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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 that 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.

1. Introduction

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; van Haren et al., 2008; Kempton et al., 2010), and in a meta-analytic review, Olabi et al. (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 (Kasai et al., 2003; Hulshoff Pol and Kahn, 2008). 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.

For the current study, we used semi-automated surface-based methods to examine whether changes in specific subregions of the

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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 (van Haren et al., 2007; Qiu et al., 2008; Takahashi et al., 2009; Harms et al., 2010). 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 (Ho et al., 2003; Andreasen et al., 2011).

2. 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 clinically stable.

2.3. MRI acquisition parameters and data processing

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

Table 1
Demographic characteristics of study sample.

	SCZ (n = 20)		CON (n = 20)		Statistic		
	Mean	(SD)	Mean	(SD)	*t*-test	df	*p*
Age (years)	31.9	(11.1)	30.4	(12.8)	0.41	38	0.68
Parental SES	3.4	(1.1)	2.9	(0.7)	1.97	38	0.06
Alcohol use (grams per year)	2049	(3973)	3235	(5399)	−0.75	34	0.46
Nicotine use (cigarettes per year)	4357	(4088)	611	(1761)	3.77	26	0.001*
Scan interval (years)	2.0	(0.9)	2.1	(0.4)	−0.41	38	0.68
Duration of illness (years)	12.4	(12.9)	–				
Chlorpromazine equivalent (2 years prior to baseline)							
1st-Generation (dose years)	1.13	(3.7)	–				
2nd-Generation (dose years)	3.47	(3.4)	–				
Chlorpromazine equivalent (between baseline and follow-up)							
1st-Generation (dose years)	0.95	(2.9)	–				
2nd-Generation (dose years)	6.64	(5.3)	–				
	N	(%)	N	(%)	X^2	df	*p*
Gender, no. (% male)	10	(50.0%)	11	(55.0%)	0.10	1	0.75
Race (%)					6.93	2	0.03*
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	0.38

* $p<0.05$.