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Optimized voxel-based morphometry of gray matter volume in first-episode, antipsychotic-naïve schizophrenia

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Abstract

This study examined gray matter (GM) volume abnormalities in first-episode, antipsychotic-naïve Indian schizophrenia patients. Magnetic resonance images of 18 schizophrenia patients and 18 matched healthy comparison subjects were analyzed by optimized voxel-based morphometry. Schizophrenia patients had significantly smaller global GM and greater global CSF volumes and smaller regional GM volume in superior frontal, inferior frontal, cingulate, post-central, superior temporal and parahippocampal gyri, inferior parietal lobule, insula, caudate nuclei, thalamus and cerebellum. Findings suggest limbic, heteromodal cortical, striatal, thalamic and cerebellar abnormalities in schizophrenia.

Keywords: Antipsychotic-naïve; Schizophrenia; Voxel-based morphometry

1. Introduction

Imaging studies examining first-episode, antipsychotic-naïve schizophrenia (FANS) patients demonstrate brain abnormalities without confounds of illness chronicity and neuroleptic treatment (Cahn et al., 2002). Most of the previous studies on FANS have used labor-intensive, manual region of interest (ROI) method, which restricts the number of brain regions that can be practically measured. This warrants the need for automated techniques (Shenton et al., 2001). Optimized voxel-based morphometry (VBM) is an automated image analysis technique that offers an improvised, rapid and unbiased whole brain survey (Good et al., 2001). Previous studies using VBM have examined FANS patients from western countries (Job et al., 2002; Kubicki et al., 2002; Salgado-Pineda et al., 2003). To our knowledge, no published study has examined the structural brain abnormalities in FANS patients from India using an automated image analysis. We used optimized VBM to analyze GM volume abnormalities in Indian FANS patients.

2. Methods

2.1. Subjects

The sample consisted of 18 antipsychotic-naïve patients [age = 24.9 ± 6.3 years, M/F = 9:9, education = 10.9 ± 4.3 years] and 18 healthy comparison subjects (HC) [age = 25.7 ± 7.5 years, M/F = 9:9, education = 12.5 ± 2.5

Abbreviations: CSF, cerebrospinal fluid; FANS, first-episode, antipsychotic-naïve schizophrenia; FDR, false discovery rate; GM, gray matter; HC, healthy comparison subjects; ICV, intracranial volume; PANSS, Positive and Negative Syndrome Scale; ROI, region of interest; SPM, statistical parametric mapping; SVC, small volume correction; VBM, voxel-based morphometry; WM, white matter.

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years]. Age, sex and education did not differ significantly between patients and HC ($p > 0.05$). All subjects (patients and HC) were right-handed. DSM-IV diagnosis of schizophrenia (American Psychiatric Association, 1994) was established using the Structured Clinical Interview for the DSM-IV (First et al., 1997). The first episode and illness duration (mean ± S.D.: 10.3 ± 5.1 months) as defined by report of psychotic symptoms were assessed using the Instrument for the Retrospective Assessment of Onset of Schizophrenia (Hafner et al., 1992). None of the patients were exposed to any psychotropic medications including antipsychotics. Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) scores (mean ± S.D.) were positive syndrome (19 ± 8), negative syndrome (23 ± 7), general psychopathology (36 ± 8) and total score (79 ± 18). None had involuntary movements.

HC subjects were screened using the 12-item General Health Questionnaire (Goldberg et al., 1997) and a comprehensive mental status examination. None of the healthy comparison subject had family history of psychiatric illness in their first-degree relatives. None of the subjects (patients and HC) scored positive for alcohol use on CAGE questionnaire (Ewing, 1984). None used stimulant or opiate drug. No subject had history of neurological/medical disorder. All subjects signed informed written consent. The Institute's ethics committee approved the study.

2.2. Scanning protocol

MRI was done with 1.5 T Magnetom 'vision' scanner. T_1 weighted three-dimensional magnetization prepared rapid acquisition gradient echo sequence was performed (TR = 9.7 ms, TE = 4 ms, nutation angle = 12°, FOV = 250 mm, slice thickness 1 mm, NEX = 1, matrix = 200 × 256) yielding 160 sagittal slices.

2.3. Image processing

The optimized VBM protocol was implemented within Matlab 6.1 (Mathworks, Natick, Mass.) through Statistical Parametric Mapping 2 (SPM2) (Wellcome Department of Imaging Neuroscience, London; http://www.fil.ion.ucl.ac.uk/spm). SPM2 has an updated segmentation model with an improved bias correction component. The segmentation model also includes a "cleanup" procedure whereby small regions of non-brain tissue that are misclassified as brain are removed. Also, the prior probability images are scaled such that they have less influence on the segmentation. Previously, segmentation of abnormal brains was problematic if it contained non-brain tissue like CSF, while the prior probability images suggested that there was no such probability. The modified segmentation code in SPM2 is able to cope slightly better with these abnormalities (reference: http://www.fil.ion.ucl.ac.uk/spm/spm2.html).

Pre-processing of structural data followed a number of defined stages (Good et al., 2001; Ananth et al., 2002). First, customized templates were created from the whole subject group, imaged with identical methods on the same scanner. The customized templates from the whole subject group rather than a subset was chosen in order to reduce any potential bias for spatial normalization (Good et al., 2001). Each structural MRI image was normalized to the standard statistical parametric mapping T_1 template; segmented into CSF, gray matter (GM) and white matter (WM) compartments; then smoothed (8-mm full width at half maximum isotropic Gaussian kernel) and averaged to create gray and white matter templates in stereotactic space (Good et al., 2001). This study-specific customized GM template was utilized for the subsequent pre-processing steps.

An automated brain extraction procedure that incorporated a segmentation step was used to remove non-brain tissue in the original structural MR images (Good et al., 2001). The extracted GM images were normalized to the customized GM template. Spatial normalization used a residual sum of squared differences as the matching criterion and included affine transformations and linear combination of smooth basis functions modeling global nonlinear shape differences (Ashburner and Friston, 2000; Ashburner et al., 1997). The normalization parameters were then reapplied to the original structural images to maximize optimal segmentation of fully normalized images, and these normalized images were re-sliced to a final voxel size of 1 mm^3 and segmented into gray/white matter and CSF/non-CSF partitions. After correcting for non-uniformity in image intensity, the statistical parametric mapping segmentation employs a mixture model cluster analysis to identify voxel intensities that match particular tissue types combined with a priori probabilistic knowledge of the spatial distribution of tissues (Ashburner and Friston, 1999). After a further automated brain extraction step, the partitioned images were modulated by the Jacobian determinants from spatial normalization to correct for volume changes introduced during the nonlinear spatial transformations. The modulation step helped to analyze the regional differences in absolute volume of gray matter (Good et al., 2001). Finally, all normalized, segmented modulated images were smoothed with a 12-mm full width at half maximum isotropic Gaussian kernel (Ashburner et al., 1997; Ashburner and Friston, 1999).

2.4. Statistical analysis

Global measures of regional gray matter (GM), white matter (WM) and CSF volumes were calculated from the non-normalized segmented images to test for group differences in overall tissue compartment volumes (Ananth et al., 2002). The total intracranial volume (ICV) was calculated from the sum of the global measures of the three tissue types (Ananth et al., 2002). Group comparisons for regional GM volume differences were performed using 'single subject: conditions and covariates' analysis within the framework of