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Longitudinal loss of gray matter volume in patients with first-episode schizophrenia: DARTEL automated analysis and ROI validation

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ABSTRACT

Region of Interest (ROI) longitudinal studies have detected progressive gray matter (GM) volume reductions in patients with first-episode schizophrenia (FESZ). However, there are only a few longitudinal voxel-based morphometry (VBM) studies, and these have been limited in ability to detect relationships between volume loss and symptoms, perhaps because of methodologic issues. Nor have previous studies compared and validated VBM results with manual Region of Interest (ROI) analysis.

In the present VBM study, high-dimensional warping and individualized baseline-rescan templates were used to evaluate longitudinal volume changes within subjects and compared with longitudinal manual ROI analysis on the same subjects. VBM evaluated thirty-three FESZ and thirty-six matched healthy control subjects (HC) at baseline (cross-sectionally) and longitudinally evaluated 21 FESZ and 23 HC after an average of 1.5 years from baseline scans. Correlation analyses detected the relationship between changes in regional GM volumes in FESZ and clinical symptoms derived from the Brief Psychiatric Rating Scale, as well as cognitive function as assessed by the Mini-Mental State Examination.

At baseline, patients with FESZ had significantly smaller GM volume compared to HC in some regions including the left superior temporal gyrus (STG). On rescan after 1.5 years, patients showed significant GM volume reductions compared with HC in the left STG including Heschl's gyrus, and in widespread brain neocortical regions of frontal, parietal, and limbic regions including the cingulate gyrus. FESZ showed an association of positive symptoms and volume loss in temporal (especially STG) and frontal regions, and negative symptoms and volume loss in STG and frontal regions. Worse cognitive function was linked to widespread volume reduction, in frontal, temporal and parietal regions. The validation VBM analyses showed results similar to our previous ROI findings for STG and cingulate gyrus. We conclude FESZ show widespread, progressive GM volume reductions in many brain regions. Importantly, these reductions are directly associated with a worse clinical course. Congruence with ROI analyses suggests the promise of this longitudinal VBM methodology.

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Introduction

Numerous cross-sectional magnetic resonance imaging (MRI) studies indicate smaller gray matter (GM) volume in schizophrenia patients at first episode (FESZ) compared with healthy controls (HC) (reviewed in (Glahn et al., 2008; McCarley et al., 1999b; Shenton et al., 2001)). The initially controversial hypothesis of post-onset progressive GM loss in FESZ has gained support through many recent studies (see, for example, citations (Bachmann et al., 2004; Cahn et al., 2002; Hoff et al., 1999; Mane et al., 2009; van Haren et al., 2008; Whitford et al., 2006) and below). One method used in many studies demonstrating longitudinal change is manually drawn Region of Interest (ROI) analysis. A previous longitudinal analysis of neocortical gray matter (NCGM) volume changes from our laboratory (Nakamura et al., 2007) showed loss of overall NCGM volume over 1.5 years, with a higher rate in temporal and frontal lobes. Other longitudinal ROI studies from our laboratory have shown progressive GM volume reduction in cingulate gyrus (CG) (Koo et al., 2008) and in superior temporal gyrus (STG) and STG

Abbreviations: VBM, voxel-based morphometry; DARTEL, Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra; SVC, small volume correction; ROI, region of interest; FDR, false discovery rate; FESZ, first-episode schizophrenia; HC, healthy control subjects; GM, gray matter; STG, superior temporal gyrus; HG, Heschl's gyrus; A/PCG, anterior/posterior cingulate gyrus; NCGM, neocortical gray matter; MMSE, Mini-Mental State Examination; BPRS, Brief Psychiatric Rating Scale.

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components of Heschl's gyrus (HG) and planum temporal (Kasai et al., 2003a, 2003b); another group has recently confirmed progression in STG and its components (Takahashi et al., 2009b). Of note, we found the degree of longitudinal volume reduction using ROI methods was greater in certain gyri (e.g., STG, CG) compared with overall NCGM, suggesting regional differences in progression.

A second method is voxel-based morphometry (VBM), defined by Ashburner and Friston (Ashburner and Friston, 2000) as "a voxel-wise comparison of the local concentration of GM between two groups of subjects". To detect regional group differences, VBM has the advantages over manual ROI methods of allowing whole brain coverage and less laborious processing. However, there is a lack of uniformity in results in VBM studies. One reason is differences in methods among the previous longitudinal analyses, and those results were not compared with results of the manual ROI analyses using the same subjects. In addition, many of the previous longitudinal VBM studies have not reported structural-symptomatic associations although they have demonstrated GM volume loss in several brain regions in FESZ (Farrow et al., 2005; Mane et al., 2009; Theberge et al., 2007; Whitford et al., 2006).

In the current study, we conducted whole brain VBM analysis to investigate progressive GM volume changes in FESZ compared with HC. For this analysis, we developed a new longitudinal VBM method. The DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra) (Ashburner, 2007) tool in the Statistical Parametric Mapping (SPM) 5 was used to evaluate within-subject changes by creating individual templates. To establish our new method (Giuliani et al., 2005), validation VBM with small volume correction (SVC) analyses were conducted for STG, HG, and CG using the same subjects and scans of our previous manual ROI analyses (Kasai et al., 2003a, 2003b; Koo et al., 2008), and results were compared. Finally, exploratory correlation analyses were conducted between changes in regional GM volumes and cognitive function and positive and negative symptoms to understand the pathology of these symptoms in FESZ.

Material and methods

Subjects

Thirty-three FESZ and 36 HC were compared in a cross-sectional study (Table 1). The patients were recruited from inpatient units at McLean Hospital, Belmont, Massachusetts. HC were recruited from the local community through newspaper advertisements. Consistent with our previous studies (Salisbury et al., 1998, 2007), "first episode" was operationally defined as the first hospitalization for psychosis (all except 6 subjects in the present cross-sectional study) or within 1 year of the first hospitalization for psychosis. Inclusion criteria for patients and HC were age 18 to 45, IQ above 75, and no history of seizures, head trauma with loss of consciousness, neurologic disorder, or an alcohol or drug detoxification within the last 5 years. Patient diagnosis was based on the Structured Clinical Interview for DSM (SCID) Patient Edition for DSM-III-R (Spitzer et al., 1990c) or *DSM-IV* (First et al., 1997) criteria. The HC were confirmed to have no Axis I or II disorders using SCID-Non-Patient Edition (Spitzer et al., 1990a) and SCID-II interviews (Spitzer et al., 1990b), and no history of Axis I disorders in their first-degree relatives per self-report.

Twenty-one FESZ and 23 HC were rescanned approximately 1.5 years later (Table 2). The groups in the cross-sectional and longitudinal studies were matched for age, gender, parental socioeconomic status (PSES) (Hollingshead, 1965), and handedness (Oldfield, 1971). Exclusion of the single mildly left-handed FESZ patient (Edinburgh index = −0.07) from the subsequent analyses did not change the results of the cross-sectional or longitudinal study.

Table 1
Demographic and clinical characteristics of cross-sectional study subjects.

	FESZ group (n = 33)	HC group (n = 36)	df [a]	*t*-test or chi-square values [b]	p
	Mean (SD)	Mean (SD)			
Age, mean (SD) [range], years	22.5 (6.7) [18–45]	22.9 (3.8) [18–34]	67	1.27	.21
Gender (male/female)	28/5	30/6	1	.03	.86
Handedness [c]	0.80 (0.22)	0.78 (0.20)	66	.24	.81
Socioeconomic status [d]					
Subject's	3.4 (1.3)	2.3 (0.9)	67	4.17	<.001**
Parental	1.9 (0.9)	1.5 (0.7)	67	1.87	.06
Years of education	13.5 (2.2)	15.0 (1.8)	65	2.98	.004**
WAIS-R Information, scaled	11.7 (2.9)	13.4 (2.3)	60	1.64	.009**
WAIS-R Digit Span, scaled	10.2 (2.6)	11.3 (2.8)	60	1.59	.12
Duration of illness, weeks	19.5 (20.3)	NA			
Antipsychotic medication dosage, CPZ equivalent	287.9 (181.0)	NA			
Medication use, no. of patients					
Neuroleptics, TYP/ATYP/overlap/non-neuroleptics [e]	7/19/6/1				
Li/VPA/overlap/non-mood stabilizer	2/5/0/26				
Duration of antipsychotic medication before scan, median [range], weeks	1.0 [0–20]	NA			
MMSE	28.1 (2.3)	28.9 (1.1)	63	1.65	.11
BPRS	39.2 (11.0)	NA			
GAS	35.9 (8.1)	NA			

Abbreviations: FESZ, first-episode schizophrenia; HC, healthy control; WAIS-R, Wechsler Adult Intelligence Scale-Revised; CPZ, chlorpromazine; MMSE, Mini-Mental State Examination; BPRS, Brief Psychiatric Rating Scale; GAS, Global Assessment Scale; NA, data not applicable.

[a] The degrees of freedom differ among variables owing to unavailability of data in some participants.

[b] *t* tests were performed between the two groups for age, handedness, SES, parental SES, years of education, WAIS-R Information and Digit Span, scaled scores, and MMSE scores. A chi-square test was performed for sex ratio between the two groups.

[c] Handedness was using the Edinburgh Handedness Inventory, where right handedness is positive.

[d] Higher scores mean lower socioeconomic status, based on the Hollingshead two factor index of socioeconomic status.

[e] One patient was antipsychotics-naïve at the baseline scan.

* $p<.05$.

** $p<.01$.