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Large-scale intrinsic functional connectivity and attention in schizophrenia

Michael Hunter

Michael Hunter
Candidate

Psychology
Department

This dissertation is approved, and it is acceptable in quality and form for publication:

Approved by the Dissertation Committee:

Vincent Clark, Ph.D. , Chairperson

Jose Canive, M.D.

Vincent Calhoun, Ph.D.

LARGE-SCALE INTRINSIC FUNCTIONAL CONNECTIVITY AND ATTENTION IN SCHIZOPHRENIA

by

Michael A. Hunter

B.A., Philosophy, The University of New Mexico, 2009

B.S., Psychology, The University of New Mexico, 2009

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ABSTRACT

It has been well-established that sustained attention and executive functioning are core deficits in schizophrenia (SZ). Growing evidence suggests that such attentional impairments may reflect disruptions in dominant intrinsic networks (INs). Functional network connectivity (FNC), described as the dependency between multiple INs, has revealed dysfunction among key INs in people with SZ. The objective of the current study was to test the hypothesis that SCZ would exhibit less specialized cognitive processing and therefore decreased FNC between dominant INs, and that any disruptions in FNC would predict neuropsychological profiles of attention. **Methods:** Thirty-five patients with SZ and thirty-three healthy controls (HC) were recruited for this study. Five minutes of eyes-closed resting-state fMRI (3T Trio scanner) was obtained for each participant. Resting-state scans were decomposed into 75 components using a group ICA suite (GIFT), and the FNC between all pair-wise components were obtained for each subject using the FNC toolbox. Participants were assessed using the Conners' CPT II and

the Wisconsin-card sorting task (WCST). **Results:** As expected, patients performed worse than HC on both tests of attention, and exhibited decreased FNC between default-mode subcomponents, a "salience" (anterior cingulate and bilateral insulae) IN and basal ganglia IN; also, patients displayed increased FNC between a subcomponent of the DMN (anterior cingulate and bilateral middle frontal gyrus) and a frontal pole IN. Regression analyses showed that the aberrant FNC between specific component pairs predicted hit reaction time and clinical index scores on the CPT II and perseveration errors on the WCST. **Conclusions:** The current study highlights the importance of examining the organization of large-scale FNC between dominant INs to investigate attentional dysfunction in SZ. These results particularly highlight the importance of differentiating the subcomponents of the DMN in discriminating between HC and SZ. Future work should continue to address the role of these particular INs as they relate to cognitive ability and clinical symptoms in SZ, with the aim of establishing treatment interventions to improve, or "normalize" the abnormal intrinsic functional connectivity observed in SZ.

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GENERAL INTRODUCTION

Investigating the human brain as an integrative network of functionally interacting brain regions provides a platform for characterizing the neural substrates of higher-order cognitive processes. The central technique quantifying network dynamics is functional connectivity. Functional connectivity is defined as the synchronization of neuronal activity between anatomically separate brain regions; namely, the temporal dependency between spatially remote neurophysiological events (Friston et al., 1994; Biswall et al., 1995; Lowe et al., 1998; Greicius et al., 2003). In the context of cognitive neuroscience, functional connectivity is a descriptive measure reflecting how whole-brain information integration relates to human behavior and neurodegenerative diseases (Bullmore and Sporns, 2009; Greicius, 2008).

At rest, the brain reveals highly correlated spontaneous fluctuations between multiple brain regions known as intrinsic networks (INs; Biswal et al., 1995; Buckner et al., 2008; Greicius, 2008). There is growing evidence that understanding the integrity and strength of intrinsic functional connectivity is important for characterizing the brain networks that support particular cognitive, behavioral and pathological processes (Fox et al., 2007). Given the specific neuroanatomical organization of INs, specifically those overlapping with well-established attention networks, there is considerable interest in investigating their importance for cognitive function. The functional connectivity of INs has been investigated in multiple psychiatric populations, with differences in INs observed in schizophrenia (SZ; Liu et al., 2008; Whitfield-Gabrieli et al., 2009; Bluhm et al., 2007; Garrity et al., 2007; Calhoun et al., 2008; 2002; 2011; Jafri et al., 2008), Alzheimer's disease (Greicius et al., 2004; Rombouts et al., 2005), dementia (Rombouts

et al., 2009), depression (Greicius et al., 2007) and attention-deficit disorder (Cao et al., 2006; see Fox and Raichle, 2007 for review).

The objective of the current study was to examine the functional network connectivity (FNC) between dominant INs comprised of brain regions that support attention-related cognitive processes in healthy controls (HC) and in people with SZ. Moreover, the goal was to investigate the relationship between the FNC between dominant INs and behavioral measures of executive and sustained attention. We hypothesized that aberrant FNC among dominant INs may inform the putative attentional dysfunctions in SZ.

The "resting" brain as a measure of intrinsic functional connectivity

The importance of INs (specifically the default-mode network) was asserted on the basis of the substantial energy demand associated with the "resting" state of the brain, which is thought to entail a finely tuned balance between metabolic demands and regionally regulated blood supply (Raichle, et al., 2001). Intrinsic networks are observed as slow (<0.1 Hz) spontaneous fluctuations in the blood oxygen level dependent (BOLD) signal that show high correlations across functionally related brain regions (Biswal et al., 1995). Neuroimaging studies have identified robust and functionally linked INs using a variety of MR scanners (at multiple field strengths, including 1.5T, 3T and 4T) and analysis techniques (Beckmann et al., 2005; Calhoun et al., 2008; Damoiseaux et al., 2006; De Luca et al., 2006; van Den Heuvel et al., 2008). More recently, using a high-dimensional independent component analysis (ICA) decomposition (components=75), 28 putative INs were identified by inspecting the aggregate spatial maps and average power

spectra of each component, and categorizing the INs based on their anatomical and functional properties (Allen et al., 2011).

The organization of intrinsic functional connectivity has been suggested to depend upon the structural connection across local and distant brain regions and upon synaptic plasticity. Donald Hebb posited that when a neuron excites another neuron, metabolic changes occur, increasing the likelihood of those neurons firing together in the future (Hebb, 1949). This line of reasoning can be applied in a larger context, namely as a distributed network throughout the brain. When one region modulates activity of other brain regions, the accompanying metabolic changes increase the likelihood that these distant brain regions will work in concert in the future. In support of this, functional connections of INs were significantly related to structural white matter connections, indicating an underlying structural core of functional connectivity networks in the human brain (van Den Heuvel et al., 2009; Honey et al., 2009; Greicius et al., 2009; Damoiseaux and Greicius, 2009; Posner 2007).

Moreover, Fox et al., 2006 proposed that since the brain is active even in the absence of a task, there must be an internal dynamic modulating the ongoing functional connectivity and suggested that these dynamics reflect specific functional roles. They propose that INs: (1) represent a record, or memorization of a temporally coherent network that modulates in a task-dependant manner, thereby providing a priori hypothesis from INs about aptitude in a variety of task conditions (e.g., attention tasks), intelligence and even personality traits; (2) organize and coordinate neuronal activity, particularly among regions that commonly work in concert, which is in accordance with the temporal binding hypothesis (as described on pg.7); and (3) represent a prediction regarding

expected use (i.e., the brain develops and maintains an intrinsic probabilistic model of anticipated events). Thus, given that these "resting-state" dynamics *intrinsically* recruit those brain regions optimized for specific functions, dysfunction of these INs may help inform complex endophenotypes associated with abnormal information processing observed in psychiatric illnesses, such as SZ.

Schizophrenia: a disconnection syndrome

Schizophrenia is a severe psychiatric disease that is characterized by the presence of delusions, hallucinations, loss of emotion and impairments in cognition. From almost the beginning of its definition, the etiology of SZ has been described as a disconnection disease. More recently, Andreasen et al. (1999) use the term "cognitive dysmetria" to describe abnormal neural circuitry that leads to impairments in the coordination of mental processes. Indeed, people with SZ show widespread functional and structural disconnectivity between multiple distributed brain networks (Andreasen et al., 1998; Friston, 1998; Friston and Frith, 1995), including frontotemporal and frontoparietal structural connections (Burns et al., 2003; Schlosser et al., 2003).

To qualify as an endophenotype, biological abnormalities must appear in persons who suffer from a spectrum of related disorders and in unaffected first-degree relatives. Recent studies are showing disruptions in intrinsic connectivity in bipolar disorder (Chai et al., 2011; Ongur et al., 2010; Calhoun et al., 2008; Anand et al., 2004) and in first-degree unaffected relatives of those with SZ (Repovs et al., 2011; Lui et al., 2010; Whitfield-Gabrieli et al., 2009). In addition, abnormal IN connectivity was observed in first-episode psychosis (Zhou et al., 2007; Lui et al., 2010) and in chronic patients with

SZ (Bluhm et al., 2007; Jafri et al., 2008 Calhoun et al., 2008), indicating that IN abnormalities persist throughout the illness.

The DMN shows aberrant functional connectivity with the anterior cingulate cortex (Bluhm et al., 2007; Whitfield-Gabrieli et al., 2009), which correlated with positive symptoms of SZ and showed significantly higher frequency fluctuations among the DMN regions (Garriety et al., 2007). In all, these studies demonstrate the important role for delineating IN disruptions in SZ, particularly focusing on the DMN network to better understand the pathophysiology of SZ (Whitfield-Gabrieli et al., 2009).

Furthermore, it has been consistently shown that structural abnormalities are also observed in SZ, such as decreased gray matter in the superior temporal gyrus (STG; see Shenton et al., 2002 for review). This has been shown to predict decreased source strength for a component peaking at 100 ms evoked by innocuous auditory stimuli, which were localized to STG and poorer performance on attention tasks (Edgar et al., 2012). In addition, decreased gray and white matter has been observed in frontal and parietal regions of SZ (Wright et al., 1995; Paillere-Martinot et al., 2001; Hulshoff Pol et al., 2004; van Haren et al., 2007). Thus, evidence supports the view that there are abnormalities in distributed brain regions for bottom-up (e.g., basic auditory sensory processing) and top-down processes in SZ, both contributing to (higher-order) attention-related processing deficits (Javitt et al., 2009). However, direct assessment of the integrity of these INs with behavioral assessments of well-studied attention measures in SZ has yet to be explored.

The heterogeneity of the default-mode networks

The most commonly found IN is the default-mode network (DMN) that links precuneus and posterior cingulate cortex with medial frontal regions and bilateral inferior parietal regions (Raichle, 2001; Greicius et al., 2003; Fox et al., 2007). Unlike other INs, the regions of the DMN show increased functional connectivity during rest and a deactivation during engagement of goal-directed cognitive tasks. Thus, the DMN is unique in that it may best reflect an *intrinsic* 'idling' of the brain that may be tightly coupled with attentional processes (Gusnard et al., 2001; Raichle and Snyder, 2007). The "coupling" between the dynamics of the DMN and attentional networks (e.g., frontoparietal networks) can be described as the so-called anticorrelation between the two networks, which suggests distinct attentional processes (Fransson, 2005). Indeed, it's hypothesized that the interplay between the DMN and task-related networks can significantly impact behavioral performance (Uddin et al., 2008). For example, a failure to suppress activity in the posterior node of the DMN resulted in attentional lapses (Weissman et al., 2005). In addition, Hampson et al. (2006) reported that greater connectivity between the posterior cingulate and medial prefrontal nodes of the DMN correlated with better performance on a working memory task, suggesting that deactivation of a brain area may require increased (rather than decreased) connectivity with the DMN. In addition to the possible influence of DMN dynamics on attentional networks, the DMN has been linked to other core processes of human cognition, including the integration of cognitive and emotional processing (Raichle, 2001; Greicius et al., 2003), monitoring the external world (Gusnard et al., 2001) and mind-wandering (Mason et al., 2007).

More recent studies are beginning to show that DMN consists of sub-components (e.g., ACC component, posterior cingulate cortex component, bilateral parietal and precuneus sub-components), which exhibit differential behavior and vary substantially in connectivity patterns, specifically in psychosis-related disorders (Uddin et al., 2008; Skudlarski et al., 2010; Rotarska-Jagiela et al., 2010; Calhoun et al., 2011). Thus, these unique characteristics of the DMN highlight the importance of examining the DMN's inter-relatedness with other INs, particularly with attention-related INs.

Moreover, the DMN has been used to distinguish between multiple psychiatric diseases, including SCZ (Calhoun et al., 2002; 2008; Garriety et al., 2006). One resting-state study observed that SZ patients displayed decreased connectivity in posterior cingulate cortex of the DMN which correlated with increased positive symptoms (e.g., hallucinations, delusions and disorganization; Rotarska-Jagiela et al., 2010). More recently, examining the spatial maps and temporal dynamics of the DMN sub-components in patients with SZ and bipolar disorder, Calhoun and Colleagues (2011) found that connectivity with posterior cingulate and precuneus regions may be the most important in future diagnostic classifications and for potential biomarker identification.

Altogether, the stability of INs across conditions suggests that the strength of these brain connections may be related to some stable subject trait such as a cognitive ability, intelligence or a personality dimension. More generally, if intrinsic connectivity between the DMN is a marker of particular cognitive abilities and so the relationship of the connectivity patterns of this network with other dominant INs could provide clinically rich information regarding neuropsychological performance.

Neural basis for intrinsic networks

Although the BOLD signal is not a direct measure of neuronal function, recent studies report correlations between the amplitude profiles of resting-state fMRI functional connectivity and electrophysiological recordings of neuronal firing (Nir et al., 2008) and fluctuations in neuronal spiking (Shmuel and Leopold, 2008). Furthermore, studies have shown that the spontaneous fluctuations at rest using local field potentials (LFP) measured from a single cortical site in monkeys (Schölvinck et al., 2010) and whole head scalp EEG in humans (Mantini et al., 2007) exhibit widespread, positive correlations with fMRI. Moreover, Schölvinck et al., 2010 found that this correlation was especially consistent in the upper gamma-range frequencies (40–80 Hz), with BOLD signal lagging by 6–8 s of neuronal activity. These results indicate that the often discarded global component of fMRI fluctuations measured during rest is tightly coupled with underlying neural activity.

Further support for a neuronal basis of resting-state fMRI signals comes from studies that observed spontaneous BOLD fluctuations dominated by lower frequencies (0.1 Hz), with minimal contribution of higher frequency cardiac and respiratory oscillations (0.3 Hz; Cordes et at., 2001; Cordes et al., 2000). In addition, spontaneous BOLD follows a 1/f distribution, with increasing power at lower frequencies; unlike random noise, which is characterized by frequencies that are present equally (Fox et al., 2007). In addition, whereas fluctuations in alpha and gamma oscillations may reflect the coordination of neuronal activity across small-scale networks, studying the slower fluctuations observed in INs may be required to investigate large-scale neuronal coordination (Fox et al., 2007).

Most importantly, as briefly mentioned above, a neuronal basis of resting-state fMRI signals comes from the observation that the brain is never at "rest", it consumes large amounts of energy, with patterns emerging between brain regions that overlap with cognitive function; for example, regions of the motor, visual, auditory and cognitive networks (Biswal et al., 1995; Damoiseaux et al., 2006; De Luca et al., 2005; Lowe et al., 2000; Salvador et al., 2005a; Van den Heuvel et al., 2008a).

Attention networks

Functional neuroimaging has allowed many cognitive processes to be characterized in terms of the brain areas that are activated during test performance (Corbetta & Shulman, 2002). Posner (2007) defined three central aspects of attention: (1) Alerting: achieving and maintaining a state of high sensitivity to incoming stimuli; (2) orienting: the selection of information from sensory input and; (3) executive attention: monitoring and resolving conflict among thoughts, feelings, and responses. The alerting system has been associated with the thalamus as well as frontal and parietal regions of the cortex and is known as the ventral attention pathway. It involves involuntary, (bottom-up) cognitive processes that are activated by salient cues in unexpected locations, among other situations. The orienting system involves aligning attention with a source of sensory signals, and is known as the dorsal attentional system, comprised by the superior parietal lobe, temporal parietal junction and the frontal eye fields (Corbetta & Shulman 2002). This aspect of attention is thought to involve voluntary (top-down) cognitive processes. Lastly, executive attention encompasses a series of high-level voluntary cognitive processes, which are often studied by tasks that involve conflict, such as the

Stroop task. Executive attention is associated with activations in the midline frontal cortex (anterior cingulate), lateral prefrontal cortex (Posner and Fox 2007) and the basal ganglia (Brown and Marsden, 1998).

Intrinsic connectivity as an indicator for cognitive ability

Given the modulation of neural activity in the parietal and frontal regions of the brain during attentional processing, dominant INs with synchronous activity within these regions could be used as a measure of the general capacity for attention-related processes. Using seed-based ROI correlations on spontaneous BOLD activity, Fox et al., 2006 observed INs partitioned into a so-called bilateral dorsal attention system and a so-called right lateralized ventral attention system. Although still speculative, this was one of the initial studies providing evidence for the use of INs to be used as an indicator of the functional integrity of attentional networks. Further support of the relationship between INs and cognitive ability comes from several studies that observed increased functional connectivity at rest of the dorsolateral prefrontal cortex predicted better intellectual performance (Song et al., 2008) and IQ (van den Heuvel et al., 2009).

In addition, Zhanga et al., 2009 used ICA to extract the INs that included bilateral inferior parietal sulcus, frontal eye fields and medial frontal gyrus (MFG). They investigated the extent that the scores of Trail Making Test (TMT) in patients with medial temporal lobe epilepsy were correlated with the (connectivity) z-scores of the voxels showing significant differences between the two groups. They observed that stronger connectivity values predicted quicker completion of the TMT. Similarly, Seeley et al. (2007) also utilized ICA on fMRI data and identified the so-called salience network (consisting of dorsal anterior cingulate, dACC, and orbital frontoinsula) and the executive

network (consisting of lateral prefrontal cortex and lateral parietal cortex) with scores from the Trails A and B and an anxiety rating scale. They observed that the intrinsic connectivity, specifically in the dACC of the salience component was related to subjective anxiety scores; whereas connectivity in the bilateral parietal lobes of the executive network was related to TMT A and B.

These findings highlight the vital and dissociable roles of intrinsic connectivity in human cognition and emotion. Moreover, although this study demonstrated that the salience and executive-control networks are distinct, they also identified three highly correlated clusters that were present in both networks, suggesting that there is either a facilitation of "switching" between networks, or there is an underling key interaction across INs, which can be further investigated by using FNC.

Functional Network Connectivity (FNC)

Jafri and Colleagues (2008) developed a novel approach to examine dependencies among networks/components. Since the spatial maps within a component are strongly coherent due to the ICA assumption of linear mixing, the authors proposed that it would be informative to also consider weaker dependencies between components. This is possible because the time courses of ICA components are not independent and may exhibit considerable temporal dependencies. Functional network connectivity (FNC), then, is a measure of the temporal dependency among ICA components. This dependency is computed by the maximum lagged cross-correlation within a specific time interval between two component's time courses, with the temporal lag indicating the causality or direction of influence between components. Utilizing FNC on a sample of HC and stable patients with SZ, Jafri et al. (2008) hypothesized that patients with SZ may not only have

deficits in the relationship of one component to another, but that their cognitive and behavioral deficits might be related to dysfunction of entire networks of regions failing to properly communicate with one another. Indeed, out of the seven components included into the FNC analysis (21 possible pair-wise combinations), the authors observed higher FNC in patients compared to controls for four pair-wise combinations, particularly with the DMN, and decreased FNC between temporal lobe and parietal lobe components. The authors hypothesized that controls have a better ability to persist in a single mental state compared to patients, which is consistent with the finding of more rapid fluctuations in the DMN in patients verses controls (Garrity et al., 2007), which consequently impacts attentional processing in SZ (Jafri et al., 2008).

In more recent FNC studies, White et al., 2010 observed a significantly weaker relationship in SZ between sub-components of the salience network (ACC and bilateral insula, STG, precentral gyrus) and sub-components of the executive and DMN components. Similarly, Calhoun et al., 2011 found decreased FNC between posterior-DMN and inferior posterior temporal lobes in patients with SZ compared to HC. Together, these studies demonstrate abnormalities in FNC between INs comprised of functionally-relevant brain regions, including executive and salience networks and the DMN; more specifically, an attenuation of switching between functional brain states in SZ may underlie the putative dysfunction of attention-related processes in SZ.

Executive attention and set shifting

The Wisconsin-card sorting Task (WCST): is one of the most widely used tests to evaluate executive functioning. Executive functioning encompasses a series of high-level processes, allowing individuals to shift their attention quickly and to adapt to diverse

situations while simultaneously repressing inappropriate ones (Wilmsmeier et al., 2010). Furthermore, the WCST measures cognitive flexibility, which is the ability to alter a behavioral response mode in the face of changing contingencies (set-shifting). The test is often termed a "frontal lobe" test in that patients with any sort of frontal lobe lesion generally do poorly at the test. Neuroimaging research shows that the primary brain regions engaged during the WCST are the mid-ventrolateral and mid-dorsolateral prefrontal areas, in addition to the caudate and putamen, which are involved more when provided with negative feedback (Monchi et al., 2001). In addition, a recent study using path analysis to determine which gray matter regions contributed most to increases in perseverations after accounting for the decrement associated with age, found that the prefrontal cortical volume explained the most variance (Head et al., 2009).

A meta-analysis showed that the most prominent WCST deficit in people with SZ was increased perseverative errors, i.e. tendency to persist in a specific response despite feedback indicating its no longer correct (Demakis, 2003). Again, suggesting that the functioning of highly evolved neural mechanisms that use past experiences and environmental sources of information to guide adaptive behavior and shape future plans are impaired in SZ.

Sustained attention: vigilance and decrement

Across cognitive domains, sustained attention deficits are considered a core feature of SZ (Fioravanti et al., 2005). Moreover, Chen et al., 1998 found that sustained attention deficit may be a genetic vulnerability marker for SZ, and it may be more useful in linkage analysis than traditional phenotype definitions of SZ. Also, Liu et al., 2006 observed substantial heterogeneity in SCZ patients' long-term pattern in sustained

attention deficits indicating that severe sustained attention impairments may reflect a stable vulnerability to SZ.

The Conners' Computerized Performance Task (CPT) is thought to assess vigilance, or sustained attention, which is defined as a readiness and ability to detect near-threshold, rarely occurring, signals over long periods of time (Parasuraman et al., 1987). In principle, vigilance takes on two constructs, both of which are thought to operate independently: (1) 'overall vigilance'—indexed by aggregate signal detection statistics including hits and false alarms, repeated over may trials; and (2) 'Vigilance decrement', a deterioration in performance over trials due to the 'taxing' of primary perceptual functioning—indexed by the variability of scores across trials (Mar et al., 1996; Lui et al., 2006). The CPT II paradigm has shown sensitivity to drug treatment change used for hyperactive children (Conners et al., 1967; Conners, 1994) and used for the evaluation for neurological disorders (Brewer, 1998).

In regard to the regions of the brain engaged during CPT administration, Tana et al., 2010 found that the largest cluster of activation was found in anterior cingulate cortex (ACC) and bilateral fronto-insular cortices, also known as the salience network. The authors explain that the ACC plays a central role in attentional processing by modulating target selection (i.e., focusing attention), motor response selection, error detection, and performance monitoring.

Although impairments are often observed as decreases in performance, Mar et al. (1996) reported a failure to decrease vigilance in a small sample of SZ in-patients compared to controls, supporting the 'hyper-attention' hypothesis in SCZ. This hypothesis is of growing interests and suggests that patients will, under certain

conditions, exceed the performance of normal controls. A more recent study compared HC and people with ADHD to SZ; Egeland et al., 2007 found that the SZ group showed an inability to initially focus attention and suppress it over time, indicating the involvement of multiple impairments in cognitive processing that influence attentional performance in patients with SZ.

Objectives and Hypotheses:

In summary, attentional impairments are a core feature of SCZ with growing evidence suggesting that cognitive deficits may be observed in dominant INs. Since, INs are thought to reflect an *intrinsic* functional baseline that affects the reactivity and adaptation of other task-related networks, it's reasonable to speculate that functional connectivity at rest keeps systems in an active state, helping to improve performance and reaction time whenever functional connectivity is needed. Currently, there are no studies investigating the significance of disruptions in FNC between dominant INs and their relation to neuropsychological performance on tests of sustained and executive attention in people with SZ. Since INs are related to mental illness and also to cognitive function – including attention, we expect to find relationships with FNC among dominant INs and neuropsychological scores of attention.

Thus, the objective of the current study was to examine any differences in the FNC across INs located in frontal-parietal (putative attention-related), frontal (as it pertains to executive functioning), superior temporal gyri (known to display abnormalities in structure and function in SZ), basal ganglia (as they pertain to dopamine regulation and executive functioning) and the DMN. Our second aim was to use these FNC measures to predict measures of sustained attention obtained from the Conners'

continuous performance task (CPT; Conners 1994) and executive attention from the Wisconsin-card sorting task (WCST; Berg, 1948; Heaton et al., 1993).

The first hypothesis was that SCZ would exhibit synchrony between functionally related components, i.e., decreased FNC. For the second objective, we hypothesize that any disruptions in FNC between attention-related INs would predict clinically impaired neuropsychological profiles of attention, with stronger correlations among FNC dependencies indicative of more intact attentional processes.

METHODS

Participants: inclusion/exclusion criteria

Thirty-five individuals with schizophrenia were recruited from the Albuquerque VAMC, UNM Mental Health Center, and mental health clinics in the Albuquerque metropolitan area. The selection for schizophrenia participants was as follows: (1) diagnosis of schizophrenia (or schizoaffective disorder) as determined by the Structured Clinical Interview for DSM-IV-Patient Edition (First et al., 2007); may have comorbid diagnosis of depression and anxiety disorders; (2) continuous treatment with either typical or atypical antipsychotic medication for at least 3 months (3) no history of amphetamine, cocaine, or marijuana dependence in the last 5 years (determined by self-report from research participants during structured interview and available medical records. No drug tests were obtained); (4) no history of alcohol or other substance abuse or dependence in the 3 months prior to entry into the study; (5) no history of head injury with loss of consciousness for more than 5 minutes; (6) no hospitalization in last 3 months; (7) age 18-65; (8) English-speaking; and (9) signed informed consent. Because

of restrictions imposed by neuropsychological testing, only English- speaking patients were studied.

Thirty-three control subjects were recruited from the local community through word of mouth, ads placed in local papers and websites, and flyers posted in the community at trade schools, coffee shops, Laundromats, etc. Selection criteria for control subjects was as follows: (1) control participants will have no history of psychotic disorder, but depression and/or anxiety disorders were allowed; (2) no self-reported history of amphetamine, cocaine, or marijuana dependence in the last 5 years; (3) no self-reported history of alcohol or other substance abuse or dependence in the 3 months prior to entry into the study as determined by the DSM-IV SCID-NP; (4) no family history of a psychotic disorder in first-degree relatives; (5) no history of head injury with loss of consciousness for more than five minutes; (6) age 18-65; (7) English-speaking; and (8) signed informed consent.

Facilities

This study was performed at the New Mexico VA Health Care System, the University of New Mexico Psychiatry Research Center and the Mind Research Network. All neuropsychological assessments were done outside of the scanner and proctored on a Dell 17 inch laptop.

MRI Scan & Preprocessing

All images were collected on a 3-Tesla Siemens TIM Trio scanner with a 12-channel radio frequency coil. High resolution T1-weighted structural images were acquired with a five-echo MPRAGE sequence. T2*-weighted functional images were acquired using a gradient-echo EPI sequence with TE = 29 ms, TR = 2 s, flip angle = 75°,

slice thickness = 3.5 mm. Resting-state scans were a minimum of 5 mins in duration. Subjects were instructed to keep their eyes closed, relax and think of nothing in particular.

Functional and structural MRI data were preprocessed using an automated preprocessing pipeline developed at MRN. The first four volumes are discarded to remove T1 equilibration effects, images are realigned using INRIalign, and slice-timing correction is applied using the middle slice as the reference frame. Data were then spatially normalized into the standard Montreal Neurological Institute (MNI) space, resliced to 3 mm × 3 mm × 3 mm voxels, and smoothed using a Gaussian kernel with a full-width at half-maximum (FWHM) of 10 mm.

In addition to the exclusion criteria above, subject data were excluded due to excessive motion, defined as more than 3.125 mm of translation in any plane or more than 5 degrees of rotation in any plane (Greicius et al., 2007). Head position is described at each time point by six parameters (translational displacements along X, Y, and Z axes and rotational displacements of pitch, yaw, and roll).

Independent Component Analysis

The initial application of ICA was to solve problems similar to the "cocktail party" scenario, where individual voices must be determined from microphone recordings of many people speaking at once. The application of ICA has been used to discover functionally related "groups" of voxels that characterize a brain network. ICA is a data-driven method that works by decomposing a set of signals into maximally independent signals (components) by minimizing the mutual information between the components

(Calhoun et al., 2009); that is, the ICA model identifies sources whose voxels have the same time course and thus each component can be considered a temporally coherent network. Mutual information measures the shared information content between two variables. Unlike PCA, which finds the direction of maximal variance, using second-order statistics; ICA finds directions which maximize independence, using higher-order statistics (McKeown et al., 1997; Calhoun et al., 2001; 2006). Statistical testing is done on each voxel to generate component spatial maps. Thus, ICA can reveal inter-subject and inter-event differences in the temporal dynamics: its major strength being the ability to reveal the dynamics of spontaneous fluctuations in resting-state scans, for which a temporal model is not available.

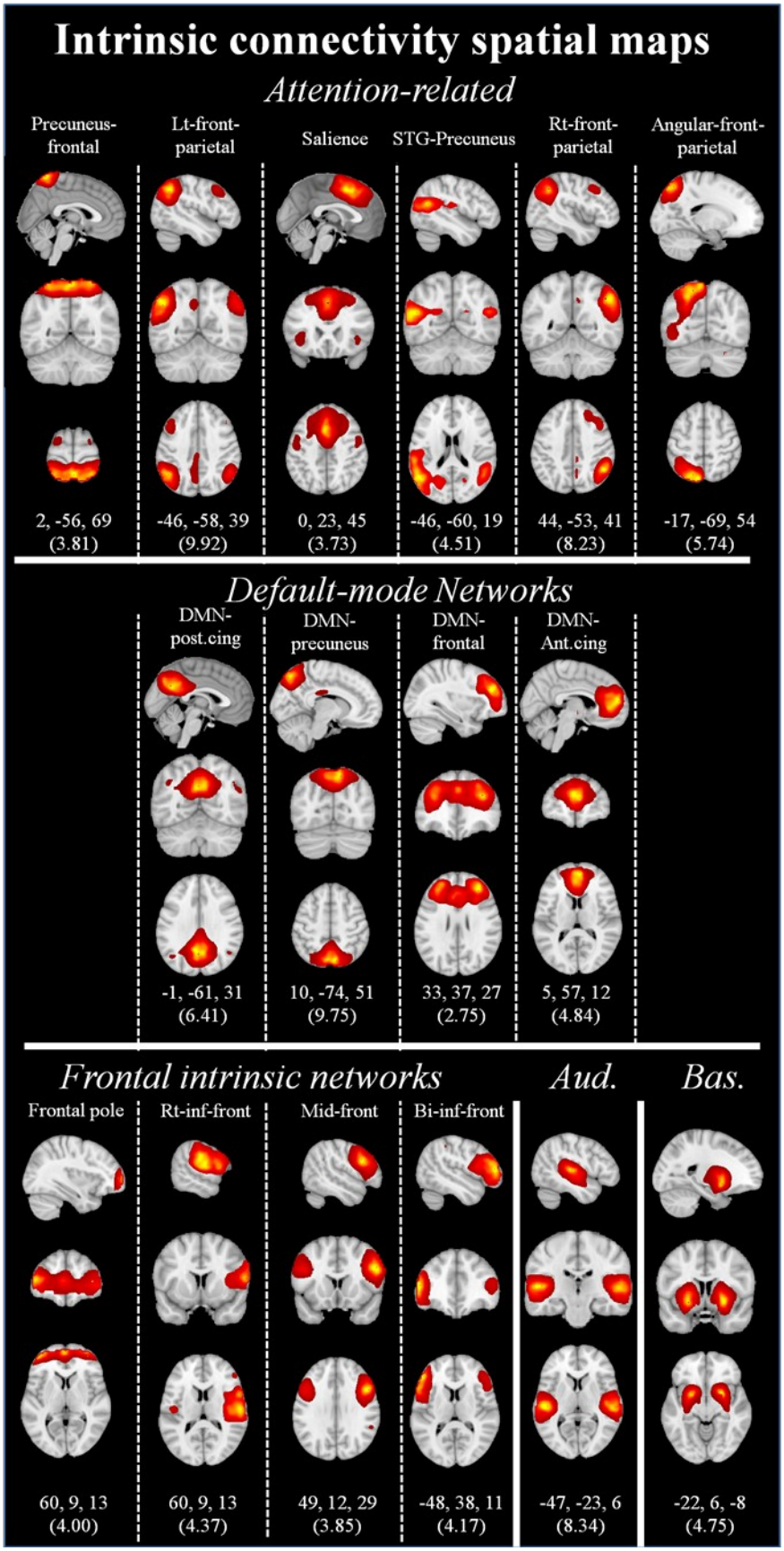
Components of Interests

Functional INs are differentially affected in SZ, and include abnormal connectivity patterns in the DMN, executive control and dorsal attention networks as well as the salience network (Woodward et al., 2011). Furthermore, Liang et al. 2006 observed disrupted functional integration of widespread brain areas at rest, including a decreased connectivity between insula, temporal lobe, prefrontal lobe and corpus striatum. In addition, since the WSCT is a multifactorial test that requires a distributed neural network that includes frontal and medial frontal cortices, parietal lobule and basal ganglia (Berman et al., 1995; Stuss et al., 2000; Parasuraman et al., 1998; Shaw et al., 2009), the basal ganglia network was also included.

High-dimensional model order (75 components) Group ICA using the Infomax algorithm was performed using Group ICA fMRI Toolbox (GIFT;

http://icatb.sourceforge.net). All 28 of the resting-state networks that were identified in Allen and Colleagues (2011), were also identified in the current study by inspecting the aggregate spatial maps and average power spectra of all 75 components (the rest of the 59 components were labeled artifacts or were not of interest). Of these 28, 16 INs were selected for further analysis, which included 6 INs whose spatial maps overlap with regions thought to be involved in attentional processing, 4 subcomponents of the DMNs, 4 frontal networks, 1 network involving auditory cortex and 1 basal ganglia network (see Figure 1). The spatial maps of the group of 6 INs consisted of left and right lateralized fronto-parietal networks (similar to the ventral attention network observed by Corbetta and Shulman (2002), a parietal and frontal-eye field network resembling the dorsal attention network identified by Corbetta and Shulman (2002), a component centered in the central and anterior precuneus, regions of the brain implicated in directing attention, a bilateral component placed at the temporo-parietal junction and overlapping the alerting system, and an anterior cingulate and bilateral insular component resembling the so-called salience network. The auditory network included bilateral STG, superior temporal sulcus and middle temporal gyrus. The basal ganglia component included putamen and palladium. The frontal components included bilateral inferior frontal gyri, middle frontal, medial prefrontal and frontal pole components.

Figure 1: Spatial maps (SMs) of the 16 components identified as intrinsic networks. SMs are plotted as Z-scores, threshold at Z = 2.0, and are displayed at the slices showing the highest connectivity within each component. Intrinsic networks are categorized based on their anatomical and functional properties, which include attentional, DMN, frontal, basal ganglia (Bas) and auditory (Aud) networks. The (x, y, z) MNI coordinates are labeled underneath each component as well as the low-frequency to high-frequency power ratio for each component. The numerator of this ratio is the integral of spectral power below 0.10 Hz over the integral of power between 0.15 and 0.25 Hz, thus higher values indicate more power in the lower frequencies (below 0.10Hz).


Intrinsic connectivity spatial maps
Attention-related
Precuneus-frontal
Lt-front-parietal
Salience
STG-Precuneus
Rt-front-parietal
Angular-front-parietal
2, -56, 69 (3.81)
-46, -58, 39 (9.92)
0, 23, 45 (3.73)
-46, -60, 19 (4.51)
44, -53, 41 (8.23)
-17, -69, 54 (5.74)
Default-mode Networks
DMN-post.cing
DMN-precuneus
DMN-frontal
DMN-Ant.cing
-1, -61, 31 (6.41)
10, -74, 51 (9.75)
33, 37, 27 (2.75)
5, 57, 12 (4.84)
Frontal intrinsic networks
Aud.
Bas.
Frontal pole
Rt-inf-front
Mid-front
Bi-inf-front
60, 9, 13 (4.00)
60, 9, 13 (4.37)
49, 12, 29 (3.85)
-48, 38, 11 (4.17)
-47, -23, 6 (8.34)
-22, 6, -8 (4.75)

Functional Network Connectivity

The sixteen component time courses were interpolated to enable detection of sub resolution hemodynamic delay differences in patients with SZ. FNC was assessed using constrained-lagged correlation between components (Jafri et al., 2008; FNC toolbox; http://icatb.sourceforge.net). The low-pass filter (normalized) was set at 0.0372 Hz and the high-pass was set at 0.372 Hz and the maximum lag interval was set from -5 s to +5 s. Pair-wise combinations of components were obtained for each subject and Fisher-transformed (z') to assess group differences and assess the relationship between neuropsychological scores.

Neuropsychological Measures

Wisconsin-card sort task (WCST) and Conner's CPT II:

In the WCST, the subject is asked to sort test cards (depicting geometric shapes) to reference cards according design elements (e.g., color, shape, or number of stimuli on the cards). Minimal feedback is provided after each match (correct or incorrect response), enabling the subject to acquire the correct rule of classification. After a fixed number of correct matches, the rule is changed without notice, and the subject must shift to a new mode of classification. Normalized T-scores were also used when tested for group differences

The standard protocol of the CPT II test uses a short practice exercise prior to the administration of the full test to ensure that the respondent fully understands the task prior to proceeding. After the practice exercise, a new administration is begun and it is a requirement of the standard protocol that an administrator remains present while the administration is taking place. CPT II respondents are required to press the space bar or

click the mouse whenever any letter except the letter ‘X’ appears on the computer screen. The inter-stimulus intervals (ISIs) vary by 1, 2 or 4 seconds with a display time of 250 milliseconds. The unique CPT paradigm is a test structure consisting of 6 blocks and 3 sub-blocks, each containing 20 trials (letter presentations). The presentation order of the different ISIs varies between blocks.

Overall Hit Reaction Time (HRT) is defined as the mean response time (in ms) for all target responses over all six blocks. HRT is thought to be a highly sensitive index of how efficiently targets are processed and compared to all the other output measures, shows the highest Split-half reliability (0.95).

Signal detection statistics were also obtained: d’ (attentiveness) and β (sensitivity bias). d’ is a measure of how well the individual discriminates between targets and nontargets: the value represents the difference between the signal (non-X) and noise (X) distributions. Thus the greater the d’ value, or the difference between distributions, the better the ability to distinguish and detect X and non-X stimuli.

It’s important to add here that a subject’s vigilance decrement, i.e., a decline in detecting the target over time, is largely determined by the strictness of the response criterion. Sensitivity measure, β, is the assessment of response style, evaluating the speed/accuracy trade off. Conceptually, test subjects who are more cautious and make sure they make the correct responses (i.e., avoiding commission errors—responding to the letter X, the non-target), tend to score higher on β index. The reasoning behind this is that in a continuous measuring vigilance task, as the subjects become less efficient, they become less strict in deciding whether there is a signal or not. Thus, individuals who obtain lower β scores tend to be less concerned about mistakenly responding to non-

targets, instead they respond more freely, ensuring they respond to most or all of the targets (i.e., avoid making omission errors).

Lastly, the Clinical Confidence Index (CCI) was obtained from the CPT II output. The CCI suggests closeness of the match to a clinical or non-clinical profile and is computed by using discriminate function analysis that included % omissions, gender, age, β, RT by ISI, SE HRT, preservations, SE HRT, and d'. Higher scores (e.g., 75) indicate more confidence that they belong to a clinical population (e.g., 75% confidence). According to the authors, scores below or equal to 40 suggest nonclinical profiles, with scores between 40-60 are relatively inconclusive and more extreme values (above 60 or below 40) provide stronger evidence for the classification. Compared to the other output measures, CCI shows the highest test-retest correlation coefficient (r=0.92).

All statistical testing was conducted on the converted T-scores, which represent the score of the individual taking the test relative to the population average of the same gender and age. The age groups for adults were defined as 18-34, 34-54 and 55+ (Conners, 2000). The average T-score for the measures were set to 50, with a SD of 10. The guidelines for interpreting T-scores are as follows: a T-score under 40 is "Very good performance"; 40-44 is "Good performance"; 45-54 is "Within the average range"; 55-59 is "Mildly atypical"; 60-64 is "Moderately atypical"; 65+ is "Markedly atypical".

The CPT II data sample consists of 2686 subjects: 378 were diagnosed with ADHD, 223 were diagnosed with a range neurological impairments (e.g., 29% Postconcusive, 21% Other organic Brain Syndrome, 11% Other, 6% Concussion with other loss of consciousness, 5% Frontal lobe syndrome, 5% Dementia, 3% Cognitive deficits) and 1,920 of non-clinical people from the general population.

Data Analysis

A series of Student's t-tests on FNC (z') values and normalized T-scores of the neuropsychological measures were computed in order to evaluate group differences on these measures. Thereafter, hierarchical linear regressions were run with a pre-defined FNC pair entered first (1st block), diagnosis (2nd block), and their interaction (3rd block), with neuropsychological measures as the dependent variable.

RESULTS

Demographics

Group means and SDs are displayed in Table 1. Two-sample t-tests were obtained and only age was significantly different between groups ($t(65)=-2.66$, $p=0.01$). No group differences observed in years of education, sex, handedness or time between the fMRI session and neuropsychological assessments (p-values > 0.19).

Table 1. Mean (SD) of sample demographic information.

	Control (n=33)	**SCZ (n=35)**
Age (yrs)*	34.06 (11.34)	42.03 (13.11)
Education (yrs)	14.14 (1.47)	13.48 (2.36)
Sex	9 Female	9 Female
Handedness	6 Left-handed	4 Left-handed
Session intervals (days)[a]	10.31 (16.77)	11.88 (17.02)
Number of subjects ≥ 30 days	4	5
Number of subjects in 8-29 days	10	9
Number of subjects in 0-7 days	19	21

*Two-sample t-test p-value is less than 0.05.

[a.] Difference in days between fMRI and Neuropsychological session.

Functional Network Connectivity:

Two-sample t-tests were obtained on all combinations of ICNs. Since the objective of the current study was to detect FNC among component pairs and any group difference patterns between those pairs, we used percentile rankings on all mean FNC measures and p-values to present these results in Figure 1. For the mean FNC values, three categories were defined based on the rankings of the data: scores with the highest values (99^{th} percentile, bright yellow-colored cells), mid range values (85^{th} percentile, dark yellow-colored cells) and below threshold values ($<70^{th}$ percentile, dark gray cells). Likewise, for the corresponding p-values, three categories were defined on the rankings of the data: scores with the highest p-values ($>20^{th}$ percentile, dark gray cells), mid range values (6^{th} percentile, dark yellow-colored cells) and below threshold values ($<1^{th}$

percentile, bright yellow-colored cells). The parameters for the graphic display, we think are conservative to avoid type-I errors, with the ranking of scores in general will reduce the amount of type-II errors, which may occur with a typical Bonferroni correction. However a family-wise Bonferroni correction was applied for each of the five functionally distinct IN domains ($\alpha = 0.05$), resulting in $\alpha_b = 0.01$.

The FNC component pairs showing the highest mean FNC values across both groups and the smallest p-values are summarized in Table 3, highlighting these particular FNC pairs for further analysis.

Figure 2. Functional Network Connectivity matrix containing mean FNC values between component pairs (top right half) and p-values obtained from Student's t-tests (SZ vs. HC; bottom left half). This table provides information about the component pairs with highest FNC values and also smallest p-values associated with the FNC differences between groups.

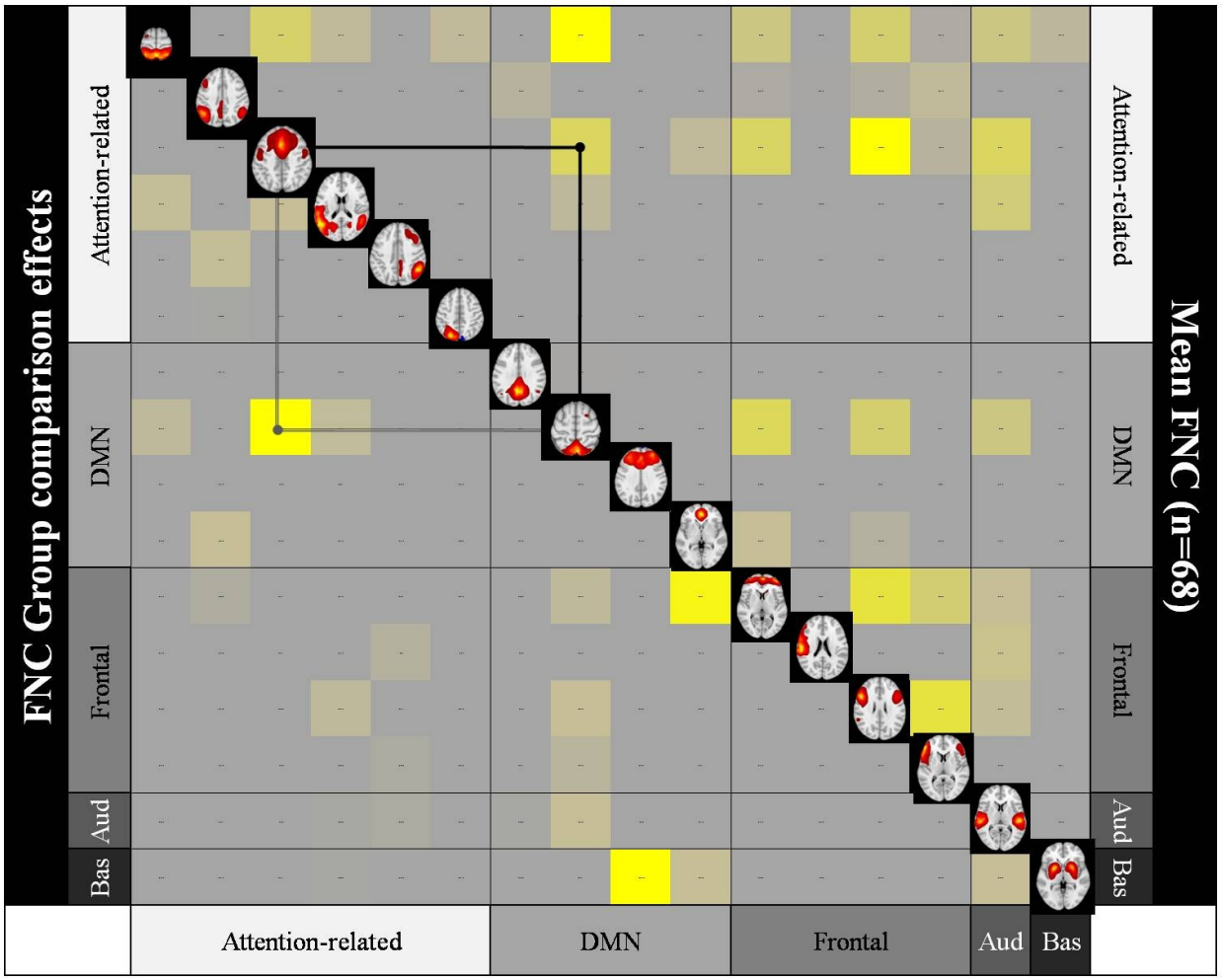


Figure 2 legend: Yellow indicates highest FNC values (on top-right half) and lowest p-values (on bottom-left half). Notice the moderately high FNC mean value between the salience attention-related component, 3rd component going from left to right, and the precuneus subcomponent of the DMN, 8th component from left to right, illustrated by the intersection of two black lines; also, on the bottom-left of the matrix, this same FNC pair is significantly different between groups, p=0.003, which is intersected by the two gray lines. (Aud=auditory; Bas=Basal ganglia).

WCST and CPT II: two-sample t-tests

Group means and SDs of neuropsychological raw scores and normative T-scores (corrected for age and sex, see Methods for more detail) are displayed in Table-2.

Table 2. Conners' CPT II and the computerized WCST 64 behavioral measures (with normalized T-scores): mean (SD) and group comparisons[1]

Conners' CPT II				
	Controls (n=29)		**SZ (n=28)**	
	Normative T-score	*Raw score*	*Normative T-score*	*Raw score*
(Hit) reaction time**	57.88 (10.42)	435.49 (63.56)	65.58 (13.27)	487.99 (83.81)
d' (sensitivity)**	49.88 (6.87)	0.72 (0.31)	43.29 (10.15)	1.02 (0.45)
β (response bias)**	46.44 (3.03)	0.40 (0.34)	52.95 (13.14)	1.06 (1.08)
Clinical Index***	48.29 (14.16)	---	63.97 (18.14)	---
(Hit) RT SE block change	50.97 (10.27)	---	53.51 (11.25)	---

Wisconsin Card Sorting Task				
	Controls (n=31)		**SZ (n=24)**	
	Normative T-score	*Raw score*	*Normative T-score*	*Raw score*
Total correct[a]	---	47.26 (11.53)	---	41.91 (13.64)
Total errors*	49.55 (9.26)	15.77 (10.37)	43.88 (11.92)	22.33 (13.42)
Perseveration errors*	50.19 (7.16)	7.19 (5.72)	45.42 (10.57)	12.21 (10.91)
Non-perseveration errors	46.97 (8.30)	8.58 (7.10)	44.04 (10.02)	10.13 (6.79)
Conceptual level responses*	49.48 (9.34)	44.74 (14.75)	43.63(12.09)	35.45 (19.01)
Categories completed	---	3.32 (1.56)	---	2.67 (1.60)

[1] Two-sample independent t-tests on Normalized T-scores as they are corrected for age and years of education.

[a.] Variable contained 7 low-score outliers (4 HCs); group differences observed when excluded, $t(46)=2.39$, $p=0.02$.

*p-value ≤ 0.05; **p-value ≤ 0.01; ***p-value ≤ 0.001.

Table 3. Rank-ordered FNC statistics: 1st percentile of p-values (top) and 99th percentile of mean FNC scores (bottom). Mean (SD) for each group are displayed.

Largest FNC group differences			**FNC mean (SD)**	
		FNC pair	HC (n=33)	SZ (n=35)
	Rank-order			
	1	$Attn_{Salience}$&DMN_{precun}[a]	0.69 (0.27)	0.47 (0.33)
	2	$Basal_g$ & $DMN_{frontal}$[b]	0.46 (0.34)	0.21 (0.38)
	3	$Front_{pole}$ & $DMN_{ant.cing}$[c]	0.33 (0.47)	0.59 (0.37)
Highest FNC			**FNC mean (SD)**	
	Rank-order		HC (n=33)	SZ (n=35)
		FNC pair		
	1	$Attn_{salience}$&$Front_{Mid,\ parietal}$	0.81 (0.36)	0.81 (0.26)
	2	$Attn_{precun,front}$&DMN_{precun}	0.85 (0.36)	0.72 (0.22)
	3	$Front_{Mid}$&$Front_{Mid,\ parietal}$	0.68 (0.31)	0.59 (0.32)
	4	$Front_{inf}$&$Front_{Mid,\ parietal}$	0.67 (0.23)	0.64 (0.27)

[a.] $t(66)=2.96$, p=0.004; [b.] $t(66)=2.82$, p=0.006); [c.] $t(66)=-2.56=0.01$.

Regressions between selected FNC pairs and neuropsychological data

CPT II

Hierarchical regressions were run with a pre-defined FNC pair entered first (each listed in Table 3), diagnosis second, and their interaction last, with CPT II measures as the dependant variable (only those that were significantly different between groups on Table 3 were analyzed). As shown in Table 4, three FNC pairs significantly predicted attention scores. No significant interactions were observed.

Table 4. Three predictor regression models on Conners' CPT II measures (R^2 values). 1st Block: Predefined FNC measure[a]; 2nd block: group; 3rd block: interaction. Significant R^2 values are shown in bold[b].

	Predictor[c]	FNC R^2	Group R^2 change	Interaction R^2 change
Predefined: FNC group differences (<1 percentile)				
Hit RT	$Attn_{Salience}$&DMN_{precun}	0.06	0.04	0
	$Basal_g$ & $DMN_{frontal}$	0.06	0.05	0
	$Front_{pole}$ & $DMN_{ant.cing}$	**0.07***	0.04	0
d'	$Attn_{Salience}$&DMN_{precun}	0	**0.15****	0
	$Basal_g$ & $DMN_{frontal}$	0.02	**0.20****	0
	$Front_{pole}$ & $DMN_{ant.cing}$	0.02	**0.13****	0
β	$Attn_{Salience}$&DMN_{precun}	0.01	0.07	0.01
	$Basal_g$ & $DMN_{frontal}$	0	**0.07***	0
	$Front_{pole}$ & $DMN_{ant.cing}$	0.01	0.07	0
Clin Index	$Attn_{salienc}$&DMN_{precun}	**0.09***	**0.08***	0.01
	$Basal_g$ & $DMN_{frontal}$	0.06	**0.10***	0
	$Front_{pole}$ & $DMN_{ant.cing}$	0.01	**0.14****	0
Predefined: FNC pairs > 0.99th percentile *(exploratory)*				
Hit RT	$Attn_{salience}$&$Front_{Mid,\ parietal}$	0.06	**0.10***	0.01
	$Attn_{precun,front}$&DMN_{precun}	0.05	0.06	0
	$Front_{Mid}$&$Front_{Mid,\ parietal}$	0	**0.07***	0.06
	$Front_{inf}$&$Front_{Mid,\ parietal}$	0	**0.09***	0
d'	$Attn_{salience}$&$Front_{Mid,\ parietal}$	0	**0.15****	0.03
	$Attn_{precun,front}$&DMN_{precun}	0.01	**0.14****	0.02
	$Front_{Mid}$&$Front_{Mid,\ parietal}$	0	**0.14****	0
	$Front_{inf}$&$Front_{Mid,\ parietal}$	0.01	**0.14****	0.04
β	$Attn_{salience}$&$Front_{Mid,\ parietal}$	0.02	**0.08***	0.03
	$Attn_{precun,front}$&DMN_{precun}	0	0.07	0.02
	$Front_{Mid}$&$Front_{Mid,\ parietal}$	0.01	0.07	0
	$Front_{inf}$&$Front_{Mid,\ parietal}$	0.05	**0.09***	0.04
Clin Index	$Attn_{salience}$&$Front_{Mid,\ parietal}$	0.01	**0.15****	0
	$Attn_{precun,front}$&DMN_{precun}	**0.09***	**0.10***	0
	$Front_{Mid}$&$Front_{Mid,\ parietal}$	0.04	**0.13****	0.01
	$Front_{inf}$&$Front_{Mid,\ parietal}$	0	**0.14****	0

[a.] FNC combinations were included only if p-values were in the 1st percentile (top) and if FNC means were in the 99th percentile. [b] p-value threshold set to 0.05. [c.] Total number of subjects in regression models was HC: n=29; SZ: n=28. When 1 outliers was taken out R^2 was 0.13, p=0.008.

Regressions: FNC and WCST

Similarly for WCST, hierarchical regressions were run with a pre-defined FNC pair entered first (each listed in Table 3), diagnosis second, and their interaction last, with CPT II measures as the dependant variable (only those that were significantly different between groups on Table 3 were analyzed). As shown in Table 5, two FNC pairs significantly predicted the number of perseveration errors. No interactions were observed.

Table 5. Three predictor regression models on WCST measures (R^2 values). 1st Block: Predefined FNC measures[a]; 2nd block: group; 3erd block: FNC X group interaction. Significant R^2 values are shown in bold[b].

Predictor[c.]	FNC R^2	Group R^2 change	Interaction R^2 change
Predefined: FNC group differences (1st percentile)			

WCST Total correct	$Attn_{Salience}$&DMN_{precun}	0.01	0.04	0
	$Basal_g$ & $DMN_{frontal}$	0	0.04	0
	$Front_{pole}$ & $DMN_{ant.cing}$	0.05	0.02	0
WCST Total errors	$Attn_{Salience}$&DMN_{precun}	0	0.06	0
	$Basal_g$ & $DMN_{frontal}$	0.04	0.04	0.01
	$Front_{pole}$ & $DMN_{ant.cing}$	0.04	0.04	0.02
Perseveration errors	$Attn_{Salience}$&DMN_{precun}	0	0.05	0.04
	$Basal_g$ & $DMN_{frontal}$	**0.18****	0.04	0
	$Front_{pole}$ & $DMN_{ant.cing}$	0.03	0.04	0.06
Conceptual level responses	$Attn_{Salience}$&DMN_{precun}	0	0.07	0.01
	$Basal_g$ & $DMN_{frontal}$	0.03	0.05	0.01
	$Front_{pole}$ & $DMN_{ant.cing}$	0.04	0.04	0.02
Predefined: FNC pairs > 0.99th percentile *(exploratory)*				
WCST Total correct	$Attn_{precun,front}$&DMN_{precun}	0.04	0.02	0.01
	$Attn_{salience}$&$Front_{Mid,\ parietal}$	0.04	0.02	0.01
	$Front_{Mid}$&$Front_{Mid,\ parietal}$	0.05	0.04	0.04
	$Front_{inf}$&$Front_{Mid,\ parietal}$	0	0.05	0
WCST Total errors	$Attn_{precun,front}$&DMN_{precun}	0.02	0.06	0.05
	$Attn_{salience}$&$Front_{Mid,\ parietal}$	0	**0.09***	0
	$Front_{Mid}$&$Front_{Mid,\ parietal}$	0.05	0.05	0.02
	$Front_{inf}$&$Front_{Mid,\ parietal}$	0.06	**0.09***	0.01
Perseveration errors	$Attn_{precun,front}$&DMN_{precun}	0.03	0.05	0.03
	$Attn_{salience}$&$Front_{Mid,\ parietal}$	0	0.07	0.02
	$Front_{Mid}$&$Front_{Mid,\ parietal}$	**0.1***	0.06	0
	$Front_{inf}$&$Front_{Mid,\ parietal}$	0.03	**0.09***	0.04
Conceptual level responses	$Attn_{precun,front}$&DMN_{precun}	0.02	0.06	0.05
	$Attn_{salience}$&$Front_{Mid,\ parietal}$	0	**0.09***	0
	$Front_{Mid}$&$Front_{Mid,\ parietal}$	0.03	0.06	0.01
	$Front_{inf}$&$Front_{Mid,\ parietal}$	0.06	**0.10***	0.02

[a.] FNC combinations were included only if p-values were in the 1st percentile (top) and if FNC means were in the 99th percentile. [b.] p-value threshold set to 0.05. [c.] Total number of subjects in regression models was HC: n=31; SZ: n=23.

DISCUSSION

The current study examined the FNC across putative INs consisting of the DMN, frontal and frontal-parietal, temporal and basal ganglia components, in healthy volunteers

and patients with SZ. These measures were then used to predict executive attention obtained from the WCST (Berg, 1948; Heaton et al., 1993) sustained attention obtained from the Conners' CPT II (CPT; Conners 1994). Three major findings emerged from this study. First, compared to HC, patients with SZ showed pervasive cognitive impairments in specific measures of sustained attention and executive functioning. Second, SZ patients displayed decreased FNC between three sub-components of the DMN (precuneus, frontal and anterior cingulate), attention-related (salience) and basal ganglia INs; in addition, patients displayed increased FNC between a frontal pole IC and the anterior cingulate sub-component of the DMN. Third, we observed modest correlations between the magnitude of pre-defined FNC pairs and performance on behavioral measures of attention. To the author's knowledge, this is the first study to examine associations between FNC and behavioral measures of attention in people with SZ.

Group differences for behavioral measures of attention: WCST

The current study also found group differences in perseveration and total errors and conceptual level responses (CLP), where patients scored more PEs and lower on CLP compared to HC. The largest group effect was on perseveration errors (see Table 2), which is a tendency to persist in a specific response despite feedback indicating it's no longer correct or relevant (Demakis 2003). More specifically, perseveration errors are thought to measure the ability to shift cognitive strategies in response to changing environmental contingencies. It's well documented that individuals with SZ demonstrate significant impairments on the WCST (Hartman et al., 2003), with poor performance also present in nonclinical populations bearing a high risk for SZ and in people with schizotypal features (see Liu et al., 2002, for review). It has been hypothesized that

decrements in PE are modulated largely by frontostriatal regions, including basal ganglia and PFC, affecting selected executive functions and processing speed. Using event-related fMRI of the WCST, it has been demonstrated that the prefrontal cortex appears to be activated specifically when the subject has to switch from a previously correct category upon receiving negative feedback to look for a new rule (Konishi et al., 1998, 2002; Monchi et al., 2001). These studies also demonstrated that patients show lower rCBF in dorsal lateral PFC regions during WCST performance, which have been interpreted to be a dysfunction linked to the pathophysiology and executive functioning in SZ.

The CLP score is the total number of consecutive correct responses in a sequence of 3 or more, measuring correct sorting principles and the capacity for abstraction. Like PE, these cognitive abilities also require the proper functioning of the frontal lobe. In conjunction with the PEs, the current results support the hypothesis that patients show a diminished capacity to generate or apply cognitive inhibition. This could manifest as cognitive control deficits and frequent distraction by non-pertinent stimuli, perhaps contributing to incoherent thought, speech and other cognitive processes. In addition, the lower CLP scores demonstrated that individuals with SZ have difficulty forming abstract concepts, which is also shown by the high number of perseveration errors (Everett et al., 2001). From this view, when one perseverates on a problem, it's due to an inability to inhibit a particular conceptual perspective. From the perspective of information processing then, perseveration can occur at several levels, with a failure in executive control to modulate response-selection processes, which may constitute the observed CLP scores (Li et al., 2004).

Group differences for behavioral measures of attention: Conners' CPT II

The CPT is considered a putative indicator of cognitive vulnerability to SZ (Nuechterlein et al. 1991). CPT performance requires subjects to minimize distractibility, maintain alertness, and focus attention on stimuli within a sensorial modality over a long period of time. In the current study, differential effects were observed between patients in comparison to HC, with patients showing impairments in hit RTs and the overall clinical index scores, while also displaying increased sensitivity (d') and response bias (β) scores.

Although sustained attention deficits are associated with poor clinical outcome and may serve as a potential trait marker for the disease, the interpretations of sustained-attention results remain inconclusive due to the multiple mechanisms affecting sustained attention. The sustained attention literature has differentiated vigilance *level* from vigilance *decrement*. Vigilance level is a measure of sensitivity to discriminate a signal from noise, and the vigilance decrement is described as the deterioration in sensitivity from the beginning to the end of the testing and is thought to be a better measure of sustained attention (Davis and Parasuraman, 1982). Although SZ patients typically show deficits in vigilance *level*, i.e. they have lower d' scores across all the CPT measures, a lack of vigilance decrement is observed in patients and their offspring (Cornblatt et al., 1989). Indeed, more recently, Mar and Colleagues (1996), reported a failure to decrease vigilance (larger d' scores) in a small sample of SZ compared to HC, supporting a 'hyperattention' hypothesis in SCZ. This hypothesis is of growing interest and suggests that patients will, under certain conditions, exceed the performance of normal controls. The hyperattention hypothesis in SZ corresponds to a failure to disattend, or gate, irrelevant stimuli including internally generated cues and general impairments in filtering (Nieoullon, 2002). More recent studies have observed such findings with regard to

sustained attention (Fleck, Sax, & Strakowsky, 2001; England et al. 2003; 2007). In particular, England et al., 2007 found that SZ patients were characterized by a training effect that reduces the impact of their initial inattention thereby making them less susceptible to a vigilance decrement over time. However, the extent that similar mechanisms affected the current samples' increased d' scores is unknown as the current sample did not differ in the hit RT standard error block change, a measure of vigilance decrement.

The current study also found that patients scored higher on the response bias measure, β. Conceptually, individuals who have higher β values respond more cautiously in order to make a correct response (with an emphasis on avoiding commission errors; Conners 1994). Indeed, individuals with SZ in the current sample showed less commission errors than controls, although this was not statistically significant (p=0.10). This pattern of results, including SZ displaying slower hit RTs, indicates an atypical profile of response patterns. Alternatively, given that the mean normative T-scores for the HC group for both d' and β were "within the average range", the current sample of SZ patients could have been particularly cooperative and high-functioning, thus not truly representative of the typical SZ population. However, the measure showing the largest effect was the CPT II confidence index score, a multivariate measure included in the CPT II, which has not been reported in other studies in people with SZ. This measure combines nearly all of the output measures from the CPT II into a discriminant function analysis to assess the likelihood that an examinee's responses fit those given by individuals with ADHD (i.e., omissions, gender, age, β, RT by ISI, SE HRT, perseverations, d', SE by block and SE by ISI were included in the final model and

ordered above by its corresponding canonical coefficients; Conners, 2000). The current SZ sample had a mean of 63.97 (±18.14), indicating that there was a 64% chance that this group mean belongs to a clinical group, while the HC group had a mean of 48.29 (±14.14). Accordingly, although these latter findings strengthen the hypothesis for an inattentiveness component to the frequently observed sustained attention impairments in SZ, further research is needed to decompose the nature of these abnormalities by using multiple assessments of sustained attention in a larger sample.

Functional network connectivity group differences

Functional network connectivity (FNC) is a measure of the relationship between component time courses, with FNC abnormalities hypothesized to underlie dysfunction in the capacity to switch between functional brain states (Jafri et al., 2008; Calhoun et al., 2011). As illustrated on Figure 2, the FNC between three component pairs were significantly different in people with SZ, all of which included a subcomponent of the DMN.

The largest FNC group difference was between an IN comprised of brain regions overlapping with the so-called salience network (anterior cingulate and bilateral insulae) and a subcomponent (comprised of bilateral precuneus) of the DMN. The decrease in FNC between these two INs in patients provides additional evidence for an abnormality in the capacity to switch between the salience network and the precuneus part of the DMN during task related performance. Indeed, disruption in the salience network has been associated with impaired deactivation of the DMN in individuals with SZ (White et al., 2010) and also in people with cognitive impairments following traumatic brain injury

(TBI; Bonnelle et al., 2012). Bonnelle et al. (2012) hypothesized that efficient inhibitory control is associated with rapid deactivation within the precuneus and posterior cingulate of the DMN. They found that TBI patients failed to deactivate within these DMN regions, which also correlated with the amount of white matter damage in the salient network tract connecting the right anterior insula and the dorsal anterior cingulate. Thus, as others have already proposed (Menon and Uddin, 2010), one primary role of this salience network is to enable switching between the default mode and task-related states of brain connectivity, and a failure of this regulation leads to impairments in attentional and executive functions. Indeed, as discussed in the next section, decreased FNC between these two INs in current results was associated with overall worse behavioral performance on the Conners' CPT II.

In regard to the precuneus part of the DMN, previous PET studies have shown that the metabolic activity is higher in the precuneus and posterior cingulate than all other brain regions during rest, suggesting a pivotal status for the precuneus node in the DMN (Gusnard and Raichle, 2001). Furthermore, another study found that the prominent features of functional connectivity within the DMN, using partial correlation analysis, included an overall strong level of interaction between the precuneus/posterior cingulate region and the rest of the DMN (Fransson and Marrelec 2008). Thus, given these results, the precuneus (and posterior cingulate) node in the DMN may act as a convergence node, integrating the information from the other DMN subsystems (Fransson and Marrelec 2008). Accordingly, studies have shown that the intrinsic fMRI signal fluctuations in the precuneus/posterior cingulate cortex are altered in SZ using seed-based ROI correlation analyses (Bluhm et al., 2007) and ICA (Garrity et al., 2007; Calhoun et al., 2011). Using

high-order ICA decomposition (c=75), Calhoun and Colleagues (2012) found the largest group effect in the precuneus subcomponent of the DMN, where patients displayed greater activity in supramarginal gyrus, inferior parietal lobule and precentral gyrus.

In regard to present result and the symptomatology of SZ, a review by Palaniyappan and Liddle (2012) suggested that the salience network receives information about internal and external sensations, representations of goals and plans, and stimulus-independent thoughts. Similarly, the precuneus, as well as the posterior cingulate, are thought to be key regions that sustain a sense of self-referential mental thoughts during rest (Fransson and Marrelec 2008) and higher-level integrative processes, which incorporate different qualities of one's coherent experience of the world (Kurth et al., 2010). Thus, the current FNC results provide evidence for a dysfunction in the information processing between these two networks at rest, which may contribute to the core psychopathology of SZ, such as altered perception and cognitive processes related to delusions. Future studies are needed to address whether increased functional connectivity in the precuneus of the DMN contributes to an attenuation of the salience network, and how this may influence cognitive ability and positive symptoms in SZ.

Another FNC group difference was observed between the basal ganglia and the anterior component (anterior cingulate and bilateral middle frontal gyri) of the DMN, suggesting an underlying dysfunction in the synchrony between these two INs in patients with SZ. To the authors knowledge, there are no other studies investigating the relationship of the IN comprised by the basal ganglia in people with SZ. The basal ganglia consist of subcortical nuclei that serve many functions, including goal directed and inhibitory processes. Alterations in the basal ganglia circuits involved with nonmotor

areas of the cortex have been implicated in a wide variety of neuropsychiatric disorders including SZ, depression, autism and attention deficit disorders (Lezak et al., 2012). Emotional flattening and a loss of drive resulting in states of inertia can occur with bilateral basal ganglia and frontal damage, with such anergic conditions resembling the negative symptoms associated with SZ, illuminating the interrelated relationships between the basal ganglia and frontal lobes (Lezak et al., 2012).

Specifically in regard to SZ, basal ganglia is the primary source of dopaminergic input to the cingulate gyrus, which has been suggested to simultaneously influence different components of the cortico-subcortical circuitry, including the anterior cingulate (Saint-Cyr, 2003). The basal ganglia is also thought to contribute to the coordination of putative anatomically and functionally separated components acting for the ability to shift cognitive strategies in response to changing environmental contingencies (Saint-Cyr, 2003). Indeed, as discussed in the next section, increased FNC among these two components predicted less perseveration errors on the WCST—a measure of the ability to shift cognitive strategies in response to changing environmental contingencies.

Lastly, compared to HC, patients displayed increased FNC between the anterior cingulate of the DMN and a frontal pole component. The frontal pole component also includes the middle frontal gyrus (see Figure 1). A similar finding of increased FNC in SZ between frontal INs has also been reported in SZ (Calhoun et al., 2011), indicating that hyperactivity between frontal components may hinder the frontal brain regions role in the integration of sensory and mnemonic information, executive function, planning and regulation of cognitive function and behavior. Indeed, as described below, higher FNC between these two components was predictive of slower hit RT on the CPT.

Abnormal FNC and attention relationships

Given that INs are thought to reflect an *intrinsic* functional baseline that affects the reactivity and adaptation of other task-related networks, the current study provides evidence for specific FNC disruptions that may underlie cognitive processes associated with performance on CPT II and WCST. Of the FNC pairs that were significantly different between groups, three significant associations were observed on CPT II measures. One of these relationships was observed on the FNC between the salience network and the precuneus subcomponent of the DMN, with higher FNC between these INs predicting lower clinical index scores (lower scores indicating that performance resembled a non-clinical population, r (57) = -0.29). The salience network is engaged during CPT performance (Tana et al., 2010) and has been observed to act as switch between central executive and DMN activity in a context-dependent manner (White et al., 2010). It was also observed that the precuneus exhibits heterogeneous functional connectivity with numerous components in motor, visual, and attentional systems, implicating the precuneus as a central core in the cortical anatomical network in HC (Allen et al., 2011). Thus, it's not a surprise that the so-called salience IN and precuneus sub-component of the DMN was significantly lower in patients and predictive of a multivariate clinical index measure on the CPT II, which was significantly lower in patients. Furthermore, a recent study investigating the differential intrinsic connectivity of the precuneus, with the medial dorsal-anterior precuneus regions showed positive correlation with the anterior cingulate cortex (Zhang and Lu, 2012), highlighting the

importance of the present FNC between these two components and its role in attentional monitoring of behavior.

Another relationship was observed between the FNC between an attention-related (frontal-precuneus) IN and the precuneus sub-component of the DMN, with higher FNC between these two INs predicting non-clinical profiles of sustained attention (r (57) = -0.30). These results highlight the importance of the FNC between the precuneus subcomponent of the DMN with multiple attention-related INs in predicting the same behavioral measure of sustained attention. However, the FNC between these two components was not significantly different between groups, however, the FNC between these two components displayed the highest FNC value (i.e., among those FNC values in the 99th percentile; r = 0.78, collapsed across both groups). Thus, future research is needed to examine the contribution of the precuneus on behavioral measures of attention, and how its functional connectivity patterns may differ as a node in an attention network compared to the patterns in the DMN.

The FNC between the frontal pole IN and the frontal subcomponent of the DMN (anterior cingulate and middle frontal gyrus) was also related to hit RT, (r = 0.27); such that, higher FNC between these two INs predicted slower RTs. These results are consist with the present finding of patients showing increased FNC between these two INs and also displaying slower reaction times compared to HC. Thus, increased FNC between these two components may contribute to inefficient information processing that affects general response time. Furthermore, these results are consistent with the disconnection hypothesis of SZ, such that, in regard to the present findings, aberrant functional

connectivity between nodes of the DMN and frontal lobe may contribute to specific cognitive and perceptual abnormalities that are characteristic with the illness.

For the WCST, two significant relationships were observed. The most statistically significant relationship among all the regression models was with the FNC between the basal ganglia and frontal (including middle frontal gyrus and anterior cingulate) subcomponent of the DMN (r = -0.42) predicting perseveration errors (PE). The other relationship was observed between two frontal ICs, one comprised of middle frontal gyrus and the other comprised of the middle frontal and parietal cortex, where higher FNC predicted less perseveration errors in both FNC pairs.

The present findings are consistent with previous studies examining the brain regions most active during the WCST. Monchi et al., 2002 used event-related fMRI while subjects were assessed on the WCST, and a network of structures involving the PFC, basal ganglia, cingulate and thalamus showed greater activity during different stages of WCST performance than during baseline. Indeed, it has been hypothesized that prefrontal and subcortical structures form the "cognitive" cortico-subcortical circuit, as originally proposed by Alexander et al. (1986), with the anterior cingulate regions showing increased activation in response to errors (Wilmsmeir 2010). Thus, since patients showed increased PE—errors which could be viewed as a difficulty in switching attention, reflecting a lack of mental flexibility, the current results highlight the importance of targeting the functional connectivity of the anterior cingulate and the basal ganglia in executive functioning, particularly set-shifting impairments in SZ (Wilmsmeier et al., 2010). Furthermore, using a simulated model of PE dysfunction in the frontal lobes, Amos (2000) found that dopamine deficits in anterior cingulate and basal ganglia would

tend to cause PE because of its effects on inhibition of learned rules, with decreased firing associated with a reduction in the likelihood of any particular unit firing. This is consistent with the hypothesis that SZ suffer from a diminished capacity to valorize a particular sorting rule due to a loss of salience of reward and punishment in a loop including the basal ganglia. Given that the inputs to the basal ganglia arise from virtually the entire cerebral cortex, the basal ganglia are well-poised to have far reaching influence on many neuronal pathways and information processing systems (Utter & Basso 2008). The present results may inform the broad influence of the basal ganglia on other neural structures as they relate to the varied and complex symptoms in patients with SZ.

CONCLUSIONS

In all, the CPT and WCST involve channeling and sharing of information between functional sub-processes. While speculative, it's reasonable to assume that functional connectivity at rest keeps brain networks in an active state, helping to improve performance and reaction time whenever functional connectivity is needed. It has been well-established that there are distinct subgroups in SZ patients that exhibit different sustained and executive attention deficits and this may have important theoretical and practical repercussions for the treatment of SZ. The current results highlight the possible importance of FNC patterns between the anterior cingulate of the DMN and basal ganglia as they relate to set-shifting deficits in SZ, and between the precuneus node of the DMN and the salience IN as they relate to sustained attention impairments in SZ. Thus, the current study highlights the importance of examining the organization of large-scale FNC between dominant INs to investigate attentional dysfunction in SZ. These results

particularly highlight the importance of differentiating the subcomponents of the DMN in discriminating between HC and SZ. Future work should continue address the role of these particular INs as they related to cognitive ability and clinical symptoms in SZ, with the aim of establishing treatment interventions capable of improving, or "normalizing" the abnormal intrinsic functional connectivity observed in SZ.

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