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Working memory in schizotypal personality disorder: fMRI activation and deactivation differences

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ABSTRACT

Background: Schizotypal personality disorder (SPD) is considered a schizophrenia spectrum disorder, sharing with schizophrenia cognitive, neuropsychological, epidemiological, and biological characteristics. Working memory may be one area of shared deficit, although to date, this is only the second study to investigate working memory in SPD using fMRI.

Methods: In a block-design fMRI study, fifteen antipsychotic-naïve SPD and sixteen healthy control subjects performed blocks of a 2back visual working memory task and 0back continuous performance task while undergoing whole-brain fMRI at 3 T. Whole-brain analyses were performed for the 0back > rest (fixation baseline) and the 2back > 0back contrasts (isolating the working memory component from the visual perception and attention component). Parameter estimates were extracted to determine whether observed differences were due to task-induced activation and/or deactivation.

Results: Activation differences emerged between the two groups, without differences in task performance. In the 0back task, SPD showed decreased task-induced activation of the left postcentral gyrus. In the 2back > 0back contrast, HC showed greater task-induced activation of the left posterior cingulate gyrus, superior temporal gyrus, insula, and middle frontal gyrus. These differences were due to SPD subjects' decreased task-induced activation in the left posterior cingulate gyrus, and task-induced deactivation in the remaining regions.

Conclusions: These findings suggest that compared to HC subjects, individuals with SPD may achieve comparable working memory performance. However, differences emerge at the level of functional neural activation, attributable to different task-induced activation and deactivation patterns. Such differential recruitment of neural resources may be beneficial, contributing to SPD subjects' ability to perform these tasks comparably to HC subjects.

1. Introduction

Schizotypal personality disorder (SPD) is characterized by odd behavior, perception, thinking, and appearance, which seem to comprise a milder but similar symptom profile as seen in schizophrenia (Kety et al., 1975; Siever and Davis, 2004; Dickey et al., 2005). SPD is fairly common, with a prevalence of 3.9% (Pulay et al., 2009), and is considered a schizophrenia spectrum disorder (Kety et al., 1975; Kendler et al., 1981; Kendler, 1985; Siever et al., 1993; Siever and Davis, 2004; Dickey et al., 2005; American Psychiatry Association, 2013). Relatives of individuals with schizophrenia are at a heightened risk for development of schizophrenia and SPD (Kendler et al., 1981; Siever et al., 1990; Battaglia et al., 1991; Thaker et al., 1993; Hazlett et al., 2008a) and do show increased rates of SPD (Kendler et al., 1981; Lowing et al., 1983; Kendler and Gruenberg, 1984; Frangos et al., 1985; Gershon et al., 1988; Kendler, 1988; Siever et al., 1990; Grove et al., 1991; Onstad et al., 1991; Maier et al., 1994; Asarnow et al., 2001; Hazlett et al., 2011). SPD shares with schizophrenia many genetic, anatomical, functional, electrophysiological, cognitive, neuropsychological, and treatment response characteristics (Kendler et al., 1984; Gunderson and Siever, 1985; Kendler, 1985; Torgersen, 1985; Siever and Davis, 1991; Cadenhead et al., 1993; Siever, 1994; Trestman et al., 1995; Buchsbaum et al., 1997b; Keefe et al., 1997; Cadenhead et al., 1999; Dickey et al., 1999; Niznikiewicz et al., 1999; Cadenhead et al., 2000; Dickey et al., 2000; Kirrane and Siever, 2000; Niznikiewicz et al., 2000; Voglmaier et al., 2000; Byne et al., 2001; Shenton et al., 2001; Buchsbaum et al., 2002; Dickey et al., 2002a,b; Mitropoulou et al., 2002; Dickey et al., 2003a,b; Koenigsberg et al., 2003; Haznedar et al., 2004; Siever and Davis, 2004;

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Dickey et al., 2005; Mitropoulou et al., 2005; Nakamura et al., 2005; Voglmaier et al., 2005; Dickey et al., 2007, 2008; McClure et al., 2008; Dickey et al., 2010, 2011; Ozeki et al., 2011).

Research suggests that the cognitive impairments shared between SPD and schizophrenia are more focal, mainly involving deficits in verbal learning (Kirrane and Siever, 2000; Voglmaier et al., 2000; Siever et al., 2002; Voglmaier et al., 2005), sustained attention (Condray and Steinhauer, 1992; Harvey et al., 1996; Roitman et al., 1997; Kirrane and Siever, 2000; Siever et al., 2002; Bergida and Lenzenweger, 2006) and working memory (Farmer et al., 2000; Kirrane and Siever, 2000; Roitman et al., 2000; Voglmaier et al., 2000; Siever et al., 2002; Mitropoulou et al., 2005; McClure et al., 2007; Goldstein et al., 2011). Such cognitive impairment may underlie day-to-day functioning difficulties; in schizophrenia, cognitive impairment is thought to be a better predictor of long-term daily functioning than the severity of psychotic symptoms (Green, 1996; Green and Nuechterlein, 1999; Green et al., 2000; Mitropoulou et al., 2002). In a twin study of SPD, Johnson et al. suggest that neurocognitive function is related to SPD symptoms, but only in the presence of genetic risk for schizophrenia (Johnson et al., 2003). While people with SPD do indeed share many facets with schizophrenia, they are not psychotic and are not as likely to have been institutionalized or medicated. Without these confounds often found in schizophrenia, SPD may serve as a useful model for studying the schizophrenia spectrum. Moreover, studying these characteristic cognitive deficits in SPD may provide insight into those specific processes reflecting vulnerability to the schizophrenia spectrum, as well as characteristics that may reflect protective factors against psychosis (Sham et al., 1993; Siever and Davis, 2004).

Functional magnetic resonance imaging (fMRI) studies have investigated the neural correlates of working memory in patients with schizophrenia, with many reporting reduced prefrontal cortex (PFC) activation in subjects with schizophrenia as compared to healthy comparison (HC) subjects, and others reporting increased PFC activation (e.g., Manoach et al., 2000; Callicott et al., 2003; Manoach, 2003; Lee and Park, 2005; Thermenos et al., 2005; Schneider et al., 2007; Kim et al., 2009). To date, however, only four studies have employed fMRI to investigate SPD (Koenigsberg et al., 2005; Dickey et al., 2008; Hazlett et al., 2008b; Dickey et al., 2010; Fervaha and Remington, 2013) and similarly to the literature on schizophrenia, there is not a clear pattern of activation differences, with some reporting greater activation than HC, thought to represent "inefficient" activation or the allocation of "excessive resources" (Dickey et al., 2008; Hazlett et al., 2008b), and some reporting decreased activation compared to HC (Koenigsberg et al., 2005; Dickey et al., 2010). Only one of these studies directly investigated working memory, and sought to replicate previous findings in HC and schizophrenia subjects, choosing a priori regions of interest (ROIs) accordingly (Koenigsberg et al., 2005). Interestingly, the main analyses in all four studies were driven by a priori ROI-based approaches (Koenigsberg et al., 2005; Dickey et al., 2008; Hazlett et al., 2008b; Dickey et al., 2010; Fervaha and Remington, 2013). However, given the research supporting the possibility that SPD subjects are able to recruit brain regions not normally recruited for certain cognitive functions (Buchsbaum et al., 1997a; Kirrane and Siever, 2000; Siever et al., 2002; Dickey et al., 2010), and may not appear to have the frontal lobe volume reductions reported in schizophrenia (Kirrane and Siever, 2000; Yoneyama et al., 2003; Suzuki et al., 2005; Hazlett et al., 2008a, 2012; Fervaha and Remington, 2013), it may be possible that an ROI-based approach, especially one based on findings in healthy controls and schizophrenia subjects, may unnecessarily narrow the scope of investigation of the neural networks involved in working memory in SPD.

There may be another side to the story: while studies showing activation differences often speculate that one subject group may show increased regional brain activation over a different subject group, there is always the possibility that task-induced *de*activation may play a role in the observed differences as well. The default network, which includes the medial PFC, the posterior cingulate/retrosplenial cortex, the inferior parietal lobule, and medial temporal lobe, is a network that increases in activity during passive states and conversely decreases in activity during more active goal-directed states (e.g., as reviewed in McKiernan et al., 2003; Buckner et al., 2008). McKiernan et al. found that task-induced deactivation of the default mode network increased with task difficulty, and suggested that task-induced deactivation represents a reallocation of processing resources from the areas showing this deactivation to the areas involved in task performance (McKiernan et al., 2003). The default network has been shown to be abnormal in subjects with schizophrenia (Garrity et al., 2007; Williamson, 2007; Buckner et al., 2008; Pomarol-Clotet et al., 2008; Broyd et al., 2009; Kim et al., 2009; Whitfield-Gabrieli et al., 2009; Ongur et al., 2010; Salgado-Pineda et al., 2011), and thus some fMRI studies examining working memory in schizophrenia have considered both task-induced activation and task-induced deactivation (Thermenos et al., 2005). Given these findings, it is possible that task-induced deactivation may play a role in functional brain activation differences in SPD as well.

Taking these factors into consideration, we thus hypothesize that functional brain activation differences in SPD may be subtly different from those implicated in schizophrenia studies, and that task-induced deactivation may contribute to these differences. Furthermore, we expect any differences in comparison to HC subjects to be subtle. While cognitive performance in SPD is generally intermediate to HC and schizophrenia groups (Cadenhead et al., 1999; Siever and Davis, 2004; Dickey et al., 2005), the difference observed between SPD and either one of the groups (HC or schizophrenia) may be subtle, reaching only trend-level (Cadenhead et al., 1999). This study therefore sought to investigate functional brain differences in subjects with SPD during a working memory task from a broader unbiased perspective. A whole-brain scope of analysis was used, rather than selecting a priori ROIs. Furthermore, the contributions of both task-induced activation and task-induced deactivation were taken into consideration in interpreting any functional differences observed in subjects with SPD as compared to HC subjects.

2. Methods

2.1. Subjects and diagnostic procedures

Subjects were recruited using advertisements on local public transit, print media, and websites. The SPD advertisements asked, "Do you believe you have ESP, telepathy, or a "sixth sense"? Do you have anxiety or discomfort in situations with unfamiliar people? Do you have few close friends?" All potential HC and SPD subjects received the Structured Clinical Interview for DSM-IV-TR Axis I (SCID) and Axis II Disorders SCID II (First et al., 1995, 1997). Criteria for inclusion were: age between 18 and 55, right-handedness, English as a first language, IQ > 80, and no history of antipsychotic use, ECT, neurological disorders, substance abuse for one year, substance dependence for five years, or active psychoactive medication use at time of scan, per subject report. Subjects with SPD had no history of bipolar disorder or psychosis. HC subjects had no diagnosis or history of Axis I or Axis II disorders, and no bipolar or psychotic disorder in their first-degree relatives, per subject report. Subjects were one-to-one matched for age within 3 years, and group-matched for parents' socioeconomic status (PSES), IQ, and years of education. IQ was calculated based on the WAIS-R Vocabulary and Block Design subtests (Brooker and Cyr, 1986). All subjects provided written informed consent. Approval for the study came from the human research committees of Brigham and Women's Hospital and VA Boston Healthcare System.

2.2. fMRI working memory task

2.2.1. Stimuli & stimuli presentation

The tasks employed were visual versions of the 2back working memory task and simple vigilance continuous performance 0back