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Visual–spatial working memory performance and temporal gray matter volume predict schizotypal personality disorder group membership

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ABSTRACT

Background: Prior work shows individuals with schizotypal personality disorder (SPD) evince temporal lobe volume abnormalities similar to schizophrenia but sparing of prefrontal cortex, which may mitigate psychosis and the severe neurocognitive impairments observed in schizophrenia. This study examined the extent to which frontal–temporal gray matter volume and neurocognitive performance predict: (1) SPD group membership in a demographically-balanced sample of 51 patients and 37 healthy controls; and (2) symptom severity in SPD.
Methods: Dimensional gray-matter volume (left frontal–temporal regions (Brodmann area (BA) 10, 21, 22)) and neurocognitive performance on key memory tasks (California Verbal Learning Test (CVLT), Dot Test, Paced Auditory Serial Addition Test (PASAT)), all salient to schizophrenia-spectrum disorders were examined in a multi-variable model.
Results: Middle temporal gyrus (BA21) volume and spatial–working memory (Dot Test) performance were significant predictors of SPD group membership likelihood, with poorer working-memory performance indicating increased probability of SPD membership. Combining across regional volumes or cognitive measures resulted in fair-to-good discrimination of group membership, but including neurocognitive and non-collinear regional volume measures together resulted in a receiver-operating-characteristic (ROC) curve with improved diagnostic discrimination. Larger BA10 volume in dorsolateral prefrontal cortex (DLPFC) significantly predicted less symptom severity in SPD.
Conclusions: These findings suggest that temporal lobe volume and spatial-working memory performance are promising biological/phenotype markers for likelihood of SPD classification, while greater DLPFC volume may serve as a protective factor.

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1. Introduction

Schizotypal personality disorder (SPD) is considered to be the prototypic schizophrenia-spectrum disorder which shares common genetic, biological, and neurocognitive abnormalities with schizophrenia, but without the psychosis and severity of cognitive impairment observed in the latter (Kendler and Diehl, 1993; Cadenhead et al., 1999; Siever and Davis, 2004). The SPD diagnosis currently follows a categorical approach prescribed by the DSM-IV (American-Psychiatric-Association, 2000), in which an individual must demonstrate multi-contextual evidence of at least five out of nine criteria broadly encompassing domains of unusual behavior, speech, cognition, and limited social contact and interest. Limitations of the current diagnostic classification systems include: high degree of comorbidity, potentially artificial disorder boundaries, and a lack of diagnostic clarity, e.g., (Widiger and Samuel, 2005; Kupfer and Regier, 2011), which undermine its clinical utility. Additionally, current categorical classification systems do not incorporate knowledge gleaned from brain science (Insel and Cuthbert, 2009).

Krueger and Eaton (2010) recommend developing a comprehensive empirically derived system based on quantitative models of psychopathology. They focus on personality traits but argue that a valid diagnostic system to drive appropriate intervention strategies could be created using a combination of neurobehavioral indices and environmental elicitors. One aim of transdisciplinary diagnostic approaches is to address some of these limitations and enhance diagnostic classification, thereby aiding our understanding of etiological mechanisms and improving clinical utility.

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Consistent with this approach, attempts to elucidate diagnostic clarity, understand disease pathology and course include, using empirical data to explore whether these variables could accurately classify diagnostic group membership and functional outcome. This strategy has proved fruitful by providing evidence indicating that neurocognitive performance (Pena et al., 2011), prodromal symptoms (McGorry et al., 2000) and activity in key brain regions as measured by fMRI scans (Whalley et al., 2006) correctly classify schizophrenia patients. Additionally, studies have shown that baseline neurocognitive performance predicts functioning five years after hospitalization for first psychotic episode (Gonzalez-Ortega et al., 2013) and psychotic symptoms predict future hospitalization (Werbeloff et al., 2012). Although there is consistent evidence that schizophrenia-spectrum disorder patients demonstrate neurocognitive performance deficits and a reduction of gray matter volume in key brain regions, no study has examined whether these measures can accurately classify patients with SPD. The extant literature primarily focuses on predicting schizophrenia group membership and differentiation of schizophrenia from other psychotic disorders. For example, Pena et al. (2011) reported that performance on the Wisconsin Card Sorting Test (WCST) correctly distinguished patients diagnosed with schizophrenia from those with bipolar disorder. Using this prior schizophrenia work as a novel model for SPD, the aim of this study was to examine the extent to which both gray matter volume in key frontal and temporal lobe regions, and neurocognitive performance effectively predict SPD group membership, and a dimensional measure of symptom severity in SPD.

There is consistent evidence supporting reduced volume of temporal lobe regions in schizophrenia (reviewed by Shenton et al., 2001; Shepherd et al., 2012). While studies in SPD report temporal lobe reductions, they are less marked than those observed in schizophrenia (Takahashi et al., 2006; Hazlett et al., 2008). Specifically, SPD-related reduced gray matter volume has been found in the superior (Brodmann area (BA) 22) (Buchsbaum et al., 1997; Dickey et al., 1999), middle (BA21) (Hazlett et al., 2008), and inferior temporal gyrus (BA20) (Downhill et al., 2001). Dickey et al. (2002) found reduced gray volume matter in the left Heschl's gyrus of SPD patients; however, a subsequent study of female SPD patients failed to reveal differences in superior temporal gyrus (STG) volume (Dickey et al., 2003). We have proposed that reduced superior (BA22) and middle (BA21) temporal lobe gyrus volume may be an important endophenotype for schizophrenia-spectrum disorders (Siever and Davis, 2004; Goldstein et al., 2009).

While temporal lobe volume has been shown to be smaller in SPD, prefrontal cortex volume findings are more mixed. Some studies reported decreased prefrontal volume in SPD (Raine et al., 2002; Matsui et al., 2008), whereas our group (Hazlett et al., 2008) and others (Suzuki et al., 2005; Kuhn et al., 2012) have found increased dorsolateral prefrontal cortex (DLPFC) volume. SPD patients also show higher glucose metabolism in BA10 of the DLPFC compared with healthy controls (HCs) and schizophrenia patients during the California Verbal Learning Test (CVLT) adapted for PET (Buchsbaum et al., 2002a), and it has been proposed that this compensatory pattern may serve to protect these individuals from frank psychosis. In our earlier study, we concluded that increased gray matter volume in BA10 of the DLPFC and relative sparing of volume loss in the temporal cortex may be a protective factor in SPD, which reduces vulnerability to psychotic symptoms (Hazlett et al., 2008). Consistent with this concept, we recently reported that compared with HCs, SPD patients have significantly lower fractional anisotropy—a measure of white matter integrity—in left BA21 of the temporal lobe while showing sparing in prefrontal regions (Hazlett et al., 2011). Taken together, MRI findings support the model proposed by Siever and Davis (2004) that similar to schizophrenia, superior (BA22) and middle (BA21) temporal gyrus abnormalities are core to both SPD and schizophrenia, while frontal reserves (e.g., BA10 of DLPFC) protect the former from decompensating into florid psychosis.

Neurocognitive studies support the perspective that working memory impairment is a core, stable feature of schizophrenia, e.g., (Goldman-Rakic, 1991; Park and Holzman, 1992; Silver et al., 2003). Working memory involves the ability to manipulate and maintain information over a short period of time and has been associated with DLPFC function (Callicott et al., 2003; Reichenberg and Harvey, 2007) and frontal–temporal circuitry (Kang et al., 2011). Working-memory deficits in schizophrenia include verbal and nonverbal domains (Park and Holzman, 1992; Kareken et al., 1995; Park et al., 1996; Manoach et al., 1999; Reichenberg and Harvey, 2007). Similarly, individuals with SPD consistently exhibit problems with working memory (Voglmaier et al., 2000; Mitropoulou et al., 2005), including visual–spatial (Voglmaier et al., 1997; Farmer et al., 2000; Roitman et al., 2000) and verbal tasks (McClure et al., 2007), although deficits are typically observed with longer time delays, suggesting these deficits are more subtle than those observed in schizophrenia. Roitman et al. (2000) reported that SPD patients demonstrate visual–spatial impairments on the Dot Test at the delayed but not the more immediate conditions. Similarly, SPD-related deficits have been reported during the CVLT, e.g., (Bergman et al., 1998), particularly after a 20-minute delay (McClure et al., 2007). Mitropoulou et al. (2002) showed that SPD patients evince marked abnormalities on the PASAT, a test of auditory working memory, compared with HCs and individuals with non-schizophrenia spectrum personality disorders. Taken together, neurocognitive deficits in SPD are more subtle than those observed in schizophrenia but compared with HCs, SPD patients have shown deficits in auditory (PASAT) working memory, as well as visual working memory (Dot Test) and verbal learning (CVLT) during the more challenging delay conditions.

Research has shown a direct relationship between structural brain abnormalities and cognitive functioning, as measured by neurocognitive tests (Goldberg et al., 1994; Antonova et al., 2004). In SPD, reduced frontal lobe size and dysfunction as measured by perseveration errors on the WCST, have been reported (Raine et al., 2002). Matsui and colleagues (Matsui et al., 2008) found that smaller left inferior frontal white matter volume was associated with better semantic clustering in SPD compared with healthy individuals and suggested the operation of a compensatory mechanism, i.e. brain areas other than the frontal lobe playing an important role in memory performance. Our lab (Goldstein et al., 2011) reported that in HCs, but not SPD patients, better spatial working memory performance was associated with larger ventrolateral prefrontal cortex gray matter volume. To date, no study of SPD has examined gray matter brain volume of key regions (frontal and temporal) and working-memory (both visual–spatial and verbal) function together in the same sample, which is an aim of this study.

Neuroimaging and neurocognitive findings in SPD suggest this disorder is characterized by reduced temporal lobe volume but frontal lobe sparing, as well as cognitive impairments, particularly on tasks involving working memory. We specifically selected cortical regions (BAs 22, 21, and 10) and variables from neurocognitive tests (PASAT, Dot Test and CVLT long-delay condition) that consistently reveal SPD differences from HC participants. This study tested the following hypotheses: (1) smaller left temporal, but not frontal lobe volume is associated with increased odds for SPD group membership; (2) poorer working memory and specifically, visual–spatial memory performance is associated with increased odds for SPD classification; and (3) frontal lobe sparing (i.e. larger frontal lobe volume) predicts less severity of SPD symptoms.

2. Methods

2.1. Participants

We studied two demographically-balanced groups of participants: 51 individuals with SPD and 37 HCs. Demographic and clinical details are presented in Table 1. A small subgroup of these participants was previously included in independent studies examining regional brain volume (Hazlett et al., 2008) and neurocognitive functioning (McClure