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Longitudinal progression of frontal and temporal lobe changes in schizophrenia

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Abstract

Cortical abnormalities are considered a neurobiological characteristic of schizophrenia. However, the pattern of such deficits as they progress over the illness remains poorly understood. The goal of this project was to assess the progression of cortical thinning in frontal and temporal cortical regions in schizophrenia, and determine whether relationships exist between them and neuropsychological and clinical symptom profiles. As part of a larger longitudinal 2-year follow-up study, schizophrenia (n=20) and healthy participants (n=20) group-matched for age, gender, and recent-alcohol use, were selected. Using MRI, estimates of gray matter thickness were derived from primary anatomical gyri of the frontal and temporal lobes using surface-based algorithms. These values were entered into repeated-measures analysis of variance models to determine group status and time effects. Change values in cortical regions were correlated with changes in neuropsychological functioning and clinical symptomatology. Results revealed exaggerated cortical thinning of the middle frontal, superior temporal, and middle temporal gyri in schizophrenia participants. These thickness changes strongly influenced volumetric reductions, but were not related to shrinking surface area. Neuropsychological and clinical symptom profiles were stable in the schizophrenia participants despite these neuroanatomic changes. Overall it appears ongoing abnormalities in the cerebral cortex continue after initial onset of schizophrenia, particularly the lateral aspects of frontal and temporal regions, and do not relate to neuropsychological or clinical measures over time. Maintenance of neuropsychological performance and clinical stability in the face of changing neuroanatomical structure suggests the involvement of alternative compensatory mechanisms.

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Keywords

schizophrenia; longitudinal; neuroimaging; frontal lobes; temporal lobes; neuropsychology; clinical symptoms

INTRODUCTION

1.1

Schizophrenia is currently conceptualized as a neurobiological disorder that develops in concert with disturbances in the formation of neural structures (Keshavan et al., 2008). While the specific neuroanatomical framework of the illness has been investigated for many years (Kraepelin, 1919), its precise pattern and evolution over time remains elusive. Current research in this area has focused on determining the timing and trajectory of changes in specific neuroanatomical structures as schizophrenia patients enter their first psychotic episode and then between subsequent psychotic relapses. Longitudinal changes in total brain volume and corresponding ventricular enlargement are the most consistent findings (DeLisi et al., 2004; Kempton et al., 2010; van Haren et al., 2008), and in a meta-analytic review, Olabi and colleagues (2011) determined that progressive reductions in frontal lobe gray matter volume, followed by frontal, parietal, and temporal lobe white matter volume were the most common across studies. In contrast, the localization of changes within specific lobular subregions is less reliable (DeLisi, 2008), with some, but not all, studies reporting gradual loss in frontal and temporal areas, particularly the superior temporal gyrus and medial frontal regions (Hulshoff Pol & Kahn, 2008; Kasai et al., 2003). Such disparities may occur because of differences across the investigation of illness phase (DeLisi, 2008); thus the question of “where” changes occur may depend on “when” in the course of illness the participants are studied.

Attempts have also been made to correlate cortical gray matter loss in schizophrenia with changes in cognition given the presence of neuropsychological deficits and their known associations between various brain regions (Antonova et al., 2004). While the presence of premorbid cognitive deficits (Bilder et al., 2006), and occurrence of further decline after initial onset have been reported (Seidman et al., 2006), current evidence also strongly indicates that cognitive impairment appears to be stable after the first episode of illness (Heaton et al., 2001; Hill et al., 2004). Consequently, the presence of stable cognitive deficits in the face of progressive changes in brain structure during the chronic phase of schizophrenia is puzzling, and deserves confirmation and further investigation.

1.2

For the current study, we used semi-automated surface-based methods to examine whether changes in specific subregions of the frontal and temporal lobe would occur over a 2-year period in schizophrenia patients (SCZ) and healthy controls (CON), and whether such changes would be correlated with changes in neuropsychological performance and psychopathology. Based on the assertion that reductions in cortical thickness would be the primary manner in which gray matter loss would be observed (van Haren et al., 2011), we hypothesized that SCZ, but not CON, participants would show significant cortical thickness reductions over time in frontal and temporal lobes, particularly the middle frontal and superior temporal gyri. This hypothesis is based on consistent evidence for abnormalities in these subregions in schizophrenia and their involvement in cognitive functions (Harms et al., 2010; Qiu et al., 2007; Takahashi et al., 2009; van Haren et al., 2007). Second, in an exploratory fashion, we assessed the relationship between longitudinal changes in cortical thickness and the severity of neuropsychological deficits and psychopathology, again

because of prior findings in the literature suggesting that changes in the cortex are related to such impairments in schizophrenia (Andreasen et al., 2011; Ho et al., 2003).

METHODS

2.1 Participants

Participants were selected from larger groups recruited as part of an ongoing study of schizophrenia. Beginning with groups of participants that returned for at least one follow-up assessment, (SCZ = 38, CON = 27), we selected subsets of participants group-matched for age, gender, and recent alcohol use based on findings that alcohol use may exacerbate gray matter loss in schizophrenia (Smith et al., 2011), and excluded age outliers that were younger than 17 and older than 65. Participants were excluded if they met DSM-IV criteria for mental retardation, substance abuse (moderate or severe) or dependence (any type) at present time or during the past 6 months. Informed consent was obtained from each subject after a complete description of the study was given.

2.2 Clinical Measures

All participants were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1996), to determine the presence of a current diagnosis of schizophrenia and a lifetime history of substance abuse or dependence. Recent alcohol use was measured as the quantity of alcohol consumed over two years prior to baseline using a semi-structured interview (Skinner, 1982; Sullivan et al., 1995). We also examined cigarette consumption as a potential confound given that nicotine use has been related to reduced gray matter density (McClernon, 2009) and the vast majority of schizophrenia patients have nicotine dependence (Van Dongen, 1999). See Table 1 for detailed demographic data.

Psychopathology and neuropsychological functioning were assessed as previously described (Smith et al., 2009). A battery of neuropsychological measures that correspond with tasks relevant to cognition in schizophrenia was administered (Nuechterlein et al., 2004). These scores were then averaged to form composite domain scores in four areas of cognitive functioning – crystallized IQ (IQ), working memory (WM), episodic memory (EM), and executive functioning (EF). Psychopathology was assessed using the Scale for the Assessment of Negative Symptoms (Andreasen, 1983), and the Scale for the Assessment of Positive Symptoms (Andreasen, 1984), for which three symptom clusters were quantified – positive, negative, and disorganized. Raw and scaled scores for all measures were transformed to z-scores using data from a previously published and overlapping reference group (Smith et al., 2009). All schizophrenia participants were assessed during treatment and after they had attained clinical stability for several weeks.

2.3 MRI Acquisition Parameters and Data Processing

MR scans were acquired at both baseline and 2-year follow-up visits using a 1.5T Vision scanner (Siemens Medical Systems) with actively shielded gradients and echo-planar capability. All scans were collected using an MPRAGE sequence (TR = 10ms, TE = 4ms, Flip angle = 30°, ACQ = 1, Matrix = 256 × 256, Scanning time = 5.6 minutes) that acquired 3D datasets with 1 mm x 1 mm x 1.25mm resolution.

MPRAGE images were analyzed and processed using the longitudinal pipeline from FreeSurfer (FS) release 4.5.0 (Dale et al., 1999), which is documented and freely available for download online (<http://surfer.nmr.mgh.harvard.edu>). Any geometric inaccuracies or topological defects were corrected using a combination of automatic and manual methods (Segonne et al., 2007). Manual editing was carefully conducted according to established guidelines. Reconstruction of the white and pial surfaces was required for estimation of

cortical measures. Algorithms in the FS longitudinal processing pipeline reduce intra-subject morphological variability that can occur in image registration, intensity normalization, and iterative processes that approximate the cortical surface (Reuter et al., 2010).

Considering prior work to localize neuroanatomical changes in schizophrenia (see above), 12 a priori regions of interest (ROIs), 6 per hemisphere, in the frontal and temporal lobes were selected for study (see Supplemental Figure). Definitions of these ROIs were based on modifications to the standard FS parcellation atlas (Desikan et al., 2006), by combining previously defined subregions into main gyri found in the frontal and temporal lobes. These regions are as follows:

- Superior Frontal Gyrus (SFG) – superior frontal
- Middle Frontal Gyrus (MFG) – caudal middle frontal, rostral middle frontal
- Inferior Frontal Gyrus (IFG) – pars opercularis, pars triangularis, pars orbitalis
- Superior Temporal Gyrus (STG) – transverse temporal region, superior temporal, banks of the superior temporal sulcus
- Middle Temporal Gyrus (MTG) – middle temporal
- Inferior Temporal Gyrus (ITG) – inferior temporal

Estimates of cortical gray matter thickness (mm), volume (mm³), and surface area (mm²) were calculated for each of these regions using embedded FS algorithms.

2.4 Statistical Analyses

Cortical thickness values were entered into repeated-measures analysis of variance (RM-ANOVA) models, testing the main effects of group (between subject factor), hemisphere, and time (within subject factors), and then group-by-time interactions. To examine change in cognition and psychopathology over time, scores from the composite domains at baseline and follow-up were entered into RM-ANOVA models, with group status as the main effect (cognition and psychopathology models), and time as a repeated factor (psychopathology model only). To control for multiple comparisons, the False Discovery Rate (FDR) procedure outlined by Benjamini and colleagues (2001), which accounts for the expected proportion of rejected hypotheses that are falsely rejected, was utilized. Secondary RM-ANOVA analyses on cortical volume and surface area were also conducted.

Scores representing a measure of change over time (i.e., slopes) were calculated for all variables as: *follow-up – baseline = change score*. Pearson correlations between change scores in cortical thickness with volume and surface area were conducted within each significant ROI to determine the relative influence on each measure. Pearson models were also used to correlate cognitive change scores with key cortical regions known to support their functions, these were designed as: frontal gyri with WM, EF, IQ; and temporal gyri with EM, IQ. Further investigation involved additional correlation models on baseline measurements for these variables. The influence of interval medication use, duration of illness (DOI), and nicotine use on cortical progression was assessed through Pearson correlations between these variables and rates of cortical thickness change in the identified ROIs. Corrections for multiple comparisons were not utilized due to their exploratory nature.

RESULTS

3.1 Longitudinal Cortical Thickness Changes in Frontal and Temporal Lobe Structures

Mean and standard deviation values with percent change for each structure are presented in Table 2. Findings from RM-ANOVA models of cortical thickness in the frontal lobes revealed significant effects for time in the SFG, MFG, and IFG (Table 3). Group-by-time interactions that survived FDR correction were observed only in the MFG. The effect of hemisphere was significant for the SFG ($L > R$: $F_{1,38} = 56.42$, $p < 0.001$), and IFG ($R > L$: $F_{1,38} = 12.9$, $p = 0.001$) only. In the temporal lobes, RM-ANOVA models revealed a significant main effect for time in the STG, and group-by-time interaction effects in the STG and MTG that survived FDR correction (Table 3). There was a significant main effect for hemisphere only in the ITG ($L > R$: $F_{1,38} = 12.07$, $p = 0.001$). Scatterplots of baseline and follow-up values are shown in Figure 1. Secondary analyses of cortical volume and surface area for frontal and temporal regions revealed only trend group-by-time interactions for SFG, MFG, STG, and MTG volume (see Supplemental Table).

Pearson models between change scores in cortical thickness with volume and surface area were conducted within the MFG, STG, and MTG for SCZ subjects (Table 4). Cortical thickness correlations were highly significant with change in volume (all $p < 0.001$) compared to those with surface area. Pearson models between DOI, interval antipsychotic medication use (both first and second generation chlorpromazine equivalents), and nicotine use with cortical thickness change scores of all frontal and temporal ROIs revealed no significant correlations at $p < 0.05$.

3.3 Longitudinal Changes in Neuropsychological Performance and Clinical Symptoms

Significant main group effects were noted on every neuropsychological domain, including IQ, WM, EM, and EF (see Table 5). However, there were no main effects for time, or group-by-time interactions. Longitudinal analyses of clinical symptom domains in SCZ subjects revealed no main effects of time.

3.4 Correlations with Neuropsychological Performance and Clinical Symptoms at Baseline and Over Time

Pearson correlations between baseline measurements of ROI cortical thickness and cognitive variables in SCZ subjects revealed strong positive relationships between IQ and the left STG ($r = 0.612$, $p = 0.002$) and EF with both the left ($r = 0.570$, $p = 0.009$) and right ($r = 0.590$, $p = 0.006$) IFG indicating poorer cognitive performance as cortical thickness in these regions decreases. There were no significant correlations with measurements of EM and WM. With regard to clinical symptoms, strong negative correlations with disorganization and the right IFG ($r = -0.486$, $p = 0.030$), and left STG ($r = -0.457$, $p = 0.043$) were observed, indicating symptom increase as cortical thickness in these regions decrease. No significant relationships emerged for positive and negative symptomatology.

Correlations between cortical thickness ROI change scores and cognitive change scores yielded no significant findings. When examining relationships between cortical ROI and clinical symptom change scores, a trend correlation between decreased right hemisphere STG and an increase in disorganized symptoms ($r = -0.450$, $p = 0.047$) was observed.

DISCUSSION

4.1

In this study, we investigated the progression of frontal and temporal cortical gray matter thickness abnormalities in schizophrenia and attempted to relate these to changes in

cognitive performance and symptom expression. Our findings suggest that schizophrenia subjects have exaggerated cortical thinning in selected subregions of both frontal and temporal lobes that occurs over a period of 2 years. In particular, the most extensive loss in cortical thickness was detected in the MFG, STG, and MTG. Furthermore, it was determined that these changes in thickness form the basis of longitudinal cortical volume loss, while unrelated to changes in surface area. Interestingly, despite progressive loss in cortical structure, neuropsychological performance and psychopathology severity remained stable in our schizophrenia subjects over this same 2-year period.

Broadly, our results are in agreement with other studies that have reported gray matter deterioration in both the frontal and temporal cortex in schizophrenia (Andreasen et al., 2011; Ho et al., 2003; Olabi et al., 2011; van Haren et al., 2007). In particular, our STG findings are very similar to those in longitudinal studies using voxel-based image analysis methods in high risk populations (Job et al., 2005; Takahashi et al., 2009), as well as first-episode patients (Asami et al., 2012), suggesting this area is principally involved in the pathophysiology of the disease. Furthermore, a recent longitudinal study of cortical thickness by van Haren and colleagues (2011) discovered excessive thinning over time in STG and MTG regions. Interestingly, they also found changes in anterior portions of the MFG, which coincides with our results.

As volume is the product of thickness and surface area in a “carpet-like” structure, such as the cerebral cortex, changes in volume would be the result of changes in one or both of these two sources. Indeed, this was evident in our own findings with associations observed between these measurements and progressive volume loss. Particularly, our assertion that volume loss would be mainly attributable to thinning of the cortex held true as these measures were highly related across regions with significant change over time. Van Haren and colleagues (2011) work also supports our data as strong relationships between progressive cortical thinning and volume change were found in their schizophrenia cohort. Cortical abnormalities in schizophrenia are believed to be primarily due to neuropathological changes such as shrinkage of the neuropil and increased neuronal density without the gliosis observed in neurodegenerative conditions (Goldman-Rakic & Selemon, 1997; Selemon et al., 1995). It has been hypothesized that two different neurodevelopmental mechanisms could explain this phenomenon, one that involves excessive pruning that begins in adolescence and extends till illness onset, and one that begins after onset and characterized by diminished neuroplasticity (Andreasen et al., 2011). This latter process would be a likely candidate for the cortical thinning observed in our post-onset schizophrenia subjects.

Both frontal and temporal lobes have been implicated in a number of cognitive processes affected in schizophrenia (Antonova et al., 2004), including attention, language, working memory, and various aspects of executive functioning, as well as with the expression of different clinical symptoms (Perlstein et al., 2001; Shenton et al., 1992). Our findings reinforce the notion of stable impaired neuropsychological profiles in schizophrenia (Albus et al., 2002; Heaton et al., 2001), but also demonstrate that this phenomenon can exist despite the progression of cortical thinning observed in these same individuals. Moreover, our failure to find support for correlated changes in neuroanatomical structure and cognition should be considered in the context of relationships between these same sets of variables at baseline. The lack of a longitudinal association suggests a more complex relationship between the capacity for cognitive performance and the integrity of cortical structure over the course of illness in schizophrenia. Perhaps to fully understand structure-function relationships over time in schizophrenia, one must consider an integrated approach with the involvement of other types of structures, such as white matter pathways or subcortical regions.

Consideration should also be given to compensatory mechanisms that may develop to maintain cognition in the face of changes in neuroanatomical structures known to support these same functions. The functional imaging literature in schizophrenia has suggested that the recruitment and engagement of alternative neural circuits, particularly neighboring regions, can occur to aid performance in schizophrenia patients that is comparable to that of healthy subjects (Quintana et al., 2003; Tan et al., 2006). For example, Murray and colleagues (2010) found that associative learning in schizophrenia stimulated activation of the frontal pole, anterior cingulate, visual, and parietal cortex, all areas outside of prefrontal regions that are activated in healthy subjects. Thus, the recruitment of additional structures and circuits may also occur to sustain performance, while the structural integrity of primary regions declines.

4.2

There were several limitations to the study. First, our sample sizes were small, thus needing replication with larger numbers, especially in groups of subjects from specific stages of the illness, to determine whether our findings are specific to a particular illness phase. However, our ability to carefully group-match subjects based on age, gender, and recent alcohol use may have compensated for some of the loss in statistical power. Additionally, despite the relationships between neuroanatomical and cognitive measures at baseline, our failure to find relationships between these measures over time may be the result of the inadequacy of our method for detecting subtle changes in cognitive performance. Further localization of time-dependent cortical changes in other regions would also be of future interest.

In conclusion, our results suggest that progressive changes in the frontal and temporal cortex occur in individuals with schizophrenia after the onset of the acute phase of their illness. Moreover, the maintenance of cognitive performance and clinical stability in the face of this structural advancement suggests that compensatory mechanisms may be available to preserve neural function. Our findings also inform current theories that the pathogenesis of schizophrenia includes a progressive component, which may be influenced by genetic and environmental factors throughout the course of the disease (Harrison & Weinberger, 2005; Rapoport et al., 2005).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Scatterplots demonstrating cortical thickness changes for selected ROIs in both healthy control (CON) and schizophrenia (SCZ) subjects at baseline (TP1) and follow - up (TP2) time points.

Table 1

Demographic Characteristics of Study Sample

	SCZ (n = 20)		CON (n = 20)		Statistic	
	Mean	(SD)	Mean	(SD)	t-test	df
Age (years)	31.9	(11.1)	30.4	(12.8)	0.41	38
Parental SES	3.4	(1.1)	2.9	(0.7)	1.97	38
Alcohol use (grams per year)	2049	(3973)	3235	(5399)	-0.75	34
Nicotine use (cigarettes per year)	4357	(4088)	611	(1761)	3.77	26
Scan Interval (years)	2.0	(0.9)	2.1	(0.4)	-0.41	38
Duration of Illness (years)	12.4	(12.9)	--			
Chlorpromazine Equivalent (2 years prior to baseline)						
1 st -Generation (Dose Years)	1.13	(3.7)	--			
2 nd -Generation (Dose Years)	3.47	(3.4)	--			
Chlorpromazine Equivalent (between baseline and follow-up)						
1 st -Generation (Dose Years)	0.95	(2.9)	--			
2 nd -Generation (Dose Years)	6.64	(5.3)	--			
Gender, No. (% male)	10	(50.0%)	11	(55.0%)	0.10	1
Race (%)					6.93	2
Caucasian	8	(40%)	16	(80%)		
African-American	11	(55%)	4	(20%)		
Hispanic	1	(5%)	0	(0%)		
Handedness R/L (%)	18/2	(90/10%)	16/4	(80/20%)	0.78	1

* = $p < 0.05$

Table 2
Mean (SD) and Percent Change of Cortical Thickness (mm) for Frontal and Temporal Regions

Structure	SCZ (n = 20)				CON (n = 20)			
	Baseline		Follow-up		Baseline		Follow-up	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Superior Frontal Gyrus								
Left	2.82	(0.1)	2.75	(0.1)	2.85	(0.1)	2.80	(0.1)
Right	(2.76)	(0.1)	(2.68)	(0.1)	2.77	(0.1)	2.73	(0.1)
Middle Frontal Gyrus								
Left	2.52	(0.1)	2.45	(0.1)	2.48	(0.1)	2.46	(0.1)
Right	2.53	(0.1)	2.46	(0.1)	2.47	(0.1)	2.45	(0.1)
Inferior Frontal Gyrus								
Left	2.61	(0.1)	2.55	(0.1)	2.62	(0.1)	2.60	(0.1)
Right	2.65	(0.1)	2.59	(0.1)	2.66	(0.1)	2.63	(0.1)
Superior Temporal Gyrus								
Left	2.74	(0.1)	2.68	(0.1)	2.77	(0.1)	2.77	(0.1)
Right	2.74	(0.1)	2.68	(0.1)	2.76	(0.1)	2.76	(0.1)
Middle Temporal Gyrus								
Left	2.90	(0.1)	2.83	(0.2)	2.86	(0.1)	2.87	(0.2)
Right	2.91	(0.1)	2.84	(0.1)	2.89	(0.1)	2.90	(0.2)
Inferior Temporal Gyrus								
Left	2.83	(0.1)	2.78	(0.2)	2.85	(0.2)	2.84	(0.2)
Right	2.75	(0.2)	2.71	(0.2)	2.75	(0.2)	2.79	(0.2)

Table 3

RM-ANOVA Cortical Thickness Comparisons of SFG, MFG, IFG, STG, MTG, and ITG

Structure	Longitudinal Analyses				Group-by-Time Interaction	
	$F(1, 38)p$					
	Group Effect	Time Effect				
Superior Frontal Gyrus *	1.07	0.307	31.53	0.001	3.17	0.083
Middle Frontal Gyrus	0.61	0.441	16.60	0.001	7.28	0.010
Inferior Frontal Gyrus †	0.48	0.495	11.20	0.002	2.87	0.099
Superior Temporal Gyrus	2.28	0.140	6.32	0.016	7.90	0.008
Middle Temporal Gyrus	0.05	0.819	4.30	0.045	8.92	0.005
Inferior Temporal Gyrus *	0.92	0.342	1.33	0.256	3.98	0.053

Bold = Significant effects surviving FDR correction for multiple comparisons

* = Significant hemisphere main effect L > R

† = Significant hemisphere main effect R > L

Table 4

Correlations of Longitudinal Changes Scores in Cortical Thickness with Volume and Surface Area within Significant ROIs

Structure	SCZ	
	Volume (<i>r</i>, <i>p</i>)	Surface Area (<i>r</i>, <i>p</i>)
Middle Frontal Gyrus Thickness	0.899, <0.001	0.338, 0.145
Superior Temporal Gyrus Thickness	0.836, <0.001	0.151, 0.526
Middle Temporal Gyrus Thickness	0.885, <0.001	0.496, 0.026

Bold = $p < 0.001$

Table 5
Descriptive and RM-ANOVA Comparisons for Neuropsychological Performance and Clinical Symptoms

Measure	Mean (SD) of variables (z-score)				Longitudinal Analyses <i>F</i> (1, 38) <i>p</i>					
	SCZ (<i>n</i> = 20)		CON (<i>n</i> = 20)		Group Effect	Time Effect	Group-by-Time Interaction			
	Baseline Mean (SD)	Follow-up Mean (SD)	Baseline Mean (SD)	Follow-up Mean (SD)						
Crystallized IQ	-0.470 (0.90)	-0.589 (0.97)	0.725 (0.53)	0.568 (0.50)	27.2	0.001	3.12	0.09	0.06	0.81
Working Memory	-0.609 (0.61)	-0.534 (0.59)	0.575 (0.72)	0.754 (0.79)	36.2	0.001	3.76	0.06	0.64	0.43
Episodic Memory	-0.610 (0.67)	-0.711 (0.67)	0.611 (0.66)	0.572 (0.61)	55.3	0.001	0.67	0.42	0.06	0.80
Executive Functioning	-0.417 (0.49)	-0.411 (0.74)	0.467 (0.46)	0.607 (0.45)	35.7	0.001	1.18	0.28	1.00	0.32
<i>F</i> (1, 19) <i>p</i>										
Positive Symptoms	0.450 (0.81)	0.612 (1.10)	--	--	--	--	0.49	0.49	--	--
Negative Symptoms	0.389 (0.82)	0.372 (0.67)	--	--	--	--	0.01	0.92	--	--
Disorganized Symptoms	0.513 (0.82)	0.395 (0.70)	--	--	--	--	0.38	0.54	--	--

Significant ($p < .05$) effects are shown in bold