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Stronger default mode network connectivity is associated with poorer clinical insight in youth at ultra high-risk for psychotic disorders

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ABSTRACT

Impaired clinical insight (CI) is a common symptom of psychotic disorders and a promising treatment target. However, to date, our understanding of how variability in CI is tied to underlying brain dysfunction in the clinical high-risk period is limited. Developing a stronger conception of this link will be a vital first step for efforts to determine if CI can serve as a useful prognostic indicator. The current study investigated whether variability in CI is related to major brain networks in adolescents and young adults at ultra high-risk (UHR) of developing psychosis. Thirty-five UHR youth were administered structured clinical interviews as well as an assessment for CI and underwent resting-state magnetic resonance imaging scans. Functional connectivity was calculated in the default mode network (DMN) and fronto-parietal network (FPN), two major networks that are dysfunctional in psychosis and are hypothesized to affect insight. Greater DMN connectivity between the posterior cingulate/precuneus and ventromedial prefrontal cortex (DMN) was related to poorer CI ($R^2 = 0.399$). There were no significant relationships between insight and the FPN. This is the first study to relate a major brain network to clinical insight before the onset of psychosis. Findings are consistent with evidence if a hyperconnected DMN in schizophrenia and UHR, and similar to a previous study of insight and connectivity in schizophrenia. Results suggest that a strongly connected DMN may be related to poor self-awareness of subthreshold psychotic symptoms in UHR adolescents and young adults.

1. Introduction

Clinical insight (CI) in schizophrenia refers to an individual's awareness of having the disorder (Amador and Kronengold, 2004). It is estimated that approximately 50% of those diagnosed with schizophrenia are unaware of their illness (Arango and Amador, 2011) and CI may predict treatment adherence and outcomes (Lincoln et al., 2007). Insight deficits are likely related to neurological dysfunction (Larøi et al., 2004), and many studies have associated distributed brain regions with CI in schizophrenia (Gerretsen et al., 2014b; Liemburg et al., 2012; Morgan et al., 2010; Shad and Keshavan, 2015). However, little is known about how variability in CI is related to brain function in youth exhibiting a prodromal syndrome (i.e., those at ultra high-risk for psychosis; UHR). Further, investigating CI prior to psychosis onset may reveal whether it is a good prognostic or diagnostic indicator and also yield important clues that can inform intervention. Thus, the aim of this study was to investigate relationships between CI and function of major brain networks in UHR youth.

In psychotic disorders, degree of CI is considered to lie on a continuum and to consist of multiple dimensions on which an individual may be impaired (Amador et al., 1993; Beck et al., 2004; Birchwood et al., 1994; David, 1990; Gerretsen et al., 2014a; Marková et al., 2003; McEvoy et al., 1981). Insight is relatively stable (Arango and Amador, 2011), but may fluctuate with symptom severity (Parellada et al., 2011; Quee et al., 2014). However, symptoms alone do not predict CI (Mintz et al., 2003; van der Meer et al., 2013). In addition, insight tends to predict treatment adherence in schizophrenia and may predict general function or specific social or work capacities (Lincoln et al., 2007).

Poor CI may be a risk factor for psychotic episodes because it appears to worsen with acute episodes and improve with treatment (Gerretsen et al., 2014c). Despite evidence linking insight impairment to acute

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episodes, there is little research on CI before psychosis onset. The only study of CI in UHR thus far found it to be moderately impaired, but less impaired than in first episode psychosis (Lappin et al., 2007). CI was not correlated with symptom severity in the UHR group, suggesting that it accounts for unique variance in the UHR phenotype. A retrospective chart review study of patients diagnosed with schizophrenia revealed that insight assessed by emergency department physicians declined leading up to a first psychotic episode and better insight at baseline predicted fewer and shorter hospitalizations as well as better treatment compliance (Bota et al., 2006). Investigating CI and related brain networks during the psychosis prodrome may offer valuable information regarding prognosis and diagnosis.

Most researchers agree that insight deficits are associated, at least in part, with neurological dysfunction (Larøi et al., 2004). Structural studies suggest that impaired CI is largely associated with reduced frontal gray matter, as well as reduced gray matter in temporal, parietal, and subcortical regions (Bergé et al., 2011; Buchy et al., 2011; Cooke et al., 2008; Flashman et al., 2001; Gerretsen et al., 2013; Morgan et al., 2010; Sapara et al., 2007; Shad et al., 2004; Spalletta et al., 2014). However, methods vary widely and some studies have found no gray matter differences between those with poor and good CI (Bassitt et al., 2007; McFarland et al., 2013; Rossell et al., 2003). Task-based functional studies of insight and self-reflection have illustrated an important role for the medial prefrontal cortex, and have implicated lateral frontal and parietal regions as well (Ćurčić-Blake et al., 2015; Shad et al., 2012; Shad and Keshavan, 2015).

Structural and functional findings that CI is associated with widespread regions suggest that networks of brain regions may work together to influence insight. Resting-state functional connectivity (rsFC) studies have illustrated that CI is associated with connectivity of the default mode network (DMN) and self-referential regions, including areas in the medial and lateral frontal and parietal lobes (Gerretsen et al., 2014b; Liemburg et al., 2012). These two studies presented conflicting findings, however, so it is still unclear how CI variation is related to connectivity of brain networks in psychotic disorders.

Nodes of the DMN have been associated with self-referential processing and social cognition, including theory of mind and distinguishing self from others (Li et al., 2014; Northoff et al., 2006; Qin and Northoff, 2011; Schilbach et al., 2008). It appears to be dysfunctional in disorders marked by social cognitive deficits, such as autism, schizophrenia, and attention deficit/hyperactivity disorder (Broyd et al., 2009; Di Martino et al., 2009; Whitfield-Gabrieli and Ford, 2012). In schizophrenia, many studies have shown hyperconnectivity of the DMN and abnormal rsFC of the dorsolateral prefrontal cortex (dlPFC) (the primary node of the fronto-parietal control network (FPN)), though the literature is mixed (Sheffield and Barch, 2016; Whitfield-Gabrieli and Ford, 2012).

Function of the DMN and FPN may contribute to CI deficits (Shad et al., 2007) through challenges in distinguishing self from other and making decisions in regards to oneself, as well as inflexible and disorganized thinking (Diamond, 2013; Gilleen et al., 2011; Nekovarova et al., 2014; Northoff et al., 2006; Northoff and Qin, 2011; Shad et al., 2007). The DMN and FPN and related cognitive processes appear to be dysfunctional in UHR, as well (Bora and Murray, 2014; Fusar-Poli et al., 2012; Nelson et al., 2012; Schmidt et al., 2014; Shim et al., 2010; Wotruba et al., 2013). Because schizophrenia is considered a neurodevelopmental disconnection disorder (Satterthwaite and Baker, 2015), investigating rsFC in UHR populations and related phenotypes such as insight may reveal important characteristics of the psychotic disorder continuum as well as potential treatment options.

Thus far, all insight neuroimaging studies have been performed with first-episode psychosis or chronic schizophrenia populations. Studying insight and associated brain networks in a UHR sample may help to inform about characteristics of insight across the continuum of psychotic disorders, particularly before onset of a psychotic disorder (Gerretsen et al., 2014a). Because CI may predict psychotic episodes and outcomes, understanding it in the prodromal population may help clinicians to design specific early interventions that may reduce duration of untreated psychosis or prevent psychosis onset. Previous research has indicated that large-scale networks are associated with psychotic disorders and CI. Therefore, we aimed to investigate the relationship between CI and rsFC of the DMN and FPN in a UHR sample. We first hypothesized that poorer CI would be associated with stronger DMN connectivity and weaker FPN connectivity. We also hypothesized that poorer clinical insight would be associated with weaker anticorrelations between the DMN and FPN (i.e. negative relationship).

2. Methods

2.1. Procedures

2.1.1. Participants

Participants were recruited at the Adolescent Development and Preventative Treatment (ADAPT) research program at the University of Colorado, Boulder under direction of Dr. Mittal. The sample consisted of 35 adolescents and young adults, ages 15–22. Adolescents and young adults were identified as UHR with the Structured Interview of Prodromal Syndromes (SIPS) by an advanced doctoral student or clinical psychologist (Miller et al., 1999). Per the SIPS, participants were considered UHR if they had moderate (score of 3 on scale of 0–6) to severe but not psychotic (score of 5) positive symptoms or a decline in functioning accompanied by schizotypal traits and/or a family history of schizophrenia. Five participants had a first-degree relative with a psychotic disorder and a decline in functioning without positive symptoms. No participants had pure schizotypal presentation. Exclusion criteria included history of head injury, diagnosis of an Axis I psychotic disorder, neurological disorder, or MRI contraindication. To assess these criteria, a trained advanced doctoral student or clinical psychologist administered the Structured Clinical Interview for DSM-IV-TR Disorders (SCID-IV) (First et al., 1997). Exclusion criteria for this imaging study further included current substance dependence and in-scanner head motion >3 mm in any direction. All participants had an IQ above 70, so no participants were excluded for this reason.

2.1.2. Clinical insight measure

CI was assessed with the Scale to Assess Unawareness of Mental Disorder (SUMD), a clinician-rated measure (Amador et al., 1993). The SUMD includes three general items: awareness of having a mental disorder, awareness of the effects of medication, and awareness of social consequences of the disorder. It also includes items for awareness and attribution of specific symptoms (these were not assessed). Each item is rated on a scale of 0–5, with 0 indicating "not applicable" (full awareness) and 5 indicating "not at all aware". The general items load on a single factor with good internal consistency (Boyer et al., 2012; Michel et al., 2013), so in the present study, these items were summed to create a score for current clinical insight, with higher scores representing poorer insight. We chose to sum the scores so that our insight measure would encompass these three important facets of CI and allow us to investigate individual differences in overall CI in a highly variable population. In addition, the awareness of illness item refers to general awareness of having a disorder, so is not limited to awareness of positive symptoms; for this reason we did not restrict our analysis to only participants with positive symptoms.

2.1.3. Scanning

Participants underwent both structural and functional magnetic resonance imaging (MRI) scans on a 3 T Siemens Magnetom TrioTim scanner. Structural images were acquired with a T1-weighted 3D magnetization prepared rapid gradient multi-echo sequence (sagittal MPRAGE; repetition time [TR] = 2530 ms; echo times [TE] = 1.64 ms, 3.5 ms, 5.36 ms, 7.22 ms, 9.08 ms; GRAPPA parallel imaging factor 2; 1 mm^3 voxels, 192 interleaved slices; FOV = 256 mm; flip angle 57°).

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