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Thalamus and posterior temporal lobe show greater inter-network connectivity at rest and across sensory paradigms in schizophrenia

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ABSTRACT

Although a number of recent studies have examined functional connectivity at rest, few have assessed differences between connectivity both during rest and across active task paradigms. Therefore, the question of whether cortical connectivity patterns remain stable or change with task engagement continues to be unaddressed. We collected multi-scan fMRI data on healthy controls ($N = 53$) and schizophrenia patients ($N = 42$) during rest and across paradigms arranged hierarchically by sensory load. We measured functional network connectivity among 45 non-artifactual distinct brain networks. Then, we applied a novel analysis to assess cross paradigm connectivity patterns applied to healthy controls and patients with schizophrenia. To detect these patterns, we fit a group by task full factorial ANOVA model to the group average functional network connectivity values. Our approach identified both stable (static effects) and state-based differences (dynamic effects) in brain connectivity providing a better understanding of how individuals' reactions to simple sensory stimuli are conditioned by the context within which they are presented. Our findings suggest that not all group differences observed during rest are detectable in other cognitive states. In addition, the stable differences of heightened connectivity between multiple brain areas with thalamus across tasks underscore the importance of the thalamus as a gateway to sensory input and provide new insight into schizophrenia.

Introduction

Functional connectivity is an approach that helps to assess the integrity of neural circuits by examining the covariance in activity across brain regions and can be assessed using a seed-based analysis approach or independent component analysis (ICA) (Calhoun and Adali, 2012; Erhardt et al., 2011a). Seed-based approaches assess the temporal correlation between a seed region and individual brain voxels (Cordes et al., 2002; Fox et al., 2005) whereas ICA is a data-driven approach which identifies spatially distinct but temporally related brain networks (Calhoun et al., 2001a).

To date, most studies have focused only on the analysis of functional connectivity during performance of a single task. Such an approach does not take advantage of the within-subject pattern of response which likely occurs across tasks, and which can be of benefit in a number of applications (Calhoun and Adali, 2009; Calhoun et al., 2006, 2008). However, one of the challenges associated with studying the resting state is that connectivity changes could reflect differences dependent on the cognitive states of the individual's brain, rather than consistent structural or functional-based differences in brain connectivity (Repovš and Barch, 2012). The results reported by previous studies limit our ability to understand whether observed cortical connectivity deficits in schizophrenia represent consistent characteristics rather than differences in cognitive state or task response.

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Functional MRI (fMRI) results have been used to better understand the pathophysiology of schizophrenia, in particular to assess the disconnection hypothesis of schizophrenia (Friston and Frith, 1995; Woodward, 2012). These differences include a link between prefrontal cortex activation and vulnerability to psychosis (Fusar-Poli, 2007), reduced network activation during executive task performance (Minzenberg, 2009), and abnormal activation patterns in working memory tasks (Glahn et al., 2005). There has been growing interest in investigating the integrity of the neural circuits in schizophrenia that work together to support sensory, cognitive, and emotional processes (Calhoun et al., 2009; Liu et al., 2012; Yu et al., 2013).

Previous seed-based and ICA studies (Allen et al., 2011; Bassett et al., 2011; Cole et al., 2011; Garrity et al., 2007; Woodward et al., 2011) that examined functional connectivity in schizophrenia during rest found reduced connectivity for schizophrenia patients (SPs) within the default mode network, frontal network, cingulo-opercular network and cerebellar network. Several other studies (Anticevic et al., 2011; Diaconescu et al., 2011; Fornito et al., 2011) examined task-related functional connectivity in schizophrenia that largely focused on specific brain networks. These studies have also provided evidence for alterations in functional connectivity across a range of tasks where each task was studied separately. ICA provides measures of functional connectivity (within component coherence) as well as functional network connectivity (FNC) which measures changes in connectivity across networks (Jafri et al., 2008).

To gain a broader understanding of brain function and dysfunction as a dynamic process, we must examine how cognition changes under an established progression of task manipulations. Dynamic changes across tasks have been investigated with FNC and functional connectivity. Arbabshirani et al. (2012) compared dynamic FNC changes across two tasks including resting state and an auditory oddball task in 28 healthy controls (HCs). Results of this study showed decreased FNC during task relative to rest among numerous network pairs. Also, Repovš and Barch (2012) examined differences in functional connectivity during rest and a working memory task with increasing memory loads; SPs and their siblings had reduced connectivity between the frontal network and cingulo-opercular network with cerebellar network relative to HCs and their healthy siblings demonstrating network differences related to genetic risk. These group differences did not change as a function of task state or memory load. Although Arbabshirani et al. (2012) compared FNC across two task in HC and Repovš and Barch (2012) identified group differences in functional network across tasks, none of these studies evaluated changes in FNC across a hierarchy of tasks between the HC and SP groups.

The goal of this study is to determine whether cortical connectivity patterns remain stable or change across a hierarchy of sensory tasks. To the best of our knowledge there has been no study to investigate this issue in a variety of different FNC networks in a multi-task hierarchy with a relatively large number of subjects. This present study examined FNC across a hierarchy of sensory tasks with varying levels of sensory load. Data for each participant were gathered across multiple fMRI scanning sessions over the course of up to two months (1–2 months) with prospective randomization of task presentation and close monitoring of SPs to ensure clinical stability. Our goal was to track connectivity changes in SPs and HCs as sensory load increased. Using multiple tasks in addition to multiple conditions within a single task allows us to recognize that individuals' reactions to sensory stimuli are conditioned by the circumstances in which such stimuli are presented and measurements at separate time points allow us to better assess state versus trait group differences. We sought to determine whether SPs and HCs showed significant FNC differences among brain regions across the task hierarchy by modeling the temporal dependency between functional networks derived from fMRI data. The tasks defined a natural hierarchy related to sensory load and included a rest task, two levels of auditory sensory gating, and two levels of multisensory perception with auditory and audio-visual stimuli. We remained skeptical of the notion that rest differences necessarily equate to characteristic differences in cognition between SPs relative to HCs. We hypothesized that data collected using a sensory load task hierarchy including rest will provide evidence of both stable (static effects) and state-based differences (dynamic effects).

Methods and materials

Participants

This study combined existing data from 95 subjects. Informed consent was obtained from all subjects according to institutional guidelines at the University of New Mexico Human Research Protections Office, and all data were anonymized prior to group analysis. Inclusion criteria for patient selection included diagnosis of schizophrenia or schizoaffective disorder between 18 and 65 years of age. Each SP completed the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 2002a) for diagnostic confirmation and evaluation for co-morbidities. The imaging sessions (three cumulative hours) were completed in 1–2 sessions within up to two months (1–2 months) to reduce subject fatigue. SP had to demonstrate retrospective and prospective clinical stability to be included in this investigation. The Clinical Core (COBRE Stability Clinic) affiliated with this project determined retrospective stability from relevant psychiatric records documenting no change in symptomatology or type/dose of psychotropic medications occurred during the three months prior to the referral. The Clinical Core assessed prospective stability during three consecutive weekly visits and during each imaging assessment. Prospective stability was defined as no change in clinical symptoms >2 points from the positive symptom items on the Positive and Negative Syndrome Scale (Kay et al., 1987), no score of "worse" or "much worse" on the Clinical Global Impression (Guy, 1976), no suicidal or violent ideation, and no psychiatric or medical hospitalizations. The doses of antipsychotic medications were converted to olanzapine equivalents (Gardner et al., 2010). SPs with a history of neurological disorders including head trauma (loss of consciousness >5 min), mental retardation, or history of active substance dependence or abuse (except for nicotine) within the past year were excluded. All SPs had a negative toxicology screen for drugs of abuse at the start of the study. HCs were recruited from the same geographic location and completed the Structured Clinical Interview for DSM-IV Axis I Disorders—Non-Patient Edition to rule out Axis I conditions (First et al., 2002a). SPs and HCs were matched on parental educational level ($p < 0.05$), a less biased estimate of premorbid educational attainment potential (Saykin et al., 1991). We assessed symptom variability among each item of the PANSS positive symptom scores. Consistent with our inclusion criteria, the included subjects had minimal variance (<2) associated with each symptom measure. Table 1 provides demographic characteristics of the participants and Table 2 lists the medications of the patient group.

Task hierarchy

The tasks represented cognitive paradigms that were analyzed separately (Mayer et al., 2012; Stone et al., 2011). Each task represented a different cognitive demand: resting state, pre-attentional sensory processing and multisensory processing. These studies were embedded in a larger study that explicitly proposed that SP would have deficits at multiple levels including pre-attentive sensory processing, integration of sensory information across modalities and impaired working memory performance. For the present investigation, we arranged the sensory tasks into five levels according to the amount of sensori-motor processing required by participants during the task. A subset of the subjects (SPs:22/42, HCs:23/53) were reported previously in Mayer et al. (2012)) based on the original hypotheses of the sensory gating response. The Stone et al. (2011) paper describes the paradigm but

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