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Resting State Functional Connectivity in People at Clinical High Risk for Psychosis

Abraham, Nachum

UNIVERSITY OF CALGARY

Resting State Functional Connectivity in People at Clinical High Risk for Psychosis

by

Nachum Omri Abraham

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Abstract

Neuroimaging studies in participants at clinical high risk (CHR) for psychosis may provide evidence into the etiology of psychosis. Abnormalities in connectivity have been reported in schizophrenia but little is known about resting state functional connectivity (RSFC) prior to the onset of psychosis. The aim of this project was to identify functional neuroimaging markers for individuals at CHR. It was hypothesized that each network investigated, including the default mode, salience, executive control and dorsal attention network, would show aberrant connectivity in the CHR sample.

Thirty-one CHR participants who met Criteria of Prodromal Syndromes and 12 healthy controls (HC) were scanned using resting-state fMRI. Seed-based region-of-interest correlation analysis was used to identify the default mode, salience, executive control, and dorsal attention networks.

Compared to HC, people at CHR demonstrated aberrancies in all four resting state networks that were tested. Results indicated resting state networks have altered patterns of connectivity in people at CHR for psychosis, when compared to HC. Each network tested was differentially affected. Aberrancies in RSFC suggest that functional specialization is altered in individuals at CHR who, in turn, may have difficulty properly allocating attentional resources between internal and external stimuli, even prior to the onset of psychosis.

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Dedication

"Gentlemen, we are going to relentlessly chase perfection, knowing full well we will not catch it, because nothing is perfect. But we are going to relentlessly chase it, because in the process we will catch excellence. I am not remotely interested in just being good."

-VL-

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List of Abbreviations

COPS	Criteria of Prodromal Syndromes
DAN	Dorsal Attention Network
DMN	Default Mode Network
ECN	Executive Control Network
HC	Healthy Control
MNI	Montreal Neurological Institute
NAPLS-2	North American Prodrome Longitudinal Study
PCC	Posterior Cingulate Gyrus
ROI	Region of Interest
RSFC	Resting State Functional Connectivity
RSN	Resting State Networks
SCID-1	Structured Clinical Interview for DSM-IV Disorders
SIPS	Structured Interview for Prodromal Syndromes
SN	Salience Network
SOPS	Scale of Prodromal Symptoms
TBI	Traumatic Brain Injury
WASI	Wechsler Abbreviated Scale for Intelligence

Chapter One: INTRODUCTION

1.1 Schizophrenia

Psychosis is a loss of contact with reality, in which people have trouble distinguishing what is real and not. Symptoms of psychosis are delusions, defined as false fixed beliefs, and hallucinations, which are sensory perceptions without sensory input (4th ed., text revision, American Psychiatric Association, 2000). The most common psychotic illness is schizophrenia, which has diagnostic criteria that incorporate psychosis as well as other symptoms (4th ed., text revision, American Psychiatric Association, 2000). A diagnosis of schizophrenia is given if, for at minimum of one month, individuals experience two of the following: delusions, hallucinations, disorganized speech, disorganized behaviour and negative symptoms. Further, social or vocational dysfunction must be experienced and continuous signs of these disturbances must be present for six months. Symptoms of schizophrenia are grouped in two categories; positive symptoms include psychosis, formal thought disorder and grossly disorganized behaviours, and negative symptoms include a lack of motivation, poverty of speech, an inability to experience pleasure, apathy, and blunted affect (Makinen et al. 2008; Tandon et al. 2009).

Clinical features not specifically related to the diagnostic process may also be present in people with schizophrenia. Mood problems, such as depression are commonly comorbid with schizophrenia and are specifically more severe during acute phases of psychosis (Buckley et al. 2009). Impairment across several cognitive domains is also highly

prevalent in schizophrenia, and has been observed in the premorbid phase, usually persisting through the long-term course of the illness (Napal et al. 2012).

Treatment for schizophrenia may vary and usually includes pharmacotherapy specifically to reduce severity of psychosis (Tajima et al. 2009). Another treatment option is individualized or group therapy, such as cognitive behavioural therapy. Utilizing both pharmacological and cognitive behavioural therapy has the most impact on symptoms of schizophrenia, more so than just one treatment strategy and other types of therapy (Rector and Beck 2012). Additionally, early implementation of these treatments is critical to prognosis (Polari et al. 2011).

1.2 Clinical high risk for psychosis

Recently, there has been a shift in schizophrenia research from illness treatment to illness prevention (Addington and Heinssen 2012, Yung and Nelson 2011). Research that examines individuals who appear to be putatively prodromal for developing psychosis offers an opportunity to examine the development of psychotic illness, from both clinical and biological perspectives. From a clinical standpoint, studying the development of psychotic illnesses relies on the examination of attenuated symptoms before the illness has fully developed. These symptoms usually begin during adolescence (Addington and Heinssen 2012). The Criteria of Prodromal Syndromes (COPS) have been developed based on such clinical symptoms, to determine which individuals are at clinical high risk (CHR) of developing psychosis (McGlashan et al. 2010;Addington and Heinssen 2012). The COPS are evaluated using the Structured Interview for Prodromal Syndromes (SIPS) and the Scale of

Prodromal Symptoms (SOPS), which determine the presence and severity of prodromal symptoms (Addington and Heinssen 2012). There are three, non mutually exclusive, prodromal syndromes (McGlashan et al. 2010; Miller et al. 2003):

1. Attenuated positive symptoms syndrome: individuals experience sub-threshold, attenuated positive psychotic symptoms beginning over the past year and having an average frequency of at least once per week in the past month, but are not fully convinced these experiences are real.
2. Genetic risk and deterioration syndrome: individuals have a first-degree relative with a psychotic disorder or have schizotypal personality disorder, and experience a functional decline during the previous year.
3. Brief intermittent psychotic symptoms syndrome: individuals have experienced frank psychotic symptoms that have abated spontaneously and not lasted longer than a week.

There are also symptoms experienced by people at CHR that are not part of COPS criteria. Cognitive deficits are commonly experienced, specifically in episodic and working memory, attention, and executive functioning (Addington and Heinssen 2012). Research focusing on biological correlates of these symptoms in people at CHR may provide insight into the etiology of psychosis. For example, some cognitive deficits have been previously associated with structural and functional brain abnormalities that can be observed through neuroimaging techniques (Hannan et al. 2010;Meijer et al. 2011).

1.3 Magnetic resonance imaging

Magnetic Resonance Imaging (MRI) is a well-utilized research tool for investigations of brain abnormalities. It provides a non-invasive, *in-vivo* tool for imaging the human brain (Huettel 2009). By using the property of nuclear magnetic resonance (NMR), MRI images specific atomic nuclei within the body. Hydrogen is most frequently imaged as it is both the most common atom in the body, due to high water content, and it is the most sensitive to the NMR phenomenon. The strong magnetic field of an MR scanner causes hydrogen nuclei to align in the direction of the magnetic field (either parallel or anti-parallel); this is because the nuclei themselves have magnetic properties as a result of their net electric charge and spinning nature. Applying additional magnetic fields, called radio frequency pulses, disturb this aligned equilibrium. When the additional fields are removed hydrogen nuclei return back to the equilibrium alignment, emitting a recordable decaying radio frequency signal. Given the distinct water, chemical, and magnetic environment of different tissue types, nuclei return to equilibrium at differing rates. As a consequence, the signals they generate also decay at differing rates. These processes are characterized by tissue specific decay constants, T1 and T2, respectively and generate tissue contrast on an MR image.

1.4 Functional Magnetic Resonance Imaging

Recent advances in magnetic resonance technology, specifically functional magnetic resonance imaging (fMRI) technology, have made it possible to investigate brain function that may accompany anatomical abnormalities observed in schizophrenia, non-invasively

and with no known risks (Huettel 2009, Holodny et al. 2011). fMRI exploits that evoked neuronal activity is an aerobic process. Neural responses necessitate increased delivery of oxygenated blood to the specific regions that are producing a response. This is accomplished by an increase in local blood flow, which is directly correlated with neural activity via a cerebral autoregulation mechanism known as the hemodynamic response (HDR). The paramagnetic properties of deoxygenated hemoglobin, prior to increased local blood flow, interfere with the MR signal, causing inhomogeneities in local magnetic fields and thus cause a loss of signal. Consequently, decreased deoxygenated hemoglobin levels as a result of increased blood flow result in a greater MR signal. When neural activity is modulated, the result is a temporal contrast, the mechanism of which is called Blood Oxygen Level Dependent (BOLD) contrast (Ogawa et al. 1990).

Prior to evoked neural activity, oxygenated and deoxygenated hemoglobin are at baseline levels. Once a stimulus is presented, a cascade occurs eventually culminating in the diffusion of a vasodilator, nitric oxide, which causes arteries to expand and increase blood flow. This process takes approximately two seconds to complete, creating a lag time in the HDR (Huettel 2009). As neurons still require increased oxygen during their response to a stimulus despite of lag time, they consume the oxygen from surrounding vessels causing the concentration of deoxygenated hemoglobin to increase; this results in a slight distortion of the MR signal and an initial undershoot observed in the BOLD signal. Following the lag there is an increase in oxygenated hemoglobin (and decrease in deoxygenated hemoglobin), resulting in a BOLD signal increase. The BOLD signal peaks at approximately 5 seconds following a neural stimulus.

Once the transient stimulus ceases, blood flow returns to normal and the active tissue depletes the oxygenated hemoglobin. As levels of oxygenated hemoglobin return to baseline, the BOLD signal decrease as well, but undershoots due slow cerebral blood volume recovery. Deoxygenated hemoglobin that is newly produced by neural tissue activity diffuses into the surrounding vessels, which can accommodate more than baseline deoxygenated hemoglobin due to their increased volume. Excess deoxygenated hemoglobin does not get flushed away, however, because blood vessels have returned to normal flow rates. Once both cerebral blood flow and volume return to baseline, deoxygenated hemoglobin concentrations also normalizes, as reflected by the BOLD signal.

1.5 Resting-State connectivity

Activation that is not in response to external stimuli, that is, activation in intrinsic cortical networks, has been demonstrated through fMRI. Over 50% of the brain's metabolic energy consumption is allocated to intrinsic signalling, with only 5% of the brain's energy being consumed during responses to external stimuli (Zhang and Raichle 2010;Shulman et al. 2001), illustrating the importance of these processes. Further, there is evidence for slow (<0.1Hz), spontaneous fluctuations in the BOLD signal. These correlated BOLD signals represent the energy-demanding intrinsic signalling that occurs between brain regions. These fluctuations are temporally correlated between functionally related brain regions (e.g., motor, visual, etc.), specifically in the absence of external signals (Purdon and Weisskoff 1998;Smith et al. 2009). Brain regions temporally correlated to one-another make up constituent components of resting state networks (RSN) that are reliably engaged

while one is at rest (Fox et al. 2005). These signals may, therefore, may represent baseline brain functioning and information integration processes (Rosazza and Minati 2011;Biswal et al. 1995;Biswal et al. 1997).

Interestingly, RSN are most visible while a person is awake but not performing any externally cued tasks, otherwise known as a resting-state (Smith et al. 2009;Cole et al. 2010). RSN have also been shown to occur during task performance, while under sedation, and during sleep (Fransson 2006; Stamatakis et al. 2010;Horovitz et al. 2009). Further, resting-state networks are present during all stages of development and are evolutionarily preserved as they are found in all species of animals that have been studied to date (Fair et al. 2007;Pawela et al. 2008). Little is known about the utility resting state intrinsic communication serve, however the high-energy demands attributed to RSN imply that it is most likely a critical phenomenon.

1.6 Resting state networks

Theories regarding the functions of RSN include developing and maintaining neural networks that function together while responding to external stimuli (Pizoli et al. 2011 Doria et al. 2010; Supekar et al. 2010; Zielinski et al. 2010). Investigating the utility of these networks may provide insight into the function of their constituent structural components during rest (Greicius et al. 2009). Further, determining the existence of anomalies in baseline activation in people with mental illnesses, such as schizophrenia, relative to healthy controls may shed light on malfunctions of brain mechanisms associated with psychiatric disease (Woodward et al. 2011).

One theory regarding the function of RSN includes increasing neural signalling and information processing efficiency and ensuring the reliability of these networks (Miall and Robertson 2006; Uddin et al. 2010; Zielinski et al. 2010). This may be accomplished in numerous ways. First, RSN are thought to have 'small-world' organization (Achard et al. 2006), characterized by a large number of local connections, which have short distances between the connected areas (van den Heuvel and Hulshoff Pol 2010). This maximizes neural signal efficiency, as information has to travel over less distance. Second, RSN may increase speed of neural activation during active tasks with low metabolic costs by keeping systems in an active but low state during rest (Xiong et al. 2009). Lastly, RSN functioning can increases efficiency of attention allocation in two ways. RSN activity and suppression occur dichotomously during rest and externally cued-task performance, respectively. This allows for appropriate allocation of attention to internal or external stimuli when necessary (van den Heuvel and Hulshoff Pol 2010;Xiong et al. 2009). Moreover, RSN function involves processing information before and after an external stimulus is presented, again increasing attention allocation efficiency. For example, higher-order RSN consist primarily of interconnections between brain regions that receive information from numerous sources (termed heteromodal association cortical regions), which work to integrate data after an externally cued event has occurred (Greicius et al. 2003).

At least four higher-order RSN have been discovered, each with distinct heteromodal association regions and functions (Woodward et al. 2011;Vincent et al. 2008). The default mode network (DMN) was the first to be discovered and is the best characterized (see Figure 2 for networks) (Raichle et al. 2001, Whitfield-Gabrieli and Ford

2012). Among other functions, the posterior cingulate cortex, which is the central hub of the DMN, assists in the processing of self-referential thought and social cognitive information. This information is integrated in the DMN, updating current processes and weighing future outcomes for decision-making (Buckner et al. 2008;Buckner and Vincent 2007;Whitfield-Gabrieli et al. 2011;Chung et al. 2008). Recent studies link DMN activity with many internally focused stimulus-independent cognition, such as autobiographical planning (Spreng et al. 2010). Investigations of these processes are relevant to the study of mental illness, specifically psychosis, because people with these types of illnesses tend to have performance deficits on tasks that involve functions believed to be reliant on the DMN. For example, people with psychosis tend to have social deficits across many domains (Bora and Pantelis 2013) that may be related to malfunctions of the DMN (Mars et al. 2012).

The salience network (SN), composed of the bilateral insula and anterior cingulate cortex, is partially responsible for sentience, interoception, allocation of attention, (Seeley et al. 2007;Cauda et al. 2011;Woodward et al. 2011) and may be involved in mediating the connectivity of the DMN. Connectivity between higher-order RSN may be indicative of the influence of one neural system on another, which is known as effective connectivity (Friston et al. 1993). Previous publications regarding effective connectivity have helped discern the direction of signalling between RSN, aiding to determine which networks regulate the functions of others (Liao et al 2010). Recent evidence suggests that the SN has effective connectivity with the DMN, in that the SN may enable switching between the DMN and task-related networks (Menon and Uddin 2010). For example, changes in SN

connectivity are associated with altered RSFC of the DMN. Specifically, a decrease in SN RSFC was associated with increased DMN FC, suggesting that the SN modulates DMN connectivity by inhibiting RSFC. Further, granger causality analysis, a method of analysis that allows for the evaluation of statistically predictive variables for fMRI and other data, has strongly suggested the SN plays a role in effective connectivity with the DMN (Liao et al. 2010). This implicates the SN as part of the mechanism that enables switching between internally and externally focused attention in healthy people. People with a psychotic illness have difficulty determining the salience of certain stimuli over others, which may lead to positive symptoms or the aggravation these symptoms. As such, the salience network has also received recent attention by schizophrenia researchers as it has been suggested to enable switching between competitive internal and external stimuli (Woodward et al. 2011, Wolf et al 2011).

Relatively little is known about the two other higher-order RSN of interest. The executive control network (ECN) includes frontal regions such as the middle frontal gyrus and dorsolateral prefrontal cortex (Rosazza and Minati 2011) and is involved in the processing of executive functions (Seeley et al. 2007) and substance dependence (Krmpotich et al 2013). The ECN can be engaged during self-referential thought, such as autobiographical planning, as well as externally goal-oriented behaviour. As such, the ECN may be coupled with the DMN and DAN serving as a mediator linking the two networks to support goal-directed cognitive processes.

The dorsal attention network (DAN) includes parietal regions such as the superior parietal lobule and intraparietal sulcus (Woodward et al. 2011) and is involved in attention

orientation for external stimuli in order to determine the behavioural significance (He et al. 2007, Ptak and Schnider 2010). For example, damage or dysconnectivity to the DAN indicates that this network controls spatial orienting by modulating the saliency of distracter stimuli according to current action goals (Ptak and Schnider 2010). Table 1 describes regions in each higher-order RSN.

Figure 2. Four higher-order resting state networks in healthy control participants

Table 1. Higher-order resting state network constituent regions

Resting State Network	**Seed ROI**					
Default Mode	Cingulate cortex	Precuneus	Ventromedial prefrontal cortex/Superior frontal gyrus	Middle temporal gyrus	Hippocampal formation	Lateral parietal cortex
Salience	Bilateral insula	Anterior cingulate cortex	Inferior frontal gyrus			
Executive Control	Middle frontal gyrus	Dorsomedial prefrontal cortex	Inferior parietal lobule	Inferior temporal gyrus	Dorsolateral prefrontal cortex	
Dorsal Attention	Bilateral superior parietal lobule	Intraparietal sulcus	Area MT+			

1.7 MRI, fMRI & RSN findings in schizophrenia

Several early findings regarding differences in the brains of people with schizophrenia and healthy control counterparts are well established. Typical results of structural and volumetric studies include increased lateral ventricular size, decreased cortical volume and thickness, and a disproportionate volume loss of temporal lobe in people with schizophrenia (Ahmed et al. 2013). When studied longitudinally, progressive gray matter reductions in the temporal lobe are associated with greater severity of positive but not negative symptoms. This, however, is regionally specific, as other structures including subcortical regions do not show a correlation with symptoms progression or severity (Ahmed et al. 2013).

Anomalies in brain function, some of which have been correlated with task performance, are also highly prevalent in people with schizophrenia (Ahmed et al. 2013 2013). Reduced activation in superior temporal region has been linked to poor performance in tasks of auditory selective attention, automatic, and controlled attentional processes. Hyperfrontality, otherwise known as an increase in activation of frontal regions relative to healthy controls, and hypofrontality, a reduction in relative activation of frontal regions, and have been found in schizophrenia, and together are believed to illustrate inefficient information processing. This is because hyperfrontality has been noted during performance of simple tasks, while hypofrontality occurs during the performance of demanding cognitive tasks. Hypofrontality is also associated with severity of psychotic symptoms (Sigmundsson et al. 2003). Finally, reduced activation in midbrain structures such as the thalamus and anterior cingulate suggest a breakdown in attention and

concentration, which may explain difficulties that schizophrenia patients have in inhibiting actions or thoughts that may be irrelevant to task completion.

Disrupted neural connectivity, which would impair communication between brain regions, has been suggested to lead to observable symptoms and problems in cognition and affect in people with schizophrenia (Karlsgodt et al. 2010). For example, abnormalities in neuronal networks that connect the parietal lobe with the temporal cortex and the prefrontal cortex have been linked to features of social dysfunction in schizophrenia (Ahmed et al. 2013). There is also some evidence to suggest that positive symptoms of psychosis may be associated with an inability to inhibit RSN while one is awake (Rotarska-Jagiela et al. 2010;Woodward et al. 2011). Broadly referred to as dysconnectivity, aberrancies in RSN can occur either as hyperconnectivity or hypoconnectivity. For example, it has been reported that individuals who have had a more chronic course of schizophrenia, for example on average ten years, demonstrate hypoconnectivity within the DMN, while people at earlier stages of the illness reportedly exhibit DMN hyperconnectivity (Jafri et al. 2008;Liu et al. 2010;Skudlarski et al. 2010;Whitfield-Gabrieli et al. 2009;Zhou et al. 2007a;Whitfield-Gabrieli and Ford 2012). Hyperconnectivity has also been confirmed in people at the earliest stage of psychosis onset, just after first episode psychosis (Guerrero-Pedraza et al. 2012).

Reduced DMN suppression during active tasks has been linked to impaired cognitive performance in healthy people (Weissman et al. 2006). Assessment of RSN while individuals with schizophrenia were performing active tasks directly after a resting state suggested that hyperconnectivity persisted during the task, beyond that of healthy controls

(HC) (Garrity et al. 2007;Meyer-Lindenberg et al. 2005;Pomarol- Clotet et al. 2008;Whitfield-Gabrieli et al. 2009;Jeong and Kubicki 2010). As active task demands were increased people with psychosis failed to suppress the DMN even further, a result usually observed in HC (Meyer-Lindenberg et al. 2005;Pomarol-Clotet et al. 2008;Whitfield-Gabrieli et al. 2009). Increased activation and hyperconnectivity within the DMN may therefore provide some explanation for poor task performance in schizophrenia (Whitfield-Gabrieli and Ford 2012). One interpretation of these results is that people with a psychotic illness fail to allocate attentional resources to external tasks. The inability to reallocate resources between resting and active networks would not only decrease one's ability to focus on external stimuli, resulting in poorer task scores, but also create a potential difficulty distinguishing between which stimuli are internally or externally generated (Whitfield-Gabrieli and Ford 2012). As such, failure to down-regulate the DMN may play a role in the positive symptoms of schizophrenia.

Studies regarding the functional connectivity of the three other higher-order RSN in people with psychotic illnesses are much more limited in number. Investigations of the SN have yielded inconsistent results including no change in RSFC (Liang et al. 2006;Woodward et al. 2011) and hyperconnectivity between the insula and anterior cingulate cortex when people with schizophrenia were compared to HC (Woodward et al. 2011). Dysconnectivity in the ECN and DAN have also been observed in samples of people with schizophrenia, though both hyperconnectivity and hypoconnectivity were reported (Woodward et al. 2011, Wolf et al. 2011;Zhou et al. 2007b;Zhou et al. 2007a). Several questions regarding higher-order RSN and psychosis still remain. For instance, it is

unknown whether dysconnectivity occurs as a consequence of a psychotic illness or contributes to disease onset and progression. To further understand the association between neural anomalies, dysconnectivity and psychosis, researchers have begun studying the structure, functioning and higher-order RSN in people at CHR for psychosis.

1.8 MRI, fMRI and RSN function in people at clinical high risk

Though there is less research regarding brain volume and function in people who are at CHR for psychosis, early studies have illustrated abnormalities that are consistent with those associated with psychosis (Addington and Heinssen 2012;Fusar-Poli et al. 2011;Karlsgodt et al. 2010;Smieskova et al. 2010). Frontal regions and temporal lobe areas, such as the superior temporal gyrus, amygdala-hippocampal complex, Heschl's gyrus have decreased grey matter volume (Harms et al. 2010;Rosso et al. 2010;Lawrie et al. 2008). Reductions in the left parahippocampus, amygdala, and fusiform gyrus may even predict conversion to psychosis, discriminating between people who go on to develop psychosis and those who do not. Task-based fMRI investigations have demonstrated that people at CHR who have increased activation in the bilateral prefrontal cortex, brainstem and left hippocampus are more likely to convert to psychosis (Allen et al. 2012).

Investigations regarding disrupted neural connectivity and impaired interregional communication have also recently begun. During the completion of a verbal fluency task, researchers observed that people at CHR who went on to convert to psychosis had greater midbrain-prefrontal cortex connectivity (Allen et al. 2012). Aberrant RSN connectivity has

also been suggested to cause certain symptoms in people at CHR, though many of these theories have yet to be tested. Deficits in memory and social cognition observed in people at CHR suggest the DMN may be malfunctioning, while negative symptoms experienced may suggest decreased salience of external stimuli, implicating the SN. Comorbid axis I substance use disorders in people at CHR implicate aberrant ECN RSFC (Krmpotich et al. 2013), and attention impairments implicate the DAN.

Shim et al. (2010) investigated DMN function in people at CHR for psychosis relative to HC and found their results to be congruent with the majority of findings in early psychosis studies (Shim et al. 2010). Those at CHR for psychosis experience dysconnectivity relative to HC (Shim et al. 2010). Specifically, a hyperconnectivity was detected between the posterior cingulate cortex and numerous other brain regions including the parahippocampal gyrus, precuneus, superior frontal and superior parietal regions. Furthermore, results suggested individuals at CHR had difficulty diverting activation from the DMN to task-related networks. This study provided the first evidence that dysconnectivity is present prior to the onset of psychosis, illustrating that symptoms experienced by people at CHR may be associated with dysconnectivity within RSN and may even suggest a vulnerability to psychotic illness.

While critical to the understanding of baseline brain functioning prior to the onset of psychosis, this study has several limitations that should be addressed in order to further understand the role of dysconnectivity in psychosis. First, as this was a pioneer study, it requires replication. Second, it was a small sample of 19 CHR people. Third, the DMN was the only RSN chosen for examination. To better understand the relevance of RSN

malfunctioning in clinical samples, it may be useful to examine several RSN. For instance, the recent data from Shim et al. (2010) suggesting hyperconnectivity in the DMN of people at CHR for psychosis implicates the upstream SN in this group, as the SN has been suggested to down-regulate connectivity within the DMN (Sridharan et al. 2008, Liao et al 2010). These network aberrancies may be related to positive symptom experiences (Menon and Uddin 2010). Further, investigating other networks may be relevant for understanding the development of other symptoms associated with being at CHR for psychosis and determining consistent dysconnectivity in heteromodal RSN may suggest a ubiquitous problem in RSFC in this clinical sample.

1.9 Aims and hypotheses

There are three aims to the present study. The first is to replicate previous findings regarding hyperconnectivity of DMN in people at CHR in a larger sample. The second aim is to determine if there are abnormalities in the SN in people at CHR, as previous results have indicated a relationship between aberrant DMN RSFC and SN RSFC. Finally, the exploratory aim is to determine if dysconnectivity is consistent across heteromodal RSN in a CHR sample by examining the functional connectivity in the ECN and DAN. More specifically the main hypotheses are:

1. People at CHR will experience hyperconnectivity in the DMN relative to HC.
2. Hypoconnectivity will be present in the SN of people at CHR relative to HC.

The exploratory hypothesis is:

1. The ECN and DAN will exhibit dysconnectivity, although not enough information is available to hypothesize the type of dysconnectivity.

Chapter Two: METHOD

2.1 Participants

Thirty-one CHR participants and 12 non-psychiatric HC participated in this study. All participants were recruited as part of the North American Prodrome Longitudinal Study (NAPLS-2) (Addington et al. 2012). The NAPLS project was established to investigate predictors and mechanisms of conversion to psychosis. This project, as part of NAPLS-2, has been approved by the University of Calgary Conjoint Health Research Ethics Board. Participants were help-seeking. They were referred from health care providers, educators, or social service agencies or they self-referred in response to intensive community education efforts. Informed consent was obtained from all individuals greater than 18 years of age, who met criteria. Consent was obtained from both the participants and the parents/guardians of participants under 18 years old. A complete list of inclusion and exclusion criteria for both CHR and HC included in this study is below.

2.1.1 Clinical high risk (CHR)

Inclusion criteria

1. Male or female between 12 and 35 years old.
2. Understood and signed informed consent (or assent for minors) document in English.
3. Met Criteria of Psychosis-risk Syndrome as per the Structured Interview for Prodromal Syndromes (McGlashan et al. 2010).

Exclusion criteria - Otherwise eligible CHR participants may not meet any of the following:

1. Criteria for current or lifetime DMN-IV-TR Axis I psychotic disorder, including affective psychoses and psychosis NOS (4th ed., text revision, American Psychiatric Association, 2000; First et al. 1994).
2. The diagnostic prodromal symptoms were clearly caused by an Axis 1 disorder, including substance use disorders, in the judgment of the evaluating clinician. Other non-psychotic DSM-IV-TR disorders were not exclusionary (e.g. substance abuse disorder, major depression, anxiety disorders, PDD, Axis II Disorders) provided they the disorder did not account for the diagnosis of prodromal symptoms (4th ed., text revision, American Psychiatric Association, 2000).
3. No treatment with antipsychotic medication unless it can be clearly demonstrated that the diagnostic prodromal criteria were present prior to the administration of antipsychotics.
4. Impaired intellectual functioning (i.e. IQ<70) (Wechsler D. 1987); however those with an IQ in the 65-69 range were included if the wide range achievement test (WRAT) reading was >75.
5. Past or current history of a clinically significant central nervous system disorder that may contribute to prodromal symptoms or confound their assessments.
6. A rating of 7 or above on the Traumatic Brain Injury screening instrument (AbdelMalik et al. 2003).

Additional exclusion criteria for this study

1. A score of 5 or higher on the Annett Handedness Scale (Dragovic and Hammond,

2007) indicating left-handedness.

2.1.2 Non-psychiatric healthy controls (HC)

Inclusion criteria:

1. Male or female between 12 and 35 years old.
2. Understood and signed informed consent (or assent for minors) document in English.

Exclusion criteria:

1. Met CHR exclusion 1-6
2. Met criteria for any prodromal syndrome (McGlashan et al. 2010), any current or past psychotic disorder or Cluster A personality disorder diagnosis (4th ed., text revision, American Psychiatric Association, 2000) and were not receiving any current treatment with psychotropic medication.
3. Family history (in first-degree relatives) of schizophrenia, schizoaffective disorder, schizotypal personality disorder, or any other disorder involving psychotic symptoms.

Additional exclusion criteria

1. A score of 5 or higher on the Annett Handedness Scale (Dragovic and Hammond, 2007), indicating left-handedness

2.2 Measures

The *Structured Interview for Prodromal Syndromes (SIPS)* and the *Scale of Prodromal Symptoms (SOPS)* (McGlashan et al. 2010) were used to determine the presence and severity of prodromal symptoms. The *Structured Clinical Interview for DSM-IV Disorders (SCID-1)* (First et al. 1994) was used to rule out the presence of Axis 1 psychotic disorders. The *Traumatic Brain Injury (TBI) Interview* (AbdelMalik et al. 2003) was used to assess previous history of head injury. Intelligence quotient was assessed using the *Wechsler Abbreviated Scale of Intelligence (WASI)* (Wechsler D. 1987). Handedness was determined using the *Annett Handedness Scale* (Dragovic and Hammond, 2007).

2.3 Statistical analyses

Descriptive statistics were used to describe the demographics for each group. Results were graphically analyzed using box plots and frequency histograms. These computations were important to determine any potential confounds, including outlier values of age or gender. Means were compared using the Student t-test to determine significant differences. Using FSL (Smith et al. 2004, http://www.fmrib.ox.ac.uk/fsl/), the groups were compared on the hemodynamic responses during rest.

2.4 Procedures

Participants were involved in a range of clinical interviews. They were subsequently scanned using MRI and fMRI technology. During functional image acquisition, participants

were asked to lie still and visually fixate on a small white cross at the center of a black video projection screen (Avotec, Inc., Stuart, FL). The structural scans were then completed and participants were reminded to remain still but were not asked to maintain focus on a fixation cross.

2.5 Data acquisition

MR images were collected using a 3-Tesla General Electric Discovery MR750 scanner (Signa VHi; GE Healthcare, Waukesha, WI) equipped with an eight-channel phased-array head coil. T1-weighted anatomical scans were collected for anatomical registration of the resting-state data (3D spoiled gradient echo: TR/echo time (TE) = 8.1s/3.2ms; matrix size = 256 · 256 ·112; voxel size=0.83·1.25·2mm). One hundred and seventy slices of 1.2mm thickness were collected. During participant fMRI scanning, lasting 5 minutes, two sets of T2*-weighted gradient-echo echo planar images were acquired with the following parameters: TR/TE = 2000/ 30ms; flip angle=77 degrees; FOV=22·22cm; 64·64 matrix. For analysis, 156 volumes of thirty 4-mm-thick axial slices were collected.

2.6 Data preprocessing and analysis

Structural data was prepared for analysis by transforming anatomical images into a common stereotactic space. Preprocessing of data collected during rest was performed using the FMRIB software library (Smith et al. 2004;FSL www.fmrib.ox.ac.uk/fsl). This consisted of brain extraction (Smith 2002), interleaved slice-timing correction, motion correction using FMRIB's linear image registration tool (MCFLIRT) (Jenkinson et al. 2002),

and temporal low-pass filtering (< 0.01 Hz).

FSL (http://www.fmrib.ox.ac.uk/fsl/) was also used for functional imaging analysis (Smith et al. 2004, FMRIB's Software Library v. 4.0). To construct participant seed-to-voxel connectivity maps, seed ROIs were generated through the use of Montreal Neurological Institute (MNI) coordinates selected from previous literature (Woodward et al. 2011;Wolf et al. 2011) in conjunction with the atlas tool in FSLView. See **Table 2** for the seed MNI coordinates regarding the RSN ROI. The average BOLD intensity time course was extracted from each RSN seed ROI. The general linear model (GLM) was used to determine voxels external to the ROI, which had time courses that were correlated with the seed time-series using FEAT (FMRI Expert Analysis Tool, version 5.98, part of FSL, FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Higher-level, mixed-effects analyses were performed using the individual subject data to establish typical statistical parametric maps for the CHR and HC groups. Further higher-level analyses were performed in order to contrast the respective group's average parametric maps. Z (Gaussianised T/F) statistic images were thresholded using clusters determined by Z>3.1 and a (corrected) cluster significance threshold of P=1 ([Worsley 2001] K.J. Worsley. Statistical analysis of activation images. Ch 14, in Functional MRI: An Introduction to Methods, eds. P. Jezzard, P.M. Matthews and S.M. Smith. OUP, 2001). The ALPHASIM program was used as a cluster correction program for the two groups. A threshold of z=3.1 and 2.3 and voxel clusters of 77 voxels or less were considered non-significant.

Table 2. Seed Montreal Neurological Institute (MNI) coordinates for RSN

	MNI coordinates		
Resting state network (ROI)	X	Y	Z
Default mode (posterior cingulate cortex)	0	-30	34
Salience (bilateral insula)	-36/36	14/16	6/6
Executive control (middle frontal gyrus)	-38/40	36/36	20/22
Dorsal attention (bilateral superior parietal lobule)	-24/24	-54/-54	52/52

Chapter Three: RESULTS

3.1 Demographics

Age, gender, and handedness criteria were used to limit variation between participants. Data from 53 participants was to be included in the study. Six CHR participants, all 13 years old, were excluded from the analysis, as they were likely to have the most brain changes occurring during maturation, differentiating them from the HC group that were of an older mean age. One HC participant was excluded from the study, as his age was significantly greater than the rest of participants (HC: 30 years old SD= 4.21). The mean age of the CHR group age was 17.4 years (SD=2.6), and of the HC group was 20.2 years (SD=5.0). There was no significant difference between mean ages of the groups once data from these individuals was excluded. Data from 3 participants was excluded, as they were left-handed. The CHR group was made up of 15 male and 16 female participants, while the HC group had 6 male and 6 female. Totalling 31 CHR participants, 90.32% (n=28) met APS criteria, 3.23% (n=1) met GRD criteria, and 6.45% (n=2) met both APS and GRD criteria.

At the time of the fMRI scans, 18.42% (n=7) of CHR participants reported taking antipsychotics, 34.21% (n=13) reported taking antidepressants, 28.95% (n=11) reported taking stimulants, 5.26% (n=2) reported taking anxiolytics, 5.26% (n=2) reported taking anticonvulsants, and 2.63% (n=1) reported taking a non-benzodiazepine hypnotic. HC participants did not report using any psychotropic medications.

3.2 Seed-to-voxel analysis

3.2.1 The default mode network (DMN)

Upon visual inspection, connectivity maps for all RSN in both groups were detected (see Figure 1). Second level analyses revealed numerous differences between people at CHR and HC participants in all networks examined (see Table 3). People at CHR demonstrated hyperconnectivity in the DMN, between the PCC seed ROI and the left hippocampus, left cerebellum, and bilaterally in the precuneus. These results lend support to the first hypothesis, that hyperconnectivity in people at CHR is present within the DMN proper when compared to HC. Other regions, not commonly part of the DMN, also showed hyperconnectivity with the PCC seed ROI, replicating the previous study by Shim et al (2010). On the left side of the brain these included the frontal and temporal poles, intracalcarine, lateral occipital (superior) and temporal occipital fusiform cortices, the supramarginal gyrus (posterior), the brainstem and the bilateral occipital pole (see Figure 2). As these regions were recruited to the DMN in CHR participants and were not functionally connected to the PCC in HC, the spatial topography of the DMN may be altered in people at CHR.

Compared to HC, people at CHR exhibited hypoconnectivity between the PCC seed ROI and several regions that were not part of HC DMN. These included the left lateral occipital cortex, bilateral occipital pole, the right thalamus, right frontal orbital cortex, and the right middle frontal gyrus, which is part of the ECN. The only region within the DMN

that showed hypoconnectivity was the bilateral posterior cingulate gyrus, the seed ROI for the DMN (see Figure 3).

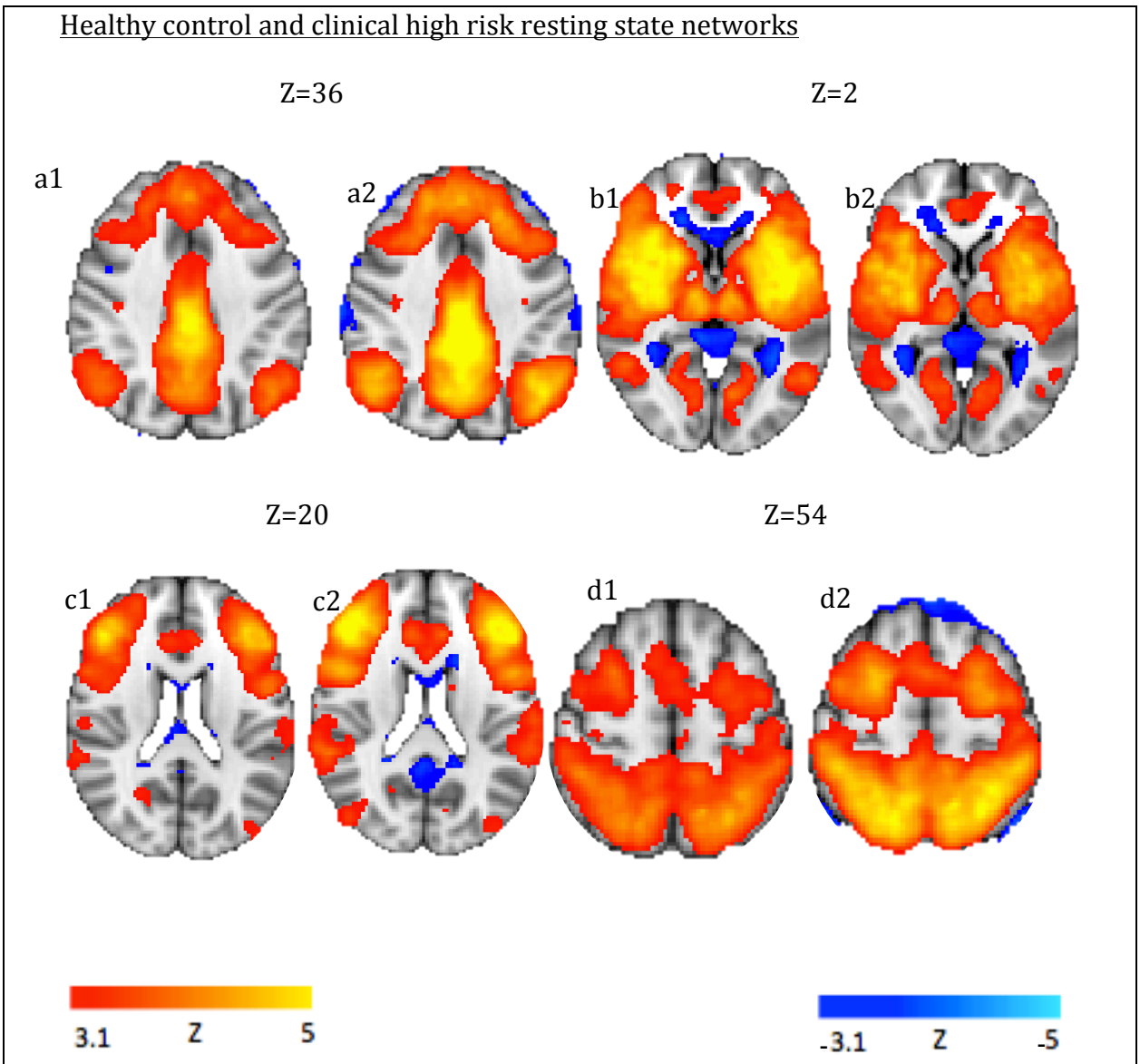

Figure 1. Four heteromodal resting state networks in healthy controls and people at clinical high risk. a1. DMN activation in HC, a2. DMN activation in CHR. b1. SN activation in HC, b2. SN activation in CHR. c1. ECN activation in HC, c2. ECN activation in CHR, d1. DAN activation in HC, d2. DAN activation in CHR.

Table 3. Resting state network alterations in people at clinical high risk for psychosis

Network	Contrast	Brain region	MNI Coordinates			Voxels	Z-MAX value
			X	Y	Z		
Default mode	CHR>HC	L. cerebellum	-30	-50	-28	1991	4.12
		L. Lateral occipital cortex (superior)	-38	-60	40	374	3.49
		L. Temporal pole	-48	6	-22	350	3.84
		L. Frontal pole	-24	62	26	288	4.3
		L. Brainstem	-4	-46	-54	284	4.12
		L. Precuneus	-8	-56	16	184	3.18
		L. Hippocampus	-24	-36	-4	183	3.38
		Mid precuneus	0	-56	56	174	3.12
		L. Frontal pole	-34	58	-20	173	4.2
		L. Lateral occipital cortex (superior)	-52	-76	22	142	3.07
		L. Supramarginal gyrus (posterior)	-60	-44	12	121	2.73
		L. Temporal occipital fusiform cortex	-40	-48	-12	109	2.92
		Bi. Occipital pole	-10	-92	14	102	3
		R. Precuneus	18	-52	18	95	3.1
		L. Intracalcarine cortex	-22	-64	8	82	2.75
	HC>CHR	L. Lateral occipital cortex	-38	-88	-28	397	4.33
		R. Occipital Pole	36	-98	-10	296	4.51
		Bi. Frontal orbital cortex	4	-8	82	295	4.53
		R. Thalamus	6	-8	18	180	3.53
		Bi. Cingulate gyrus (posterior)	4	-22	38	151	3.61
		R. Middle frontal gyrus	38	20	30	139	3.44
		L. Occipital Pole	-14	-98	-22	110	3.34
		R. Putamen	24	26	-6	82	3.31
Salience	CHR>HC	L. Cerebellum R. Cerebellum	-22	-54	-44	720	4.25
		R. Frontal Pole	22	-58	-44	477	4.42
		L. Cerebellum	66	32	6	351	3.64
		R. Inferior temporal gyrus	-38	-60	-28	346	4.24
		R. Cerebellum	44	-42	-6	140	3.52

		L. Temporal occipital fusiform cortex	52	-60	-30	134	3.82
			-20	-46	-16	95	3.66
		R. Middle frontal gyrus	28	30	24	87	2.97
	HC>CHR	R. Intracalcarine cortex	26	-66	12	1217	4.2
		R. Middle temporal gyrus	68	-14	-8	460	3.38
		L. Occipital pole	-26	-94	36	282	3.38
		L. Frontal orbital cortex	-32	30	-6	282	4.64
		Precentral gyrus	24	-16	82	107	3.29
Executive control	CHR>HC	L. Brain stem	0	-36	-16	536	4.67
		L. Cerebellum	-6	-66	-14	200	3.47
		R. Cingulate gyrus (posterior)	8	-18	26	169	3.31
		R. Frontal pole	48	50	0	139	4.68
		R. Thalamus	6	-14	2	121	3.17
		R. Postcentral gyrus	32	-32	34	79	3.39
	HC>CHR	L. Frontal orbital cortex	-36	28	-6	448	4.13
		L. Middle temporal gyrus	-28	34	30	169	3.23
		R. Temporal pole	54	20	-10	159	3.61
		R. Middle temporal gyrus	74	-14	-8	152	3.72
		R. Angular gyrus	58	-58	46	134	3.54
		L. Middle temporal gyrus	-50	-4	-22	97	3.61
Dorsal attention	CHR>HC	R. Parahippocampal gyrus	18	-36	-6	1406	4.45
		R. Precuneus	18	-68	32	1352	3.61
		R. Lingual gyrus	8	-70	-8	337	3.23
		L. Parahippocampal gyrus	-16	-38	-4	327	3.76
		R. Cerebellum	22	-38	-40	299	3.82
		R. Lateral occipital cortex	32	-72	8	93	3.27
	HC>CHR	L. Middle temporal gyrus	-52	0	-30	1666	4.29
		R. Central opercular cortex	42	-6	10	1402	4.13
		L. Frontal Pole	-20	50	26	1360	4.56
		L. Parietal Operculum cortex	-42	-30	14	714	3.76
		R. Inferior temporal gyrus	52	0	-36	184	3.5

		L. Putamen	-22	4	-2	161	3.25
		L. Precentral gyrus	-12	-24	64	118	3.47
		R. Precentral gyrus	48	2	38	111	3.31
		L. Postcentral gyrus	-54	-16	44	110	3.47
		L. Precentral gyrus	-24	-18	74	95	3.13
		R. Middle temporal gyrus	66	-22	-8	90	2.9
		Bi. Anterior cingulate gyrus	4	-4	40	82	2.77

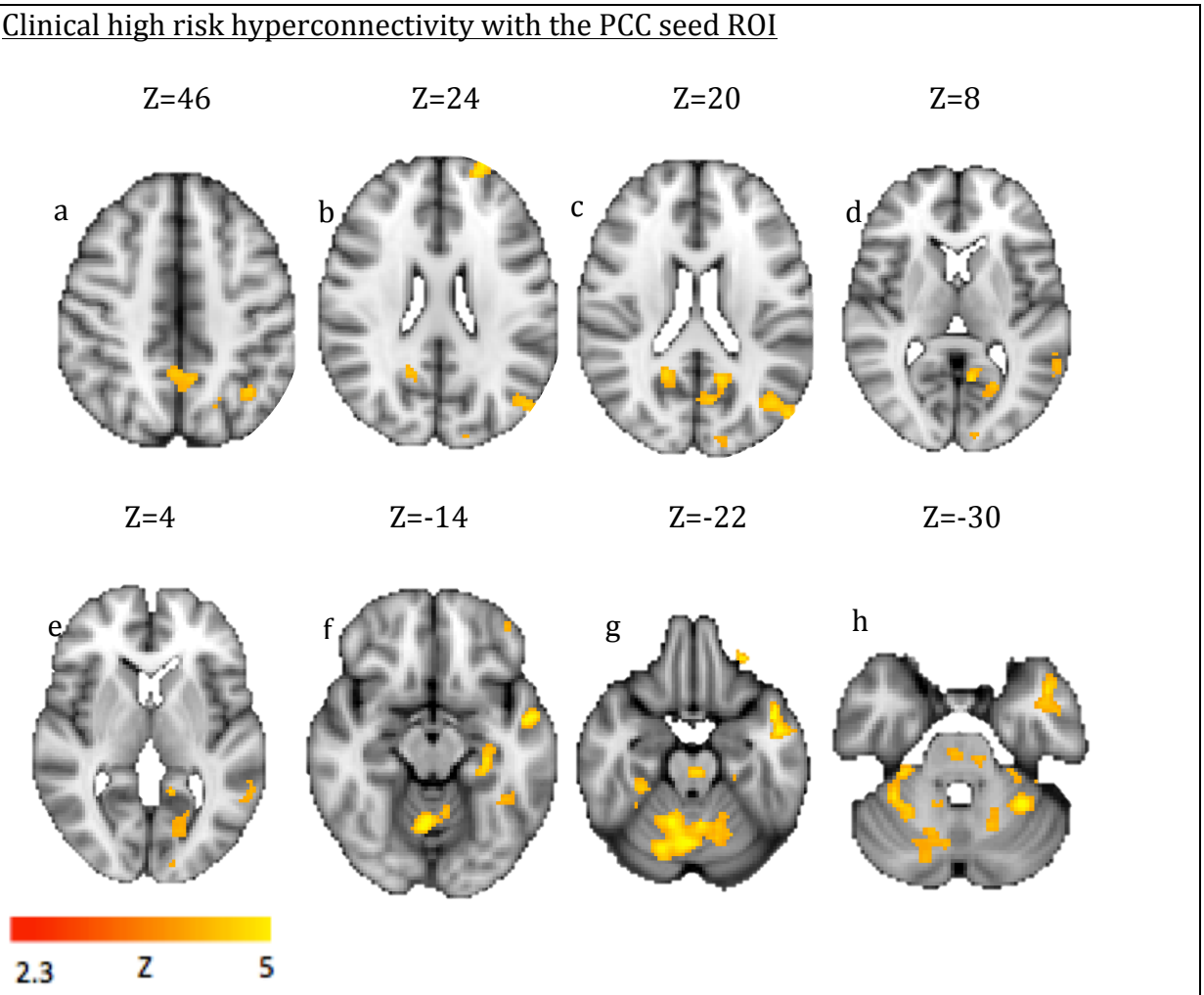

Figure 2. Resting-state functional connectivity differences between people at clinical high risk and healthy control participants in the default mode. Compared to HC, CHR participants demonstrated greater connectivity between the PCC seed ROI and the (a) precuneus, lateral occipital cortex, (b) frontal pole, lateral occipital cortex, precuneus (c) precuneus, lateral occipital cortex (d) precuneus, intercalcarine cortex, MTG, occipital pole (e) cingulate gyrus, precuneus, intracalcarine cortex, MTG, occipital pole (f) frontal pole, superior/temporal gyrus, left HPC, left pHPC gyrus, temporal fusiform gyrus, inferior temporal gyrus, temporal occipital fusiform gyrus, cerebellum (g) frontal pole, temporal pole, MTG, pHPC gyrus, brainstem, cerebellum, right temporal occipital fusiform gyrus, temporal fusiform gyrus (h) inferior temporal gyrus, MTG, temporal pole, cerebellum, temporal fusiform cortex.

Clinical high risk hypoconnectivity with the PCC seed ROI

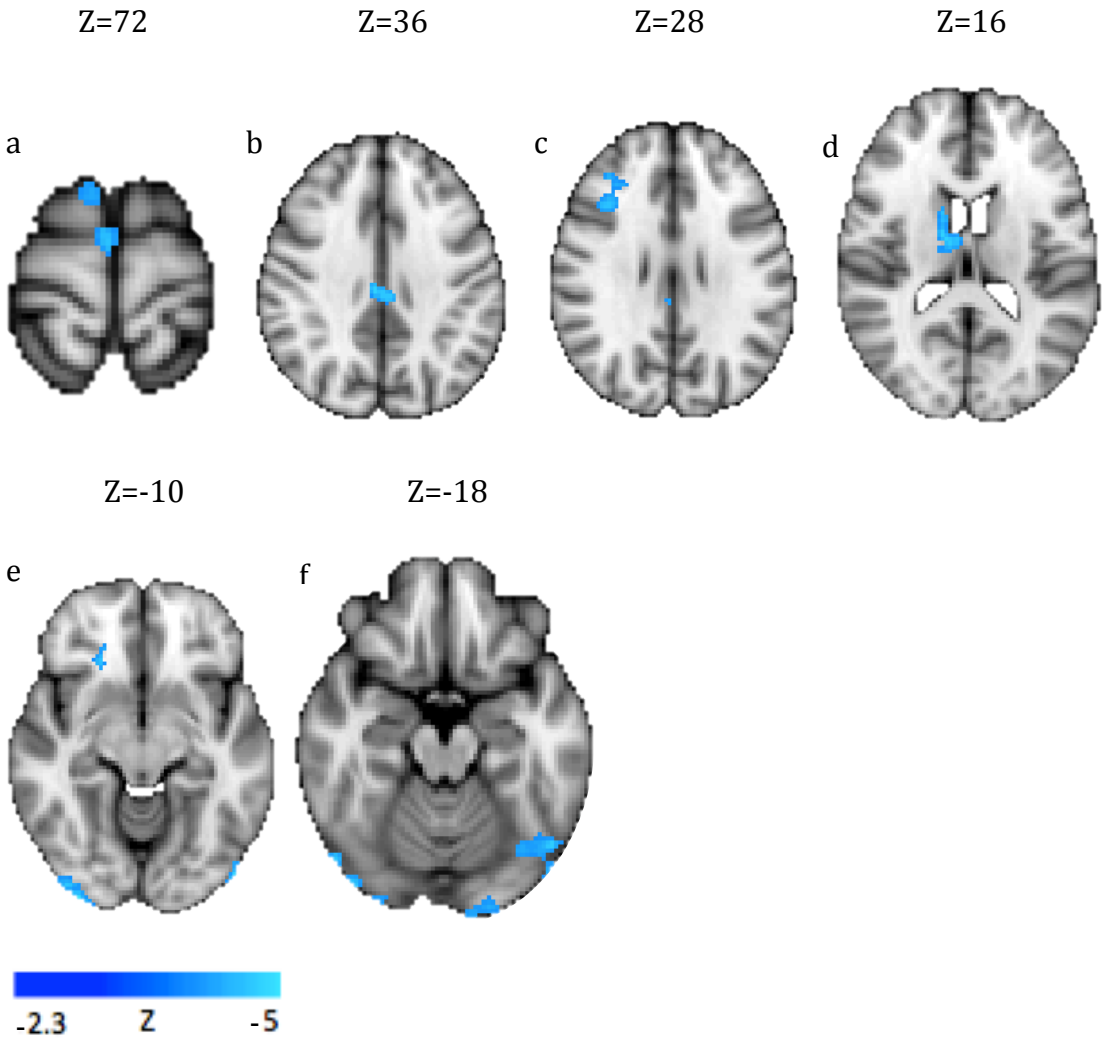

Figure 3. Resting-state functional connectivity differences between people at clinical high risk and healthy control participants. Compared to HC, CHR participants demonstrated less connectivity between the PCC seed ROI and the (a) superior frontal gyrus, supplementary motor cortex, (b) bilateral PCC, (c) frontal pole, middle frontal gyrus, PCC (d) right thalamus, right caudate (e) lateral occipital cortex, occipital pole, frontal orbital cortex (f) occipital fusiform gyrus, lateral occipital cortex, occipital pole.

3.2.2 The salience network (SN)

Hypothesis two was not supported, as hypoconnectivity was not observed between the regions of the SN, the insula seed ROI and the anterior cingulate cortex in people at CHR when compared to HC**.** A decrease in RSFC was observed in CHR participants between the seed ROI and the precentral gyrus, left frontal orbital cortex and occipital pole, as well as the intracalcarine cortex, and finally the right middle temporal gyrus (see Figure 4), which is part of the DMN.

People at CHR demonstrated hyperconnectivity between the SN seed ROI and the left temporal occipital fusiform cortex, the right inferior temporal gyrus, right frontal pole, right middle frontal gyrus, as well as bilaterally in the cerebellum, when compared to HC (see Figure 5). None of these regions were a part of the SN in HC. Further, clusters of increased connectivity with the insula, specifically the middle frontal gyrus, overlapped with the ECN of HC suggesting aberrant patterns of functional specialization (Woodward et al. 2011).

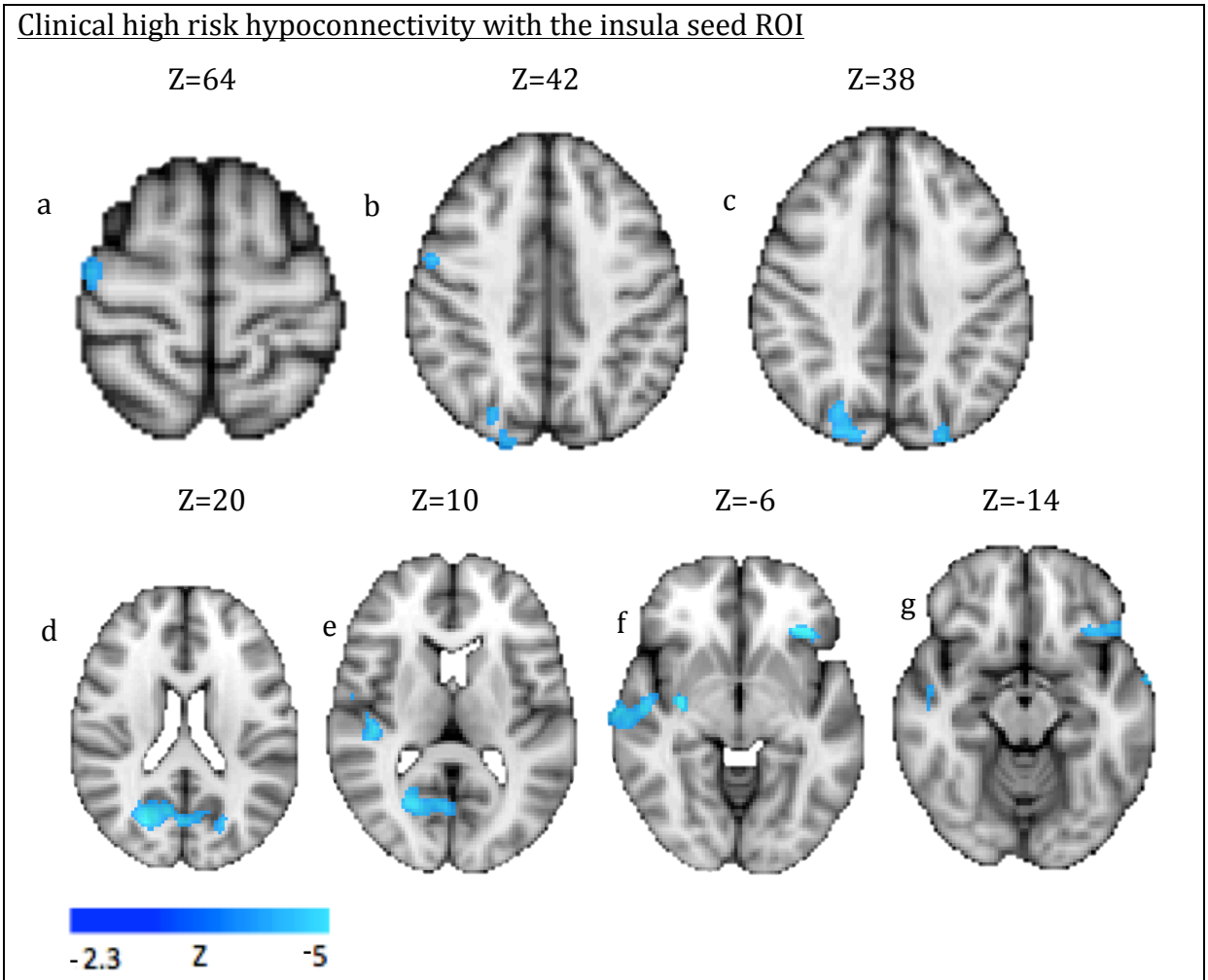

Figure 4. Resting-state functional connectivity differences between people at clinical high risk and healthy control participants in the salience network. Compared to HC, CHR participants demonstrated less connectivity between the insula seed ROI and the (a) precentral gyrus (b) right precentral gyrus, lateral occipital cortex, occipital pole (c) bilateral lateral occipital cortex, bilateral occipital pole (d) bilateral cuneal, bilateral precuneus, right supracalcarine cortex (e) right precuneus, intracalcarine cortex, planum tamporale, Heschl's gyrus, central opercular cortex (f) left frontal orbital cortex, right putamen, right insula, right planum polare, right superior temporal gyrus, right MTG (g) right frontal orbital cortex, bilateral superior temporal gyrus (left is more anterior; Right is more posterior), bilateral MTG.

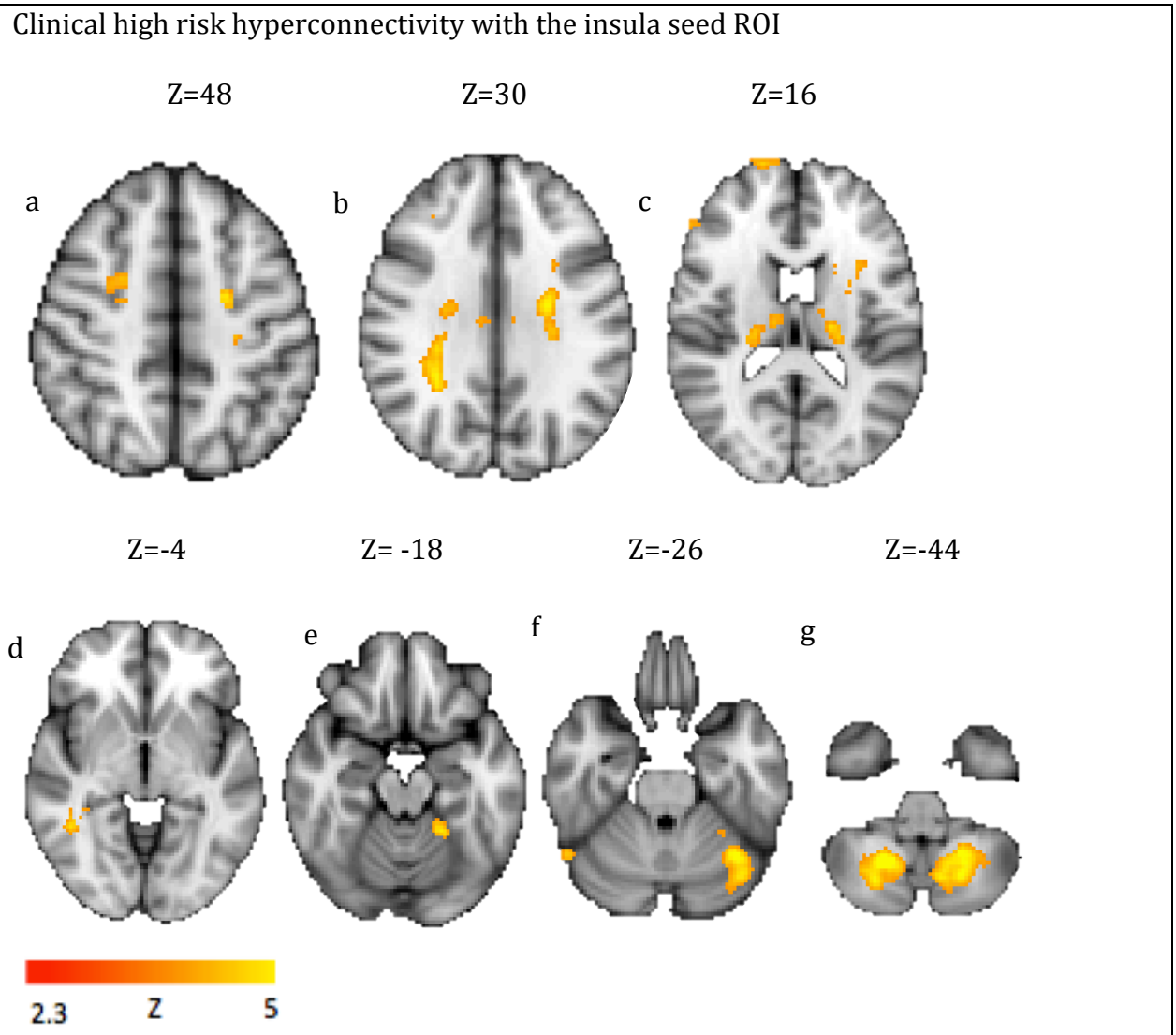

Figure 5. Resting-state functional connectivity differences between people at clinical high risk and healthy control participants in the salience network. Compared to HC, CHR participants demonstrated greater connectivity between the insula seed ROI and the (a) bilateral superior frontal gyrus, bilateral middle frontal gyrus, bilateral precentral gyrus, (b) white matter (c) inferior frontal gyrus, left caudate, frontal pole, frontal operculum cortex, bilateral thalamus, insula/putamen (d) right lingual gyrus, bilateral temporal occipital fusiform cortex, inferior temporal gyrus (e) left temporal occipital fusiform cortex, temporal fusiform cortex, parahippocampal gyrus (f) bilateral cerebellum (g) right inferior temporal gyrus, temporal occipital fusiform gyrus, left cerebellum.

3.2.3 Consistency of dysconnectivity in higher-order resting state networks

Results from investigating RSFC of the ECN and DAN in people at CHR supported the exploratory hypothesis, in that dysconnectivity was found for each of the heteromodal RSN. Hyperconnectivity was present in the ECN in people at CHR, between the middle frontal gyrus seed ROI and regions not usually recruited by the ECN. These included the left brainstem and cerebellum, and the right frontal pole, right thalamus, right postcentral gyrus, and right posterior cingulate gyrus (see Figure 6). Hyperconnectivity between the cerebellum, part of the DMN, and the posterior cingulate gyrus, the seed ROI for the DMN, suggests overlap between the RSN in people at CHR and is indicative of altered functional specialization within the ECN network.

A decrease in functional connectivity between the ECN seed ROI and the left frontal orbital cortex, right temporal pole, right angular gyrus and bilateral middle temporal gyrus was observed (see Figure 7). The middle temporal gyrus is part of the DMN in HC. Decreased functional connectivity between the ECN seed ROI and this region of the DMN may demonstrate an altered bidirectional relationship between the two networks in people at CHR, given results indicating that the DMN also shows hypoconnectivity with the seed ROI of the ECN.

Clinical high risk hypoconnectivity with the middle frontal gyrus seed ROI

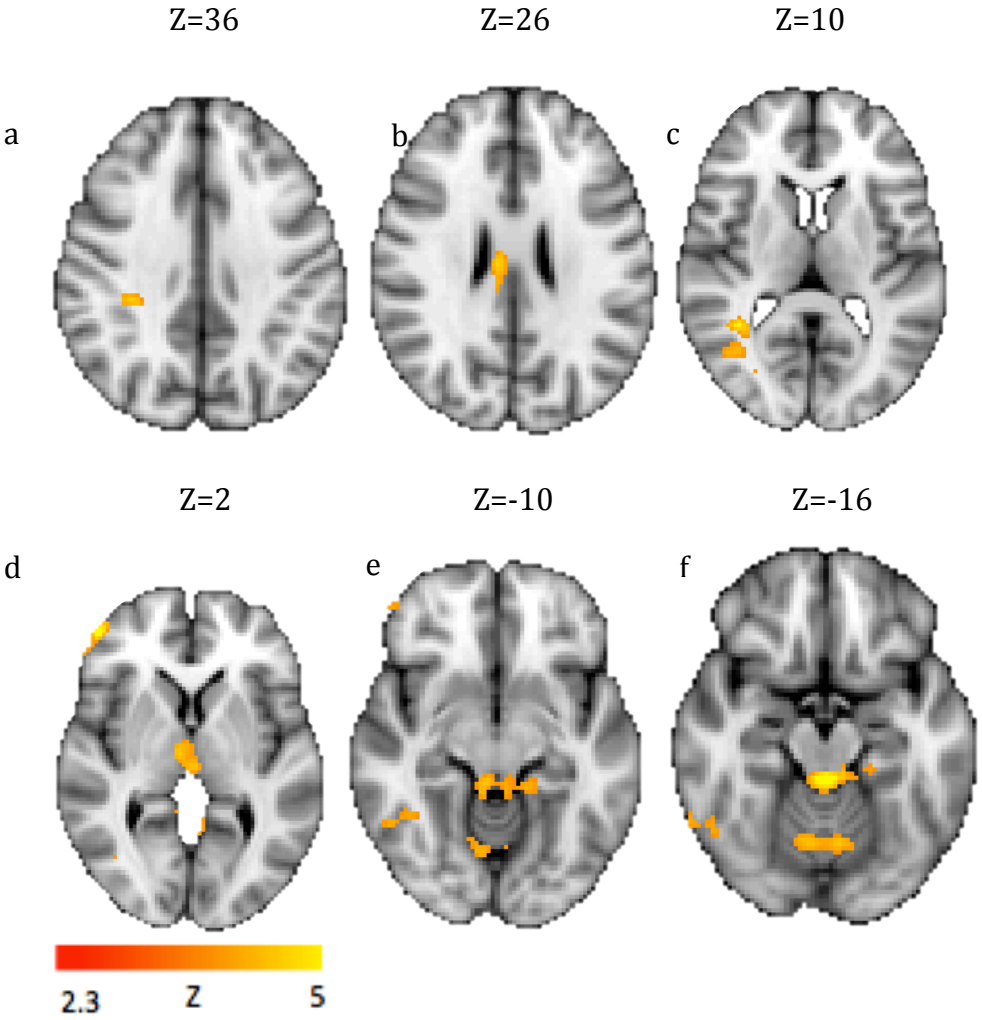

Figure 6. Resting-state functional connectivity differences between people at clinical high risk and healthy control participants in the executive control network. Compared to HC, CHR participants demonstrated greater connectivity between the middle frontal gyrus seed ROI and the (a) postcentral gyrus (b) PCC (c) right supramarginal gyrus, right MTG, right precuneus, right lateral occipital cortex, (d) right frontal pole, bilateral thalamus, bilateral PCC, left lingual gyrus, right lateral occipital cortex (e) right frontal pole, bilateral brainstem, left pHPC gyrus, bilateral lingual gyrus, right temporal occipital fusiform gyrus, right inferior temporal g, (f) bilateral brainstem, left parahippocampal gyrus, right inferior temporal gyrus, bilateral cerebellum.

Clinical high risk hypoconnectivity with the middle frontal gyrus seed ROI

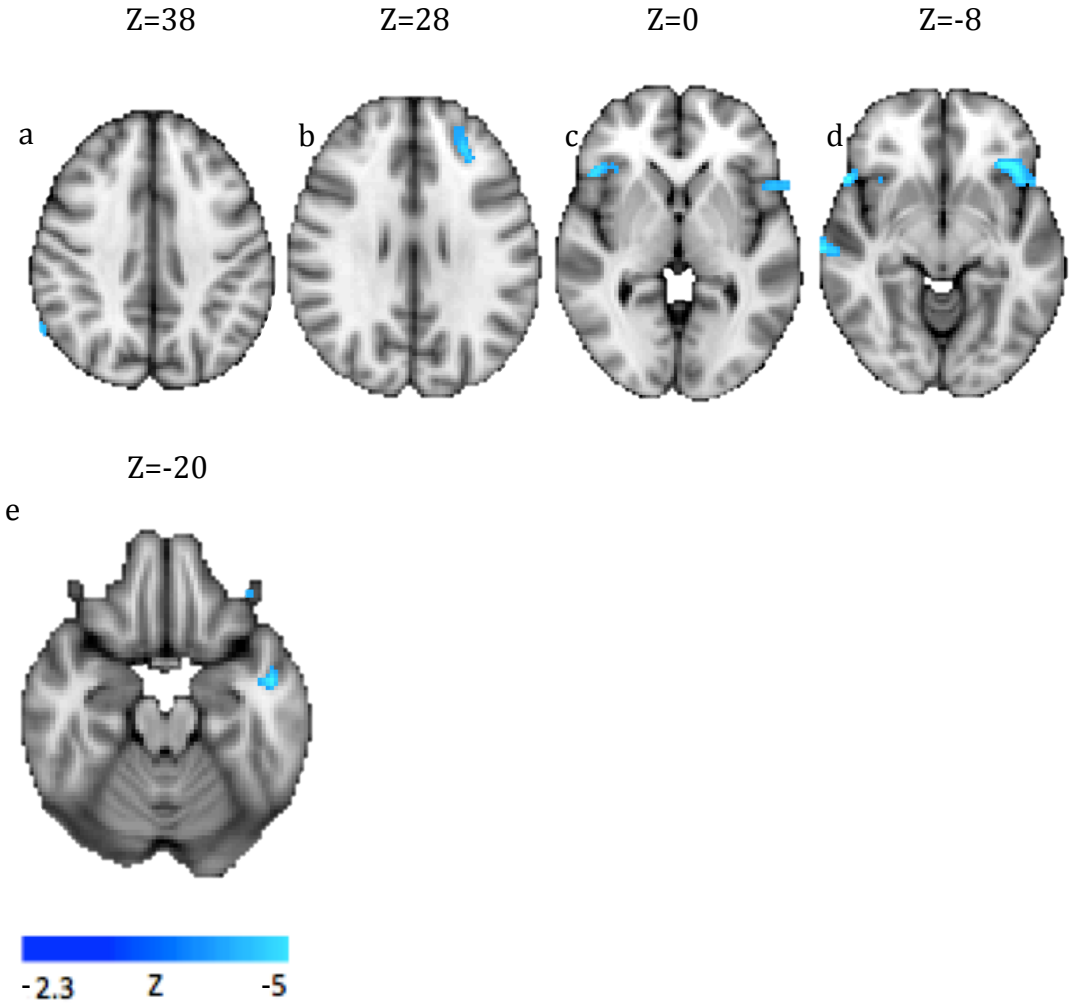

Figure 7. Resting-state functional connectivity differences between people at clinical high risk and healthy control participants in the executive control network. Compared to HC, CHR participants demonstrated less connectivity between the middle frontal gyrus seed ROI and the (a) right lateral occipital gyrus, (b) left frontal pole, left middle frontal gyrus, (c) left inferior frontal gyrus, right insula, right frontal operculum, right Inferior frontal gyrus, right frontal orbital cortex (d) bilateral insula, bilateral frontal orbital cortex, bilateral temporal pole, right MTG.

Upon investigation of the DAN, people at CHR exhibited hyperconnectivity between the superior parietal lobule seed ROI and the right precuneus, lingual gyrus, lateral occipital cortex, cerebellum and the bilateral parahippocampal gyrus (see Figure 8). With the exception of the cerebellum and parahippocampal gyrus, all regions found to have hyperconnectivity are part of the DAN, suggesting that the DAN stays spatially intact for the most part, though functional connectivity increases between network areas.

Hypoconnectivity was found between the DAN seed ROI and itself, the superior parietal lobule, the left frontal pole, postcentral gyrus, parietal operculum cortex and putamen, the right central opercular cortex, and the bilateral precentral gyrus. Further, a decrease in RSFC was found between, right inferior temporal gyrus, part of the ECN, the anterior cingulate gyri, part of the SN, and the middle temporal gyrus, part of the DMN (see Figure 9).

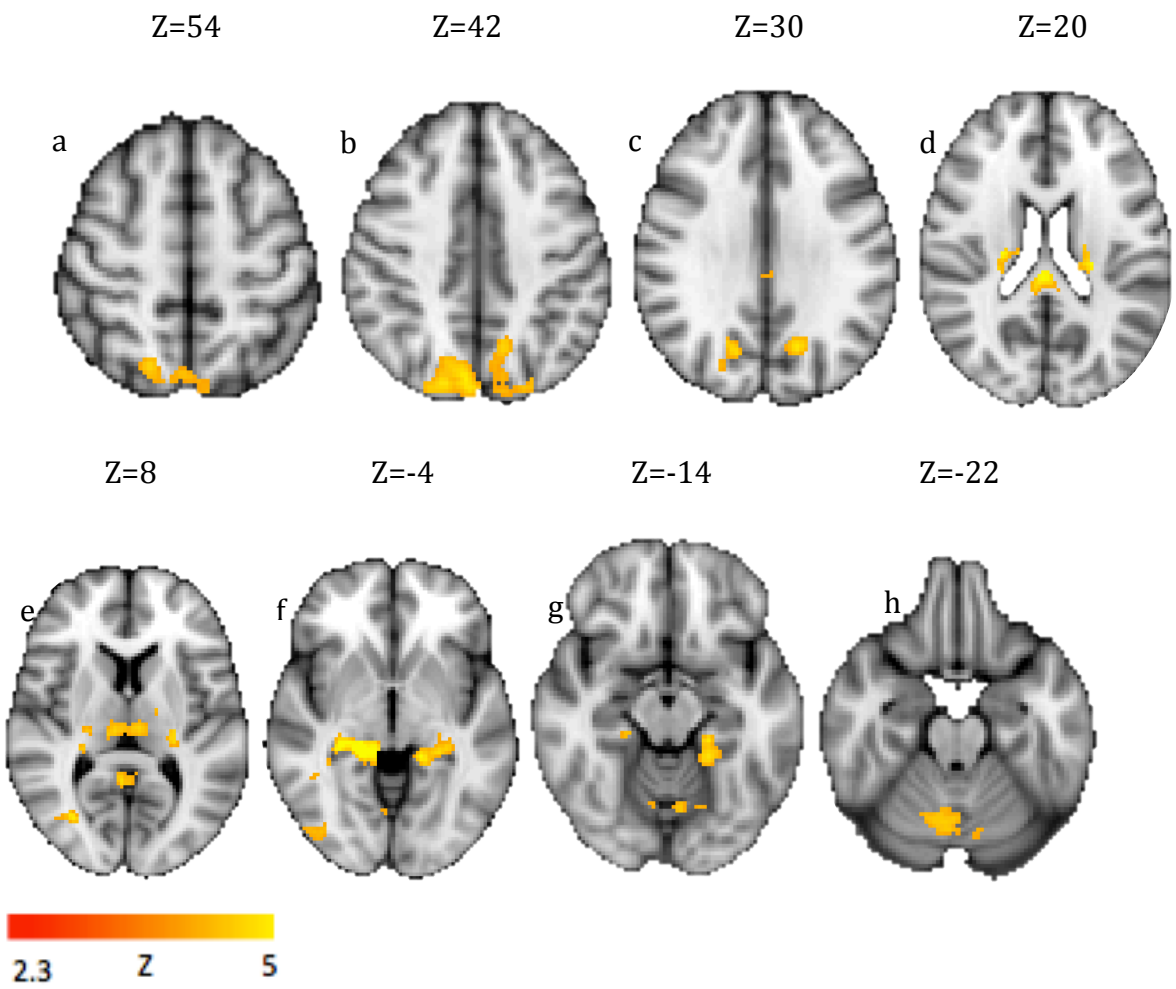

Figure 8. Resting-state functional connectivity differences between people at clinical high risk and healthy control participants in the dorsal attention network. Compared to HC, CHR participants demonstrated greater connectivity between the superior parietal lobule seed ROI and the (a) bilateral lateral occipital cortex, bilateral precuneus cortex, (b) bilateral lateral occipital cortex, bilateral precuneus cortex, right cuneal cortex (c) bilateral lateral occipital cortex, bilateral precuneus cortex, bilateral PCC (d) bilateral caudate, bilateral PCC (e) bilateral thalamus, bilateral PCC, bilateral precuneus, right lateral occipital cortex (f) right lateral occipital cortex, right lingual gyrus, right inferior temporal gyrus, bilateral hippocampus, bilateral parahippocampal gyrus, bilateral PCC (g) bilateral cerebellum, bilateral lingual gyrus (mostly left), bilateral parahippocampal gyrus, (h) bilateral cerebellum.

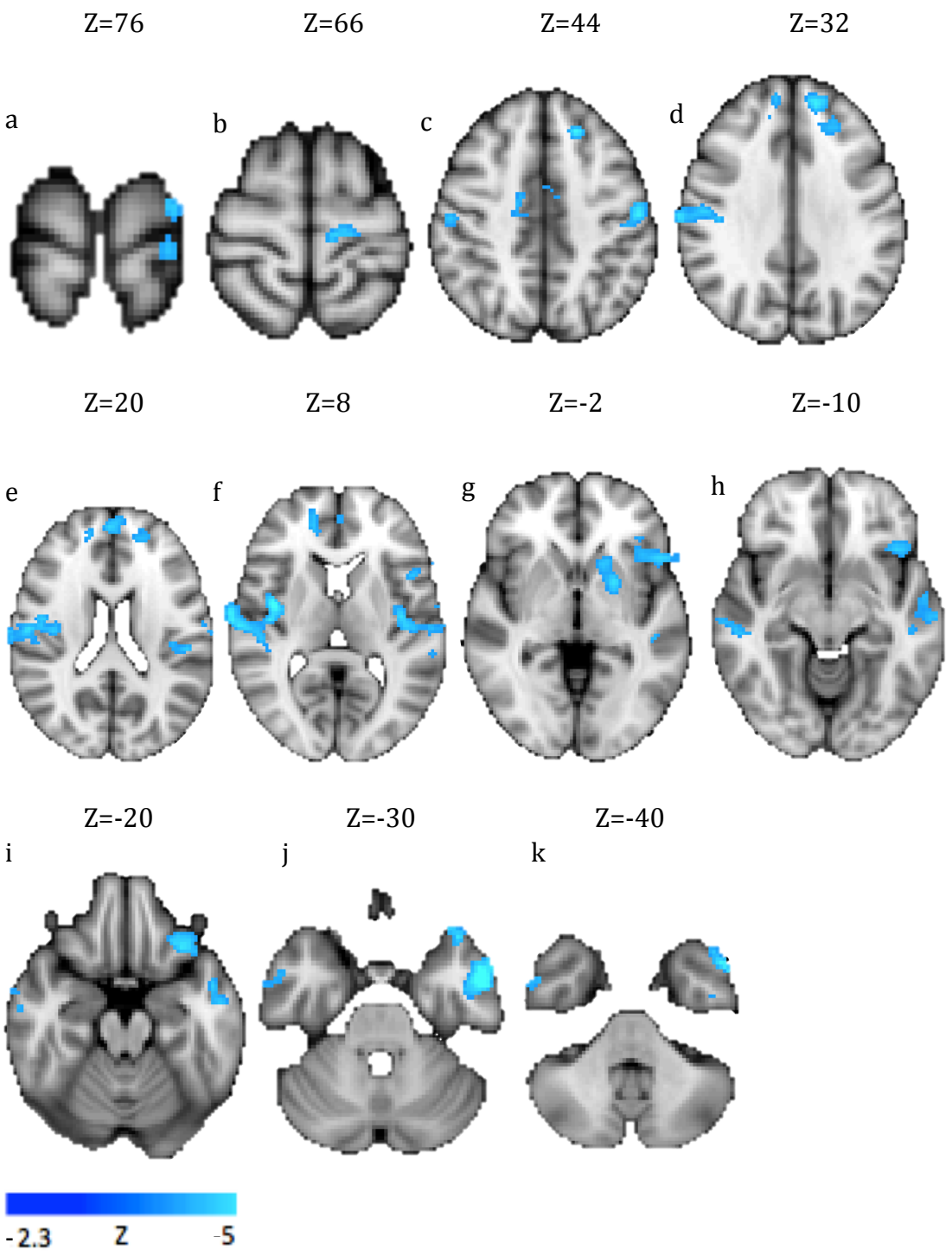

Figure 9. Resting-state functional connectivity differences between people at clinical

high risk and healthy control participants in the dorsal attention network. Compared to HC, CHR participants demonstrated less connectivity between the superior parietal lobule seed ROI and the (a) left precentral gyrus (b) left precentral gyrus, left postcentral gyrus (c) bilateral postcentral gyrus, right PCC, right precentral gyrus, right supplementary motor cortex, left anterior cingulate gyrus, left superior frontal gyrus (d) right supramarginal gyrus, right postcentral gyrus, bilateral superior frontal gyrus, bilateral frontal pole, left middle front gyrus (e) bilateral frontal pole, bilateral superior frontal gyrus, bilateral paracingulate gyrus, (f) middle-right paracingulate gyrus, left paracingulate gyrus, left anterior cingulate cortex, bilateral central opercular cortex, bilateral planum temporale, bilateral Heschls, bilateral Insula, bilateral superior temporal gyrus (g) left frontal orbital cortex, left insula, left inferior frontal gyrus, left caudate, left putamen, left pallidum, left superior temporal gyrus (h) left frontal orbital cortex, left superior temporal gyrus, bilateral middle temporal gyrus, (i) left frontal orbital cortex, left superior temporal gyrus, bilateral middle temporal gyrus, (j) left temporal pole, left superior temporal gyrus, bilateral middle temporal gyrus, left inferior Temporal gyrus (k) left temporal pole, bilateral inferior temporal gyrus.

Chapter Four: DISCUSSION

Results will first of all be discussed in the context of existing research. Limitations will be presented followed by the implication of this research. Finally, avenues for potential future work will be discussed.

4.1 Aberrant default mode network functional connectivity

4.1.1 Hyperconnectivity within the default mode network (DMN)

Hyperconnectivity was found within the DMN of people at CHR, supporting the first hypothesis. These results generally fit with those previously reported by Shim et al. (2010), as data from both studies indicate hyperconnectivity in people at CHR between the PCC seed ROI and regions both within and outside of the DMN. Within the DMN of the current study's CHR participants, the PCC seed ROI showed hyperconnectivity with the precuneus and hippocampus. This is inline with MRI studies previously implicating the precuneus for functional abnormalities as it has reduced grey matter volume in people at CHR (Borgwardt et al. 2007). Moreover, Shim and colleagues (2010) also found hyperconnectivity between the PCC and precuneus. One possible explanation for these findings is that the precuneus plays a role in reflective-self awareness, episodic, and source memory (Cavanna and Trimble 2006). It is possible that hyperconnectivity between the PCC seed ROI and the precuneus reflects a compensatory mechanism whereby the PCC seed ROI inhibits the over-activation of the precuneus, contrary to what is found in people with schizophrenia (Liu et al. 2012). This would be congruent with the lack of severity of

symptoms experienced by people at CHR relative to people with a psychotic illness (Addington and Heinssen, 2012).

The finding of hyperconnectivity between the PCC seed ROI and the hippocampus was not reported by Shim et al. (2010) and is at odds with schizophrenia research. Authors have reported that hypoconnectivity is more common between the DMN seed region and the hippocampus, and that this may play a role in the generation of psychotic symptoms due to impaired source monitoring (Rotarska-Jagiela et al. 2010;Weiss et al. 2004). Indeed, reduced hippocampal connectivity has correlated with higher scores of hallucinations and delusions on the PANSS (Rotarska-Jagiela et al. 2010). Our finding of increased connectivity between these two brain regions may illustrate a compensatory mechanism in people at CHR, in conjunction with that of the precuneus, which occurs prior to the onset of psychosis. Again, this would be congruent with the lack of severity of symptoms experienced by people at CHR relative to people with a psychotic illness. As these individuals do not have full conviction of their psychotic-like experiences (Addington and Heinssen 2012), it is possible that a shift from hyperconnectivity to hypoconnectivity between the PCC and hippocampus decreases the amount of restraint the DMN has on hippocampal activation. This is supported by previous findings suggesting that the hippocampus becomes more active than expected while individuals with schizophrenia have hallucinations, a potential indication that any inhibitory action of the DMN is no longer effective (Dierks et al. 1999;Oertel et al. 2007). Positive symptoms of psychosis may, therefore, be associated with an inability to attenuate networks or regions that should only

be online during rest, while one is awake (Rotarska-Jagiela et al. 2010;Woodward et al. 2011).

4.1.2 Hypoconnectivity within the default mode network (DMN)

In the current study, the only region that demonstrated hypoconnectivity within the DMN when comparing people at CHR to HC was the seed ROI, the PCC (Figure 3). Shim et al. (2010) did not observe this finding, but hypoconnectivity in the PCC of people at CHR is congruent with schizophrenia RSN literature. Hypoconnectivity in the PCC during resting state has been previously reported in people at several stages of schizophrenia, as well as in people who do not have a psychotic disorder but have high genetic loading for schizophrenia (Rotarska-Jagiela et al. 2010;Bluhm et al., 2007;Garrity et al., 2007;Wolf et al. 2011;Jang et al. 2011). It has been suggested that hypoconnectivity in the DMN may impede the ability of the network to perform its functions properly (Buckner et al. 2008;Jang et al. 2011). Due to a lack of inhibition that would result from hypoconnectivity of the PCC seed ROI, the DMN would be less restrained and may perform its duties both when appropriate and when not. One such function is monitoring internal thoughts. Failure to detect the origins of thoughts, for example confusing internal thoughts for external stimuli, due to increased monitoring would likely lead to confusion as to which thoughts are one's own may; a notion believed to be fundamental to the positive symptoms of schizophrenia (Frith 1995). There is evidence to support this as hypoconnectivity within the DMN has been correlated with positive symptoms of schizophrenia (Rotarska-Jagiela et al. 2010). Our findings therefore support the view that functional pathology in the DMN of people at CHR

reflects a malfunction in the ability to monitor and detect differences between internal thoughts and external stimuli, which may contribute to psychotic-like symptoms (Jang et al. 2011).

4.1.3 Hyperconnectivity outside of the default mode network (DMN)

Due to a lack of research in the area, support for the findings of PCC seed ROI hyperconnectivity outside of the DMN is from publications assessing individuals with schizophrenia, not with people at CHR. These publications are congruent with our findings of spatial overlap the between PCC seed ROI and regions outside of the DMN (Whitfield-Gabrieli et al. 2009;Woodward et al. 2011). For example, hyperconnectivity and altered spatial topography was reported between the PCC seed ROI and fronto-temporal areas of the brain in people with schizophrenia (Woodward et al. 2011). In the current study PCC hyperconnectivity was observed with the frontal pole of people at CHR, which would possibly lead to increased inhibition of the brain region. One of the roles of the frontal pole is holding onto an alternative course of action while performing an ongoing one (Olson et al. 2007). This process is critical for successful reasoning, problem solving and multitasking and inhibition of the frontal pole may lead to deficits in these abilities (Olson et al. 2007). Interestingly, people at CHR have cognitive deficits in domains of executive function, which may be related to inhibition of the frontal pole from the PCC (Fusar-Poli et al. 2012). Given the qualitative similarities between cognitive deficits in CHR and schizophrenia samples, one might expect similar anomalies to be found in frontal regions of the two groups. The current study also found hyperconnectivity in the temporal pole, similar to results in

schizophrenia literature (Woodward et al. 2011). This region of the brain is involved in regulating mood states such as severity of depression, face processing, and supporting theory of mind processes (Olson et al. 2007;Vollm et al. 2006). Inhibition of the area in both people at CHR and those with schizophrenia would likely lead to impairments is all of these domains, which is in fact the case (Olson et al. 2007).

From an etiological standpoint, it is possible that the current findings suggestive of altered RSN spatial topography reflect compromised maturational processes that occur throughout brain development (Woodward et al. 2011). Normal brain maturation includes a shift between diffuse to local processing by strengthening long-range connections and increasing segregation between neural networks, creating a small-world organization (Fair et al. 2007, 2009;Stevens et al. 2009;Uddin et al. 2010). Once these connections are made, there is very little spatial overlap between the DMN and other networks in HC (Vincent et al. 2008), contrary to the current results in the CHR group. This supports the notion of irregular developmental changes in brain networks in this sample.

4.1.4 Hypoconnectivity outside of the DMN

Compared to HC, people at CHR exhibited hypoconnectivity between the PCC seed ROI and regions that were not part of HC DMN. One such brain region was the frontal orbital cortex. This finding is complementary to previous publications that reported reductions in the GM of bilateral orbital frontal gyri of people with schizophrenia (Takayanagi et al. 2010), and people at family high-risk for psychosis (Rosso et al. 2010). The finding of decreased functional connectivity in CHR participants is, however,

incongruent with schizophrenia fMRI connectivity research, which suggests that people with schizophrenia have increased connectivity between the frontal orbital cortex and the DMN (Cole et al. 2012). Dopamine modulates the activity of the frontal orbital cortex and the posterior cingulate (Tomasi and Valkow 2011). There is evidence to suggest that high dopamine levels are related to greater frontal orbital cortex-DMN connectivity in people with schizophrenia (Cole et al. 2012). We show hypoconnectivity in CHR participants relative to controls, which may be indicative of an overactive frontal orbital cortex. Hypoconnectivity and over activity of the frontal orbital cortex would likely be suggestive of depleted dopamine levels in people at CHR for psychosis (Howes et al., 2012). Relative to HC, however, dopamine is still elevated in people at CHR (Egerton et al. 2013). It is possible that hypoconnectivity may be protective against dangerously high levels of dopamine, by decreasing inhibition of the frontal orbital cortex, allowing it to deplete levels of dopamine faster than usual. If this mechanism fails and levels of dopamine are exceedingly high, as is the case in schizophrenia (Cole et al. 2012), hyperconnectivity becomes present and individuals at CHR may eventually experience a conversion to psychosis. This idea is supported by studies that suggest positive symptoms are responsive to dopamine depletion in people at CHR a well as in schizophrenia (Bloemen et al. 2013; Tajima et al., 2009).

4.2 Aberrant salience network (SN) functional connectivity

4.2.1 Hyperconnectivity and hypoconnectivity within the SN

Relative to HC, people at CHR did not have any remarkable change within the SN. The second hypothesis, that hypoconnectivity will be present between the regions comprising the SN in people at CHR when compared to controls, was not supported.

4.2.2 Hyperconnectivity outside of the SN

In the current study, hyperconnectivity outside of the SN is the most robust between the insula seed ROI and the cerebellum. Though not directly tested, it is possible that the increase in functional connectivity present in CHR participants is an example of an inability to reduce activation in regions associated with active tasks, otherwise known as reduced anti-correlations (Shim et. al 2011). There is much evidence to suggest the cerebellum functions in both motor and non-motor domains (Strick et al. 2009). In fact, the insula and cerebellum share several functional responsibilities including perception of pain, emotion and language (Baliki et al. 2009; Craig 2009;Strick et al. 2009). There is also evidence that the insula and cerebellum are components of a network specifically associated with speaking out loud (Riecker et al. 2000). As all participants were verbally screened for contraindications prior to entering the fMRI scanner, all participants spoke just prior to the resting state. It is possible that this network was not appropriately attenuated in the CHR sample. Though this explanation is speculative, reductions in anti-correlations have been

demonstrated in both schizophrenia and CHR samples (Jeong and Kubicki 2010, Shim et al. 2010).

4.2.3 Hypoconnectivity outside of the SN

Results indicating hypoconnectivity between the insula seed ROI, and regions that are not commonly part of the SN were found. These regions included the middle temporal gyrus, a component of the DMN, and the frontal orbital cortex.

One function of the SN may be to facilitate switching from networks online during rest, specifically the DMN, to task-positive networks, while one becomes engaged with external stimuli (Sridharan et al. 2008;Liao et al. 2010). A number of studies support this notion, as disruptions in SN functional connectivity are associated with impaired deactivation of the DMN, demonstrating the necessity of proper SN functioning to the attenuation of the DMN (Garrity et al. 2007;Whitfield-Gabrieli et al. 2009). Further, the SN may be sufficient in the prediction of activation of the DMN (Skudlarski et al. 2010). In order for the SN to effectively facilitate switching from RSN to task-positive ones, it would need to be coupled to task-related brain networks. For example, selecting proximal salience, described as the action the brain takes in order to prepare for an appropriate behavioural response in the presence of a stimulus, would necessitate network coupling of the SN to task-positive networks when appropriate (Palaniyappan and Liddle 2011). Aberrancies in coupling may cause inappropriate proximal salience, which would likely lead to misattribution of importance to certain internal or external stimuli. Specifically, the irregular allocation of proximal salience to an internally generated stimulus may lead to

recruitment and increased connectivity of RSN, causing more proximal salience to internal stimuli, which could subsequently lead to further aberrancies in functional connectivity (McGuire et al. 1995;Blakemore et al. 2000;Seeley et al. 2007;Palaniyappan and Liddle 2011). SN activation has been reported during hallucinations in people with schizophrenia, suggesting proximal salience may be occurring inappropriately specifically during acute phases of psychosis (Palaniyappan and Liddle 2011).

Hypoconnectivity was observed between the SN and DMN in our sample of people at CHR; the insula seed ROI had decreased functional connectivity with the middle temporal gyrus. The function of the middle temporal gyrus is related to semantic processing and control (Whitney et al. 2011). During auditory verbal hallucinations activation of the middle temporal gyrus increases, suggesting this area plays a role in inappropriate perception of verbal stimuli (Jardri et al. 2011), and increased connectivity between the insula and middle temporal gyrus has been found in people with schizophrenia when compared to controls (Liu et al. 2009). Given that people at CHR experience only perceptual abnormalities, as apposed to hallucinations, it is possible that the hypoconnection between the insula and middle temporal gyrus may be related to attenuate positive symptoms experienced by people at CHR for psychosis. It would be expected that connectivity between the DMN seed ROI and the middle temporal gyrus would be unaffected in CHR participants as long as perceptual abnormalities were not exacerbated. This was found to be the in the current sample.

Hypoconnectivity was observed between the insula seed ROI and the frontal orbital cortex of people at CHR in the current study. The frontal orbital cortex is believed to

support several cognitive functions such as attention and working memory as well as social cognitive functions, some of which are impaired in CHR samples (Addington and Heinssen 2011;Jeon et al. 2012).

Decreased functional connectivity between the insula seed ROI and the frontal orbital cortex in people at CHR may be related to deficits observed in people at CHR, as one of the potential functions of the insula is to determine which competing stimuli are the most salient. For example, both the insula and frontal orbital cortex are implicated in the process of selecting which competing representations in working memory are most salient via emotional information (Levens and Phelps 2010). A breakdown in connectivity between these regions may be related to an inability in determining which stimuli are the most relevant. This may translate behaviourally as inattention or deficits in cognition.

4.3 Consistency of dysconnectivity in higher-order resting state networks

All heteromodal RSN display dysconnectivity either within the network itself or altered connections with regions outside of the networks. As dysconnectivity was present across these networks, these findings support the exploratory hypothesis.

4.3.1 Hyperconnectivity and hypoconnectivity within the ECN

There were no changes in connectivity observed within the ECN network when comparing people at CHR to HC.

4.3.2 Hyperconnectivity outside of the ECN

Results from the current study suggest that there is significant hyperconnectivity between the ECN seed ROI and parts of the brain that are not commonly associated with this network during resting state in people at CHR for psychosis. This is suggestive of altered spatial topography of the ECN. Previous publications regarding RSN dysconnectivity in people with schizophrenia corroborate these findings (Woodward et al. 2011;Wolf et al. 2011;Rosazza & Minati 2011). Woodward, for example found that the DMN had expanded to include regions of the ECN (Woodward et al, 2011). We show that this expansion of the DMN and ECN may be bidirectional in people at CHR for psychosis. Specifically, the ECN seed ROI exhibits hyperconnectivity with regions such as the right PCC seed ROI of the DMN in people at CHR. Previous publications in people with schizophrenia have not reported this, however there are several possible explanations accounting for the discrepancy. First, the people in our sample do not have a diagnosis of a psychotic illness. Given previous reports that symptom severity correlates with dysconnectivity in schizophrenia, it is expected that dysconnectivity in RSN of people at CHR would be different, potentially correlating with CHR symptoms. Second, the sample in the current study is younger than many samples of published studies in schizophrenia (Kuhn and Gallinat 2011). As networks tend to segregate with age (Fair et al. 2007), it is possible that RSFC in the younger group of participants reflects processes that have yet to occur. Further, given previous reports indicating that neurodevelopmental complications likely arise in schizophrenia (Fusar-Poli et al. 2011), results in people at CHR may reflect the delayed or irregular maturation of RSN relative to their HC counterparts.

Alternatively, ECN overlap of the PCC may play a protective role in people who are at CHR. A function of the ECN seed ROI, the middle frontal gyrus, is to preserve certain aspects of input processing (Talati and Hirsch 2005). If the PCC was to become compromised, the middle frontal gyrus may take over part of the DMN's responsibilities. This may be accomplished by the middle frontal gyrus assisting in the discrimination of inputs that are internally or externally generated, allowing people at CHR to discern between reality and psychosis-like experiences. Given that there is little evidence of ECN overlap of the PCC in people with schizophrenia, and that people at CHR can at least doubt the reality of psychosis-like experiences, it is possible that hyperconnectivity between the middle frontal gyrus of the ECN and the PCC of the DMN may be protective against hallucinations (Wolf et al. 2011;Woodward et al. 2011).

Lastly, hyperconnectivity between the ECN seed ROI, the frontal pole was and the brainstem was found in our study. This is not surprising as the role of the frontal pole is directly relevant to cognitive processing and decision-making (Olsen et al. 2007) processes that are supported by the ECN (Seeley et al. 2007). It is possible, however, that additional recruitment of the frontal pole is indicative of worsening malfunctions in the brain, though this was not directly tested in the current study. Previous examinations in CHR participants suggested that an overactive frontal pole is associated with increased risk of conversion to psychosis (Allen et al. 2012). We also found that the ECN had a robust increase in functional connectivity with the brainstem. Increased activation in this region was also associated with increased conversion to psychosis CHR participants, and can even lead to hallucinations if damage to this area occurs (Allen et al. 2012;Silva and Brucki 2010). It is

possible that increased functional connectivity between the ECN and these areas may indicate anomalies in brain function of people at CHR for psychosis.

4.3.3 Hypoconnectivity outside of the ECN

Reduction in connectivity between the ECN and regions outside of this network included the right angular gyrus and the temporal pole. These findings are congruent with reductions reported in grey matter volume and neural activation in the middle frontal gyrus in CHR participants (Fusar-Poli et al. 2011). Further, neuroimaging research has suggested the angular gyrus severs as an integration hub for converging multisensory information, supporting many functions such as, memory retrieval, theory of mind, conflict resolution, semantic processing and other executive functions (Seghier 2013). Hypoconnectivity between angular gyrus and the ECN may be relevant to several deficits experienced by people at CHR for psychosis. This is because the middle frontal gyrus of the ECN supports executive functions that are related to angular gyrus activation. A decrease in connectivity between the regions may indicate malfunctioning communication, which could lead to impaired recruitment of the necessary regions for executive functioning.

RSFC between the ECN and the temporal pole was reduced in CHR participants when compared to HC. The temporal pole is believed to have several functions. These include linguistic integration, a process that links semantic information to create understanding of language (Dupont et al. 2002). Decreased functional connectivity between the executive control network and the temporal pole may influence CHR

symptoms in cognition, specifically, verbal IQ, memory and fluency. The temporal pole has also been implicated to play a role in face processing and theory of mind (Olsen et al. 2007). Decreased ECN influence on the temporal pole could suggest that this areas is recruited less in CHR, leading to symptoms associated with the functions of this brain region. Though this has never been demonstrated in CHR samples, decreased grey matter thickness of the temporal pole has been in CHR samples that eventually convert to psychosis (Fornito et al. 2008). Evidence to the contrary comes from findings suggesting that deficits of social cognition stay relatively stable over the course of transition from CHR to schizophrenia and that the temporal pole has increased activation in schizophrenia (Fahim et al. 2005). This discrepancy illustrated the necessity of further research to determine the relationship between activation, connectivity and deficits in performing tasks of social cognition.

4.3.4 Hyperconnectivity within the DAN

Hyperconnectivity within the DAN was found between the superior parietal lobule seed ROI and the right precuneus. The DAN controls spatial orientation by changing saliency of stimuli, while the precuneus directs attention in space and influences context dependent memory (Cavanna and Trimble 2006;Nagy et al. 2012;Grill-Spector et al. 2001). Hyperconnectivity may indicate the influence of the DAN on the precuneus whereby increased attention in space is necessary for determining saliency of spatial stimuli in CHR participants. This is speculative but is supported by publications reporting that CHR individuals who developed subsequent psychosis displayed more thinning in the

precuneus, suggesting reduced capacity to perform their functions properly (Ziermans et al. 2012).

4.3.5 Hyperconnectivity outside of the DAN

Several regions outside of the DAN were noted to have hyperconnectivity with the superior parietal lobule seed ROI. These included the lateral occipital cortex and lingual gyrus. Interestingly, these regions have functions related to visual attention and processing. The lateral occipital cortex, for instance, helps process faces and objects, and the lingual gyrus facilitates the encoding of complex images and identification and recognition of words (Cavanna and Trimble 2006;Nagy et al. 2012;Grill-Spector et al. 2001). These aberrancies are unique to people at CHR because individuals with schizophrenia tend to display hypoconnectivity within this network (Woodward et al. 2011). In one of the only studies to investigate DAN functional connectivity in people with schizophrenia, the DAN seed ROI and the lingual gyrus showed decreased connectivity (Woodward et al. 2011). The authors suggested that deficient RSFC in the DAN might be associated with cognitive impairment observed in schizophrenia. As there are striking similarities in neuroanatomical location of DAN dysconnectivity of people at CHR and individuals with schizophrenia, it is possible that increased connectivity may play a protective role in CHR functioning, and the decline of connectivity seen in people with schizophrenia may serve as an indication of worsening symptoms or even progression towards first episode psychosis. This notion is supported by findings that the DAN functions to control spatial orientation

4.3.6 Hypoconnectivity outside of the DAN

Significantly reduced RSFC was observed between the DAN seed ROI, the frontal pole, and the pre and postcentral gyri. Decreased functional connectivity between the DAN and the frontal pole may be indicative of a deficit in attention allocation to cognitive functions, such as spatial orientation, supported by the region. Given intermediate results on cognitive functioning tasks in CHR participants compared to HC and people with schizophrenia (Addington and Heinssen 2012), it stands to reason that other brain areas would likely compensate for this deficiency by increasing functional connectivity with the frontal pole. Indeed, this is the case for all other RSN assessed. Reduction in RSFC between the DAN and the pre and postcentral gyri are suggestive of reduced attention to motor and sensorimotor functions in the CHR sample. Though no conclusive evidence to date suggests significant motor deficits in people at high risk for psychosis, it is possible that perception of motion may be disturbed as has been reported in schizophrenia (Wang et al. 2010). Though previously discussed in regards to its non-motor functions, the finding that functional connectivity is increased between the cerebellum and all RSN may suggest a possible explanation for why symptoms related to disconnectivity of the motor cortex are not present in this sample. The exact function of the DAN and its relevance to psychotic illnesses is poorly understood, however results of the current study do implicate it as having significantly altered activity in people at CHR, specifically aberrant functional connectivity between the DAN and other regions of the brain related to cognitive and motor functions.

4.4 Limitations

There were several limitations to the current study. First, although our sample size was bigger than the previous study (Shim et al. 2010) it was a relatively small sample with only 31 CHR and 12 HC participants. Nonetheless, significant differences were observed between the two groups. Second, many of the CHR participants were taking medication at the time of their fMRI scan (see results). Several publications have described changes in RSN functional connectivity due to antipsychotic and other psychotropic medications, leading to RSFC changes that are not necessarily due to endogenous changes in the brain (Lui et al. 2010). This limitation, however, did not seem to greatly impact our results as they were in conjunction with previous findings from both the CHR and schizophrenia literature. Third, the current data is cross sectional. It is therefore not possible to decipher between state and trait characteristics of RSFC in people at CHR. While this does limit the interpretation and extrapolation of the results, our motivation was to first determine the existence of aberrant connectivity in our sample at all, as there is a lack of published investigations available. Fourth, it is possible that aberrancies in functional connectivity reflect only a change in arousal between CHR and HC participants. This is unlikely, however, as several different changes in connectivity were found in all four networks. Finally, the results presented here may not be unique to individuals at CHR for psychosis, as not all CHR individuals develop a psychotic disorder. Data reported may demonstrate more broad functional connectivity issues in people who may go on to develop several possible mental illnesses (Pettersson-Yeo et al. 2011).

4.5 Conclusion

The findings of the current study illustrate RSN functional connectivity in the development of mental illness. A marked difference in connectivity was found when comparing HC and people at CHR. Data are therefore suggestive of aberrant RSFC prior to the onset of psychosis. Further, results indicate that the alterations in connectivity vary across networks rather than a global increase or decrease. These findings are a stepping-stone upon which future research can continue to investigate baseline brain connectivity prior to the onset of psychosis.

4.6 Future work

Future investigations of RSFC in people at CHR should consider utilizing diffusion tensor imaging to assess the white matter tracts that may underlie functional connectivity. This would allow for the detection of disrupted white matter, which may influence patterns of RSFC in people at CHR. Future studies should also consider effective connectivity so that the influence of aberrant connectivity from one RSN to another may be understood. Another avenue for future work is the examination of the relationship between RSN functional connectivity and CHR symptoms. This could help determine the clinical relevance of aberrant RSFC in this population. Further, following CHR samples longitudinally, assessing both RSFC and symptom progression could lead to a better understanding of the impact aberrant RSFC may have on conversion to psychosis.

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