handedness (R/L)	27/1
Race (White/Non-White)	23/11
WRAT Sum IQ	111.31 ± 12.55
Framewise Displacement	0.195 ± 0.093
Mother's Education	15.50 ± 1.76
Father's Education	15.24 ± 3.22
GAF Current	63.14 ± 15.40
Positive Symptoms	12.23 ± 5.80
Negative Symptoms	9.17 ± 7.12
Disorganized Symptoms	5.63 ± 4.07
General Symptoms	6.66 ± 4.67
Awareness of Mental Disorder	2.14 ± 1.42
Awareness of Medication Effects	1.00 ± 1.39
Awareness of Social Consequences	1.74 ± 1.56
Total Clinical Insight	4.89 ± 3.13