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Relationship between prefrontal gray matter volumes and working memory performance in schizophrenia: A family study

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ABSTRACT

Diffuse structural abnormalities in the prefrontal cortex have been reported in both schizophrenia patients and their nonpsychotic biological relatives. Additionally, working memory difficulties have long been documented in schizophrenia patients and have been associated with the genetic liability for the disorder. The present analysis investigated the relationship between prefrontal regional gray matter volumes and two facets of working memory in schizophrenia using a family study. Structural neuroimaging scans provided measurements of rostral middle, superior, and inferior prefrontal cortical gray matter volumes. Participants also completed a spatial working memory task that measured both short-term maintenance and manipulation of material in memory. Both schizophrenia patients and relatives had reduced superior and inferior frontal gray matter volumes. Schizophrenia patients demonstrated a spatial working memory deficit compared to both controls and relatives, with no greater impairment when required to manipulate material. Smaller prefrontal volumes in schizophrenia patients were associated with worse working memory performance. These relationships were absent in the nonpsychotic relatives and controls. Despite normative behavioral performance, nonpsychotic relatives demonstrated abnormalities in brain structure similar to those found in schizophrenia patients. Manipulation abilities were not more impaired than maintenance in schizophrenia patients. Consistent with other neuroimaging research, our results suggest that direct measures of the underlying biology may be more sensitive to the effects of the genetic liability for schizophrenia than behavioral measures.

1. Introduction

Prefrontal structural abnormalities and working memory difficulties have long been documented in schizophrenia patients and have also been found in their nonpsychotic family members (Cannon et al., 1998, 2002; Snitz et al., 2006). The goal of the present study was to investigate prefrontal gray matter abnormalities and examine their relevance to different aspects of spatial working memory in schizophrenia patients and nonpsychotic first-degree biological relatives by using a cognitive neuroscience task that isolated working memory maintenance from manipulation processes (Kim et al., 2004; Cannon et al., 2005). Inclusion of both patients and family members allowed a better examination of genetic (familial) liability, as well as disease-related processes.

The prefrontal cortex has been shown to be consistently involved in working memory. Distinct components of the middle frontal region, the rostral and caudal areas, have been demarcated, with differing roles in working memory (Wager and Smith, 2003). The rostral area encompasses parts of Brodmann's area 46, which is considered part of the dorsolateral prefrontal cortex, whereas the caudal area is considered part of the premotor region (Kikinis et al., 2010). In a meta-analysis, Brodmann's area 46 was identified as being consistently activated during the manipulation of information held in working memory (Owen et al., 2005). Additionally, the superior frontal region had a role in continuous updating of content (Wager and Smith, 2003). Activations of the inferior frontal region were related to manipulation of information, primarily switching and inhibition (Wager and Smith, 2003). Furthermore, a meta-analysis of N-back working memory studies (which required remembering the stimulus that occurred "N" positions previously) demonstrated that the middle frontal region and inferior frontal region were consistently hypoactive, and the middle frontal and superior frontal regions were consistently hyperactive in schizophrenia patients compared to controls (Glahn et al., 2005). In a meta-analysis of working memory studies in the relatives of schizophrenia patients, relatives showed hypofrontality in the right middle and inferior frontal regions and hyperfrontality in the right middle frontal region compared to controls, suggesting that these abnormalities are related to the genetic liability for the disorder and cannot wholly be accounted for

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by disease process and medication (Goghari, 2010). Concurrent with the prefrontal cortical activation abnormalities found to be associated with the genetic risk for schizophrenia (Goghari, 2010; Walton et al., 2013a,b), prefrontal gray matter volume, including the sub-regions assessed in this paper, have shown associations with the genetic risk for the disorder (Rosso et al., 2010; Bhojraj et al., 2011a,b; Chen et al., 2013); however, this is not a wholly consistent finding (Goghari et al., 2007a,b), likely due to the heterogeneity in the samples studied and methods. Regardless, the current literature supports investigating the relationship between prefrontal gray matter volumes and working memory abilities.

Working memory ability has been consistently demonstrated to be impaired in schizophrenia patients (Dickinson et al., 2007; Forbes et al., 2009) and in their family members (Snitz et al., 2006). One influential model of working memory by Baddeley (1992) includes a cognitive construct called the central executive, which controls attention and manipulates information, and secondary constructs called the phonological loop and visuospatial sketchpad, which store and rehearse information in short-term memory. Despite the acceptance of the varied processes termed working memory, the majority of schizophrenia studies have used tasks, such as the N-back and letter-number sequencing, which do not distinguish maintenance from manipulation processes. More recently, Cannon and colleagues have investigated maintenance and manipulation components using a task informed by findings from cognitive neuroscience approaches (Glahn et al., 2002; Kim et al., 2004; Cannon et al., 2005). Two studies have employed this task to investigate the maintenance and manipulation of spatial working memory content in schizophrenia (Kim et al., 2004; Cannon et al., 2005). The behavioral study demonstrated that schizophrenia patients were impaired in both aspects of spatial working memory, but were particularly impaired when manipulation of information was required (Kim et al., 2004). A second study evaluated the neural correlates of maintenance compared to manipulation, finding that when spatial manipulation of information was required, controls recruited the dorsolateral prefrontal cortex (BA 45 and 46) to a greater degree than schizophrenia patients (Cannon et al., 2005). Additionally, schizophrenia patients showed greater impairment in accuracy when manipulation of information held in working memory was required (Cannon et al., 2005). However, greater impairment when manipulation is required compared to maintenance is not a uniform finding in schizophrenia (Schlosser et al., 2008; Hill et al., 2010; Quee et al., 2011; Thakkar and Park, 2012). Thakkar and Park (2012) suggest that these divergent finding may be due to the differing demands on encoding and maintenance processes that are also present in the manipulation task.

To the best of our knowledge, maintenance and manipulation aspects of working memory have not been investigated using the Cannon spatial working memory tasks (Kim et al., 2004; Cannon et al., 2005) with a family study design. A better understanding of how genetic liability for schizophrenia affects different aspects of working memory could be an important advancement in mapping cognitive phenotypes onto genes predisposing the disorder. First, we examined whether prefrontal gray matter was reduced in schizophrenia patients and first-degree biological nonpsychotic relatives compared to controls. Second, we examined whether greater spatial manipulation than maintenance impairments would be replicated in an independent sample of schizophrenia patients and whether that pattern would also be found in relatives. Third, we investigated the relationship of spatial maintenance and manipulation working memory processes with prefrontal gray matter volume in schizophrenia patients, relatives, and healthy controls to determine whether behavior and brain abnormalities were related. We hypothesized that schizophrenia patients and relatives would have less prefrontal volume compared to controls. We also predicted that schizophrenia patients and relatives would demonstrate impaired performance during the spatial working memory task, with greater impairment in the manipulation compared to maintenance condition. Last, we predicted that in schizophrenia patients, less gray matter in prefrontal areas would be related to worse spatial working memory task performance.

2. Materials and methods

2.1. Participants

Schizophrenia and schizoaffective probands were recruited from the Minneapolis VA Medical Center outpatient clinics and community support programs for the mentally ill. Research staff identified first-degree biological relatives by completing a pedigree with the proband. Controls were recruited through posting announcements in the community.

Twenty-four schizophrenia and schizoaffective patients (hereafter schizophrenia), 21 nonpsychotic relatives of schizophrenia patients, and 37 community control subjects participated in the structural MRI protocol and 30 schizophrenia patients, 25 nonpsychotic relatives, and 30 controls participated in the working memory task protocol. Seventeen schizophrenia patients, 15 relatives, and 18 controls participated in both the structural MRI and working memory task protocols. Schizophrenia patients and controls were excluded if English was their second language, for mental retardation, current alcohol abuse, current drug abuse/dependence, a current or past central nervous system condition, history of head injury with skull fracture or substantial loss of consciousness, a history of electroconvulsive therapy, and an age less than 18 or greater than 60. Controls were further excluded for a family history of psychosis or bipolar disorder. To maximize relative recruitment, relatives were excluded only if they were under the age of 18 and over the age of 60, had a lifetime diagnosis of a psychotic disorder, or unable to complete the protocol. However, no relative met criteria for an Axis II Cluster A disorder or current substance abuse/dependence, had IQ in the mental retardation range, or English as a second language. Three relatives had a history of a head injury and one relative had migraines. One control was on antipsychotic medications for his/her diagnoses of major depressive disorder (MDD), post-traumatic stress disorder (PTSD), and borderline personality disorder. The Minneapolis VA Medical Center and University of Minnesota Institution Review Boards approved the protocol.

2.2. Diagnosis and assessment

The Structured Clinical Interview for DSM Disorders and the Psychosis Module of the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994) were completed with each participant. Axis II Cluster A traits were assessed with the Structured Interview for Schizotypy in relatives and controls (Kendler et al., 1989). A clinical psychologist reviewed all materials to determine DSM-IV-TR diagnoses. Schizophrenia patients' current symptomatology was assessed using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1981) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1983). All participants had their psychiatric functioning assessed using the Brief Psychiatric Rating Scale (BPRS; Ventura et al., 1993). Handedness was determined by asking participants which hand they preferred overall.

Nonpsychotic relatives and controls were largely asymptomatic in terms of their *current* Axis 1 diagnoses, as also reflected in their BPRS scores: 3 relatives had current Axis I diagnoses (1 individual with anxiety not otherwise specified (NOS), 1 individual with PTSD and MDD, and 1 individual with specific phobia) and 6 controls had current Axis I diagnoses (1 individual with depression NOS, 1 individual with PTSD, 1 individual with PTSD and dysthymia, and 3 individuals with specific phobia). The breakdown for a *lifetime* Axis I disorder diagnosis in the relatives was: 5 individuals with MDD; 2 individuals with PTSD; 1 individual with a specific phobia; 3 individuals with anxiety NOS; 8 individuals with alcohol abuse; 1 individual with substance (other than alcohol) dependence; 2 individuals with substance (other than alcohol) abuse; and 1 individual with an eating disorder NOS. The breakdown for