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Title

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Journal

Schizophrenia Research, 199

ISSN

0920-9964

Authors

Fernandez, Vindia G
Asarnow, Robert
Narr, Katherine L
[et al.](#)

Publication Date

2018-09-01

DOI

10.1016/j.schres.2018.02.038

Peer reviewed



Published in final edited form as:

Schizophr Res. 2018 September ; 199: 221–225. doi:10.1016/j.schres.2018.02.038.

Temporal Lobe Thickness and Verbal Memory in First-degree Relatives of Individuals with Schizophrenia

Vindia G. Fernandez, Ph.D.^{a,b}, Robert Asarnow, Ph.D.^a, Katherine L. Narr, Ph.D.^{a,c}, Kenneth L. Subotnik, Ph.D.^a, Heidi Kuppinger, Ph.D.^a, David Fogelson, M.D.^a, and Keith H. Nuechterlein, Ph.D.^{a,b}

^aDepartment of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, Geffen School of Medicine at UCLA, Los Angeles, CA

^bDepartment of Psychology, UCLA, Los Angeles, CA

^cAhmanson-Lovelace Brain Mapping Center, Department of Neurology, UCLA, Los Angeles, CA

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

Corresponding author: Vindia G. Fernandez, UCLA Semel Institute for Neuroscience & Human Behavior, 760 Westwood Plaza, #47-429A, Los Angeles, CA 90095-1795, (310)206-6001 (office), (310)206-8525(fax), vfernandez@mednet.ucla.edu.

Contributors

Keith Nuechterlein, Robert Asarnow, and Katherine Narr designed the research and participated as co-principal investigators on the two key studies from which this data was collected. They assisted with data analysis and editing of the present manuscript. Kenneth Subotnik, David Fogelson, and Heidi Kuppinger each contributed to the design of the Family Study and writing the protocols for data collection. Vindia Fernandez undertook the statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of Interest

None of the authors have any actual or potential financial, personal, or other conflicts of interest to disclose. Dr. Nuechterlein has research support for other projects from Janssen Scientific Affairs, Posit Science, and Stanley Medical Research Institute and has been a consultant to Astellas, Genentech, Janssen, Otsuka, Takeda, and Teva.

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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.

Keywords

schizophrenia; MRI; cortical thickness; verbal memory; temporal lobe

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, Andreasen, Nopoulos, & Magnotta, 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, Rehm, Carter, & MacDonald, 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, Chakravarty, Bergeron-Gagnon, Patel, & Lepage, 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 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, Truong, & Spilka, 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, McIntosh, Johnstone, & Lawrie, 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.

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 (SCID-I/P) (M. First, Spitzer, Gibbon, & Williams, 2001). Community control subjects and all family members received the Structured Clinical Interview for DSM-IV – Non Patient Version (SCID-I/NP) (First, Spitzer, Gibbon & Williams, 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, Nuechterlein, Asarnow, Subotnik, & Talovic, 1991; Ventura, Liberman, Green, Shaner, & Mintz, 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 = 1×1×1 mm³, acquisition time: 32 minutes). 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 Test, Second Edition (CVLT-II) and a subtest of Wechsler Memory Scale III, Logical Memory.

2.4 Statistics

The UCLA Family Study utilized a comprehensive battery of neurocognitive tests on which both schizophrenia patients and their unaffected first-degree relatives have demonstrated deficits. A set of composite scores was created for use in data analyses with variables from clinical, genetic, and neuroimaging domains. To account for the wide age range, regression models were developed with the community control samples to allow normal age effects and sex effects to be removed. A combination of factor analytic and clustering techniques was applied to the resulting standardized scores to identify subgroups of measures with shared variance. The final composites were derived by averaging the resultant sets of scores using unit weights, resulting in five composite scores that measure attention, working memory, verbal learning, verbal retention, and memory for faces. This procedure is described in detail elsewhere (Sugar, In preparation). The Verbal Learning factor included loadings from the CVLT-II Total Recall on Trials 1–5, CVLT-II Recognition, and Logical Memory Immediate Memory scores, each of which had been residualized for age and sex. The factor scores were also residualized for age and sex and the final score was expressed in terms of standard deviation units based on the community control sample.

Mean cortical thickness for the temporal cortex was computed based on the average of all temporal lobe ROIs from the Freesurfer Desikan atlas as described above. Cortical thickness data was analyzed for outliers. Two individuals, one in each group, were removed due to unusually low cortical thickness relative to others in the sample ($<2.6\text{mm}$, greater than 2 standard deviations from the mean).

Using the GLM approach within IBM SPSS Statistics software, univariate ANOVAs were conducted to explore the effect of group and verbal memory on temporal lobe thickness and on frontal lobe thickness. A bivariate Pearson's correlation between the verbal learning factor and temporal lobe thickness was computed for each group in post-hoc analyses. Additional correlational analyses were conducted using key subtests of the verbal memory measures and regions of the temporal lobe.

Results

3.1. Demographic characteristics

The demographic characteristics of the relatives of schizophrenia patients and relatives of healthy controls are shown in Table 1. Age, sex, handedness, and IQ did not significantly differ between the two groups.

3.2 ANOVA

A statistically significant interaction of group and verbal memory on temporal lobe cortical thickness was established, $F(1, 132) = 6.44$, $p = .01$. The main effect of verbal learning, but not group, on temporal lobe thickness was also statistically significant, $F(1, 132) = 5.57$, $p = .02$. Neither the interaction between group and verbal memory on frontal lobe cortical thickness, $F(1, 132) = 1.67$, $p = .20$, nor the main effect of group, $F(1, 132) = .94$, $p = .34$, or verbal memory, $F(1, 132) = 1.27$, $p = .26$, on frontal lobe cortical thickness was statistically significant.

3.3 Post-hoc analyses

Post-hoc analyses revealed statistically significant Pearson correlations between temporal lobe thickness and the verbal learning factor, $r = .41$, $p = .001$ only in the relatives of schizophrenia probands. Further follow-up analyses with relatives of the schizophrenia group was conducted using each of the three verbal learning scores used to calculate the verbal learning factor, revealing that the temporal lobe was significantly correlated with CVLT-II Total Recall on Trials 1–5, $r = .37$, $p = .003$ and with Logical Memory Immediate Recall, $r = .38$, $p = .004$.

We also examined correlations separately between the verbal memory factor and the various regions that comprise the temporal lobe, including the left and right entorhinal, fusiform, inferior temporal, middle temporal, parahippocampal, superior temporal, temporal pole, and transverse temporal regions. Significant correlations were found only within the relatives of schizophrenia patients, in the left inferior temporal, left parahippocampal, left superior temporal, left temporal pole, right entorhinal, and right inferior temporal. While all of these correlations were in the same directions, only the left temporal pole correlation with verbal learning survives correction for multiple comparisons using the Hochberg and Benjamini (1990) model ($r = .47$, $p = .001$).

Discussion

Despite numerous studies documenting deficits in cognitive functioning and structural abnormalities in the cortex of individuals with schizophrenia (Ehrlich et al., 2012; Guimond, et al., 2016; Hartberg et al., 2010), less research attempts to clarify the impact of cortical architecture on cognitive performance in unaffected first-degree relatives of individuals with schizophrenia. This study set out to investigate the nature of temporal lobe thickness, commonly associated with episodic memory functioning, on verbal learning in relatives, in order to better understand the degree to which the structural integrity of the cortex contributes to cognitive impairments outside of the disease process. Our primary hypothesis

that cortical thickness in the temporal lobes would be related to verbal learning was supported. Additionally, a statistically significant correlation between temporal lobe thickness and our verbal memory factor score was observed in the first-degree relatives of the schizophrenia probands. These results are consistent with fMRI research demonstrating hypoactivation of temporal regions in unaffected relatives during memory encoding tasks (Pirnia et al., 2015). Unaffected individuals at high-risk of developing psychosis (who later converted to psychosis) have also demonstrated reduced connectivity between MTL regions and auditory-verbal and visual-association regions (Haut et al., 2015).

Conversely, the correlations between temporal lobe cortical thickness and scores on the verbal memory factor were not statistically significant in the first degree relatives of healthy controls. The discrepancy was somewhat unexpected, insofar as temporal lobe structures are known to support episodic memory functioning. Perhaps among the relatives of controls differences in verbal memory are due to variable strategies for encoding and retrieval that involve other functional circuits rather than temporal lobe thickness. For instance, activation in the prefrontal cortex has been identified in functional neuroimaging tasks of episodic memory in both schizophrenia patients (Heckers et al., 1999; Ragland et al., 2009) and healthy controls (Ragland et al., 2015), as well as in studies using PET (Fletcher et al., 1998). In relatives of schizophrenia patients, the relationship may be clearer because a minimal level of temporal lobe tissue (or intact neural organization) is required to support mnemonic strategies beyond simple rehearsal, making cortical thickness a more relevant factor in memory performance. In fact, deficits in mnemonic strategy have been documented among individuals with schizophrenia (Roofeh et al., 2006), a phenomenon attributed to frontal/executive dysfunction. Greater dependence on simple rehearsal may make temporal lobe cortical thickness a stronger determinant of learning performance.

This study was limited by lack of access to information about learning strategy on the CVLT-II, something that future research may be able to clarify. It is interesting to note that the individual test scores with the strongest correlations with temporal lobe cortical thickness in the relatives of schizophrenia patients tended to reflect initial encoding and immediate memory rather than recall after a long delay. Functional activation maps of the cortex during learning and memory tasks could be helpful in identifying whether there is a difference in the network of brain regions being utilized to perform verbal memory tasks between the relatives of controls and the relatives of schizophrenia patients. Perhaps the relatives of controls are better able to recruit additional neural resources to facilitate retrieval (e.g., the dorsolateral prefrontal cortex for immediate working memory demands). To date, these questions have not been examined in the first-degree relatives or individuals with schizophrenia. Future research should replicate these results and also examine relationships between memory performance and cortical thickness in frontal regions known to contribute to memory function, including the dorsolateral prefrontal cortex which is often implicated in working memory.

Acknowledgments

Role of Funding Source

This research was supported by the following grants: T32 MH096682, R01 MH49716, R37 MH45112, R01 MH37705, and P50 MH066286. Aside from funding the initial research proposal, these entities did not play a significant role in the collection of data, analysis of results, conclusions of the study, or writing of the manuscript.

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Demographic variables; relatives of community control participants and unaffected first-degree relatives of schizophrenia probands

Table 1

	Control Relatives N=70	Relatives of Schizophrenia Probands N=62	Analysis		
			t/ χ	df	p-value
Age	44.37 $\pm$ 15.43	48.31 $\pm$ 14.83	-1.49	130	0.14
Sex	F=40	F=37	0.09	1	0.77
Handedness [*]	6.6	6.4	0.58	130	0.57
WASI IQ ^{**}	112.66 $\pm$ 12.23	108.51 $\pm$ 15.6	1.67	125	0.10

^{*} Number of items utilized with right hand on a 7-item handedness test

^{**} Based on 2 subtests (Vocabulary and Matrix Reasoning)

Data given as mean $\pm$ standard deviation.

Table 2

Pearson correlations between cortical thickness in the temporal lobe, verbal memory factor, and key verbal learning subtests

Group	Verbal learning factor	CVLT-II		Logical Memory
		Total 1–5	Short Delay Recall	Immediate Recall
Control Relatives	–0.02	0.09	0.06	–0.06
Relatives of Schizophrenia Probands	.41 **	0.37 **	0.22	.38 **

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Outliers have been removed (L and R temporal lobe thickness < 2.6), n=1 in each group respectively