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Temporal lobe thickness and verbal memory in first-degree relatives of individuals with schizophrenia

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ABSTRACT

Cortical thinning in frontal and temporal regions has been reported in individuals diagnosed with schizophrenia and, less consistently, among their unaffected first-degree relatives. Likewise, first-degree relatives demonstrate attenuated differences in neurocognitive performance relative to healthy controls, indicating that neurocognitive performance may be an important endophenotype of the disorder. Less is known about how cortical thickness relates to neurocognitive performance in these individuals. Given the robust nature of temporal structural abnormalities in schizophrenia, this study aimed to identify how temporal lobe cortical thickness might relate to verbal memory in first-degree relatives. Unaffected parents and siblings of individuals with adult-onset schizophrenia ($N = 62$) and individuals in healthy control families ($N = 70$) participating in the UCLA Family Study received a structural MRI and completed a battery of neurocognitive tests. Cortical thickness was estimated across the cortex and thickness measures of all regions in the temporal lobe were summed, averaged, and residualized for age and sex to produce a variable. A verbal learning factor was derived from two common tests of verbal learning and memory, the CVLT-II and Logical Memory of the WMS-III. Results demonstrated a significant interaction between group and verbal learning in relationship to temporal lobe thickness. Post-hoc analyses revealed significant correlations between verbal learning and cortical thickness in the relatives of schizophrenia patients which were driven by immediate recall scores on the CVLT-II and Logical Memory. These findings indicate that cortical thickness in the temporal cortex may represent a structural correlate for encoding verbal information in unaffected relatives of individuals with schizophrenia.

1. Introduction

Schizophrenia is a neurodevelopmental disorder characterized by structural abnormalities in the brain including cortical thinning (Kuperberg et al., 2003; Narr et al., 2005; Schultz et al., 2010; White et al., 2003). Cortical thinning has also been reported in first-degree biological family members of individuals with schizophrenia that are not affected by the disorder (Byun et al., 2012; Goghari et al., 2007; Hedman et al., 2016; Sprooten et al., 2013; Yang et al., 2010). Notably, across patients and their first-degree relatives, structural differences in focal temporal lobe regions are among the most consistently reported. Although verbal memory and cortical thinning have been found to have a significant relationship among individuals with schizophrenia (Ehrlich et al., 2012; Guimond et al., 2016; Hartberg et al., 2010), little has been done to establish this relationship in unaffected first-degree relatives. Doing so will further support the view that verbal memory deficits are important endophenotypes of the disorder with identifiable neuroarchitectural correlates.

1.1. Cortical thickness

Cortical thinning appears to occur in individuals with schizophrenia across a broad range of focal regions, including frontotemporal (Kuperberg et al., 2003), frontopolar, cingulate, and occipital regions (Narr et al., 2005). Thinning in the temporal cortex is among the most consistently reported effect, and a more detailed analysis has pointed to the superior temporal gyrus as a region in which both volume loss and cortical thinning have been found in schizophrenia patients (Ohi et al., 2016).

In first-degree relatives unaffected by the disorder, individuals who are known to carry an increased genetic load for schizophrenia; cortical

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thinning is reported in fewer focal brain regions, and when it is reported, typically it occurs to a lesser degree than it does in individuals with the disorder. We found small but statistically significant reductions in cortical thickness among unaffected siblings relative to age-similar community controls within the left parahippocampal gyrus and inferior occipital cortex (Yang et al., 2010). More prominent reductions have been reported in the middle temporal gyrus (Sprooten et al., 2013), right anterior cingulate, left paracingulate and posterior cingulate regions, bilateral frontal regions, ventromedial prefrontal cortex, bilateral temporal regions, and bilateral inferior parietal and occipital regions (Byun et al., 2012), and in the cingulate gyrus (Goghari et al., 2007). In a longitudinal twin study, more pronounced cortical thinning over time, particularly for the left superior temporal cortex, was observed in both monozygotic and dizygotic twin pairs discordant for schizophrenia as compared with healthy control twin pairs (Hedman et al., 2016). Others have found either no differences compared to controls (Goldman et al., 2009) or regional increases in cortical thickness in comparison to both schizophrenia patients and controls (Goghari et al., 2007; Goghari et al., 2015).

1.2. Memory impairment

In a meta-analysis of studies examining memory impairment in schizophrenia, Aleman et al. (1999) found that the impairment was stable, wide ranging, and not substantially affected by potential moderating factors such as severity of psychopathology and duration of illness. A selective impairment in declarative memory has also been identified in first-degree relatives. A meta-analysis of 21 studies with several hundred first-degree relatives and healthy controls demonstrated that the unaffected relatives performed more poorly on all memory tests examined, and found that effect sizes ranged from small to moderate with the largest effect sizes for the following: Trial 1 list recall = 0.65, Immediate story recall = 0.53, and Delayed story recall = 0.52 (Whyte et al., 2005).

1.3. Correlations between cortical thinning and neurocognitive performance

Despite the large body of research examining both cortical thickness and neurocognitive performance in schizophrenia, less research has been dedicated to examining the relationship between the two, and none to date has analyzed this relationship in first-degree relatives. Furthermore, methods for examining this relationship vary widely and only one study has focused on memory impairment and its relation to cortical thickness. In patients diagnosed with schizophrenia and divided by group in terms of the severity of verbal memory impairment, the group with more "moderate to severe" impairment demonstrated significantly thinner cortex in the left frontal lobe and the parahippocampal gyri (Guimond et al., 2016). Similarly, Hartberg et al. (2010) found that in individuals with schizophrenia and in healthy controls, there existed a statistically significant relationship between aspects of the Rey Auditory Verbal Learning Tests (RAVLT) and cortical thickness in bilateral temporal regions. Other studies with a broad focus have not found a relation between temporal thickness and measures of verbal memory (Ehrlich et al., 2012; Hartberg et al., 2010).

1.4. Aims and hypotheses

We set out to build on our previous findings that demonstrated statistically significant reduced parahippocampal thickness in first-degree relatives of individuals with schizophrenia, as well as on other research suggesting cortical thinning in temporal regions represents a structural marker of schizophrenia genetic liability in this population. Due to the large body of work suggesting significant memory impairment in schizophrenia patients and their first-degree relatives, we aimed to examine the relation between memory impairment and cortical thickness localized to the temporal cortex, expecting to see that Verbal Learning, a factor score derived from performance on verbal memory tests and residualized for age and sex, would be positively correlated with temporal cortical thickness in the first-degree relatives of schizophrenia patients and the members of the community control families. We also planned to follow up the overall factor score finding with an examination of the relationship of temporal cortical thickness to discrete measures of the CVLT-II and WMS-III Logical Memory.

2. Experimental materials/methods

2.1. Participants

This study is part of the UCLA Family Study, a large, multidisciplinary study of schizophrenia (Asarnow et al., 2002; Nuechterlein et al., 2002). This component of the project involved adult-onset schizophrenia patients (probands) and their unaffected, biological first-degree relatives (siblings and parents). Only the first-degree relatives ($n = 62$) of schizophrenia patients and healthy community controls ($n = 70$) were included in the present analysis.

Individuals with schizophrenia and their relatives were recruited from the UCLA Aftercare Research Program (Fogelson et al., 2010; Nuechterlein et al., 2002). Community control families were recruited from a list provided by a survey research company and telephone contact. All participants provided informed consent in accordance with the rules and regulations of the UCLA Institutional Review Board (IRB). To determine eligibility for the UCLA Family Study, schizophrenia patients received a Structured Clinical Interview for DSM-IV–Patient Version (SICD-I/P) (First et al., 2001). Community control subjects and all family members received the Structured Clinical Interview for DSM-IV–Non Patient Version (SCID-I/NP) (First et al., 2002). A DSM-IV schizophrenia diagnoses was determined by information gathered by a clinical psychologist from the patient during a direct interview, collateral information provided by caregivers, parents, and/or clinicians involved in their care, and/or review of medical records. A diagnosis was confirmed by blind review by senior clinicians that resulted in consensus diagnoses as described in prior publications (Asarnow et al., 2001; Fogelson et al., 1991; Ventura et al., 1998).

Exclusion criteria for probands included neurological disorders, intellectual disability, and a history of drug dependence or alcoholism in the six months prior to the assessment. Additionally, for schizophrenia patients, their psychotic episode should not have been immediately preceded by a period of drug use that may have triggered the psychosis.

2.2. MRI acquisition and processing

High-resolution T1-weighted structural magnetic resonance imaging (MRI) scans were collected on a Siemens 1.5 Tesla Sonata system using a 3D MPRAGE sequence with four averages (TR = 1900 ms; TE = 4.28 ms; TI = 1100; flip angle: 15°; field of view = 256 × 256; voxel size = $1 \times 1 \times 1$ mm^3, acquisition time: 32 min). Cortical thickness, measured as the shortest distance between the cortical white/gray matter boundary to the pial surface, was estimated for each subject within particular gyral regions using the Freesurfer Desikan-Killiany Atlas (https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation). To estimate temporal lobe cortical thickness specifically, cortical thickness was averaged over entorhinal, fusiform, inferior temporal, middle temporal, parahippocampal, superior temporal, temporal pole, and transverse temporal regions.

2.3. Tasks

Each family member received a comprehensive battery of neuropsychological tests by either a clinical psychologist or trained and supervised psychometrist blind to the diagnosis of the proband. The tests included two verbal memory measures: the California Verbal Learning

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