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Functional connectivity when detecting rare visual targets in schizophrenia

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ABSTRACT

Individuals with schizophrenia demonstrate difficulties in attending to important stimuli (e.g., targets) and ignoring distractors (e.g., non-targets). We used a visual oddball task during fMRI to examine functional connectivity within and between the ventral and dorsal attention networks to determine the relative contribution of each network to detection of rare visual targets in schizophrenia. The sample comprised 25 schizophrenia patients and 27 healthy controls. Psychophysiological interaction analysis was used to examine whole-brain functional connectivity in response to targets. We used the right temporo parietal junction (TPJ) as the seed region for the ventral network and the right medial intraparietal sulcus (IPS) as the seed region for the dorsal network. We found that connectivity between right IPS and right anterior insula (AI; a component of the ventral network) was significantly greater in controls than patients. Expected patterns of within- and between-network connectivity for right TPJ were observed in controls, and not significantly different in patients. These findings indicate functional connectivity deficits between the dorsal and ventral attention networks in schizophrenia that may create problems in processing relevant versus irrelevant stimuli. Understanding the nature of network disruptions underlying cognitive deficits of schizophrenia may help shed light on the pathophysiology of this disorder.

1. Introduction

Individuals with schizophrenia demonstrate deficits of attention, especially in terms of control processes that guide selection of task-relevant inputs (Luck and Gold, 2008; Nuechterlein et al., 2009). Input selection may be driven by bottom-up signals based on salience or top-down biases such as expectation and behavioral goals (Corbetta et al., 2008). Impaired sustained attention has been directly linked to poor community functioning in schizophrenia (Prouteau et al., 2004), while aberrant salience processing may contribute to symptoms (Palaniyappan and Liddle, 2012; Wolf et al., 2008).

Functional neuroimaging studies have provided important information about the spatial distribution of cortical activation during attention tasks. The key regions identified can be organized into two distinct, interacting networks associated with different aspects of attentional control: a ventral network and a dorsal network (Corbetta and Shulman, 2002; Kim, 2014; Ptak, 2012; Vossel et al., 2012; Weissman and Prado, 2012).

The ventral network is thought to involve automatic alerting or reorienting of attention to novel and salient events in a "bottom-up" manner (Kucyi et al., 2012). This network tends to be right lateralized and includes the temporo-parietal junction (TPJ), anterior cingulate cortex (ACC), and anterior insula (AI). Several lines of evidence suggest that the TPJ is critical to salience detection and stimulus-driven attention (Kucyi et al., 2012) and is modulated by target search and detection (Serences et al., 2005; Shulman et al., 2003). Importantly, TPJ activity may play a key role in the interruption of ongoing cognitive activity (e.g., sustained attention) in order to facilitate the analysis of potentially behaviorally relevant stimuli, including targets and unexpected sensory events (Corbetta and Shulman, 2002; Todd et al., 2005). The dorsal network is thought to control voluntary, sustained orienting of attention, including modulation of visual cortex, in a "top-down" fashion. It includes the medial intraparietal sulcus (IPS; located in posterior parietal cortex between the superior parietal lobule and supramarginal gyrus) and inferior frontal junction (IFJ; located in posterior lateral frontal cortex, including the frontal eye fields). The IPS is thought to play a key role in the computation of an attentional priority map, integrating converging sensory information (including salience selection) with top-down signals that represent behavioral goals and expectations for the control of spatial attention (Ptak, 2012; Szczepanski et al., 2013).

A variety of tasks have been used to examine attention deficits in schizophrenia, including visual search tasks (Davenport et al., 2006; Kurachi et al., 1994), continuous performance tasks (Kurtz et al.,

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2001), and auditory and visual oddball tasks (Ford, 1999; Neuhaus et al., 2013; Oribe et al., 2013). During oddball tasks, subjects are instructed to detect infrequent, irregularly occurring target stimuli embedded within an otherwise repetitive stream of frequent nontarget stimuli. Accurate performance requires ongoing stimulus monitoring while attending to salient stimuli (i.e., targets) and ignoring distractors (i.e., non-targets). Oddball tasks are thus particularly useful as they implicate both top-down and bottom-up aspects of attention. Accordingly, oddball tasks tend to activate regions within both the dorsal and ventral attention networks (Ardekani et al., 2002; Calhoun et al., 2008; Clark et al., 2000; Gur et al., 2007a, 2007b; Kiehl et al., 2005; Stevens et al., 2000).

Prior fMRI studies of the visual oddball task in schizophrenia have revealed abnormal activity to targets in regions within both of these networks in patients (Collier et al., 2014; Gur et al., 2007a, 2007b; Hasenkamp et al., 2011). In the ventral network, reduced activity has been observed in cingulate cortex, insula, and superior temporal gyrus. Within the dorsal network, reduced activity has been found in the superior frontal lobe, while increased activity has been found in the inferior parietal lobule. In a recent study, we similarly found group differences in both networks when examining regional fMRI data alone (Wynn et al., 2015). Specifically, patients showed reduced activity in frontal, parietal, and occipital regions, including TPJ, as well as ACC. This study also used a specialized analysis that combined information from both fMRI and event-related potentials (ERPs) (joint independent component analysis, ICA), and found that regional group differences in activation were seen mainly in the ventral network, including ACC, AI, and TPJ (Wynn et al., 2015). These joint ICA findings for the ventral network suggest that dysfunction during target detection in schizophrenia may be linked to problems orienting to salient stimuli in the environment, aside from any difficulties in sustaining general attention to the task.

Fundamental questions remain about the way these regions functionally interact within network, and how the networks interact with each other (Calhoun et al., 2009; Hutchison et al., 2013). The auditory oddball task has been used previously to examine alterations in temporal lobe networks (e.g., (Çetin et al., 2014; Garrity et al., 2007; Yu et al., 2011). Interestingly, reduced connectivity in patients with schizophrenia in the dorsal attention network has also been shown during the auditory oddball task (Calhoun et al., 2008; Kim et al., 2009). How the two attention networks, which serve distinct and complementary purposes, communicate during visual target detection in schizophrenia is not known.

To address these questions, we used a visual oddball task to examine functional connectivity of the ventral and dorsal attention networks in patients with schizophrenia and healthy controls. Given our *a priori* interest in the ventral and dorsal attention networks, we used psychophysiological interaction (PPI), a seed-based approach, for functional connectivity analysis (Rogers et al., 2007). For the seed regions, we selected areas that might be considered "hubs" of their respective networks: right TPJ for the ventral network (Kucyi et al., 2012) and right IPS for the dorsal network (Ptak, 2012). Using these seed regions, we conducted whole-brain analyses to investigate how connectivity is organized within and between networks while processing rare targets during visual oddball detection.

2. Methods

2.1. Participants

Twenty-five patients with schizophrenia (4 female) and 27 healthy controls (4 female) were recruited for the study. The participants in this study were largely overlapping with those in Wynn et al. (Wynn et al., 2015) that examined regional activation and EEG, but did not consider connectivity. Patients were recruited from outpatient treatment clinics at the Greater Los Angeles VA Medical Center (GLA) and the community. Patients met diagnostic criteria for schizophrenia based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 1997b). Selection criteria were the same as previous studies from this laboratory. Patients were between 18 and 60 years of age, and were excluded from participation if they had: self-reported substance abuse in the past month or dependence in the last six months, IQ < 70 based on examination of medical records, history of loss of consciousness for more than one hour, identifiable neurological disorders, or were not sufficiently fluent in English to consent and understand procedures. Psychiatric symptoms were evaluated using the 24-item University of California, Los Angeles (UCLA) version of the Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1995) and Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982). For the BPRS we report means for the "positive symptom," "negative symptom," "agitation/mania," and "depression/anxiety" factors (Kopelowicz et al., 2008). For the SANS we report four global scales (Blanchard and Cohen, 2006): Affective Flattening, Alogia, Avolition-Apathy, and Anhedonia-Asociality.

Healthy controls between 18 and 60 years of age were recruited through internet postings and interviewed with the SCID-I and portions of the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) (First et al., 1997a). Exclusion criteria for potential controls included: an identifiable neurological disorder or head injury, a first-degree relative with schizophrenia or another psychotic disorder, insufficient fluency in English, a personal history of schizophrenia or other psychotic disorder, bipolar disorder, recurrent depression, a lifetime history of substance dependence, or any substance abuse in the last 6 months, and any of the following Axis II disorders: avoidant, paranoid, schizoid, or schizotypal.

All interviewers were trained through the Treatment Unit of the Department of Veterans Affairs VISN 22 Mental Illness Research, Education, and Clinical Center (MIRECC) to a minimum kappa of 0.75 for key psychotic and mood items. The study protocol was reviewed and approved by the Institutional Review Boards of the University of California, Los Angeles and Greater Los Angeles VA Medical Center. All participants had the capacity to give informed consent and provided written informed consent after all procedures were fully explained.

2.2. Procedures

2.2.1. Task design

Participants completed a visual oddball task, modeled after prior studies (Ardekani et al., 2002; Ford et al., 2005; Stevens et al., 2000), in which they viewed images of two letters, X and K; one letter served as a target and the other as a nontarget in a counterbalanced fashion. We used an event-related design and presented the stimuli in three separate blocks using magnet-compatible goggles (Resonance Technology, Northridge, CA). Each stimulus was displayed for 100 ms followed by an interstimulus interval (ISI) that was either 900, 1900, or 2900 ms (mean ISI=1900 ms). The ISIs were equiprobable and randomly distributed. Participants were instructed to push a button on a MRI-compatible button box whenever they detected the target and had 3000 ms to make a response.[1] Within each block a total of 150 stimuli were presented: 12% were targets (n=18) and 88% were non-targets (n=132). Additionally, null trials were interspersed throughout each block and consisted solely of a fixation point. Duration of each block was 5 minutes. The task took approximately 20 minutes to complete.

2.2.2. fMRI data acquisition and preprocessing

Scanning was performed on a Siemens 3 T (Erlangen, Germany)

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[1] Note that although the response window to targets (3000ms) overlapped with the onset of non-targets, the vast majority of participants responded faster than 1000ms and responded almost exclusively to the target. See Wynn et al. (Wynn et al., 2015) for further comment on the justification for this design.