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Motor function deficits in schizophrenia: an fMRI and VBM study

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Abstract

Introduction—To investigate whether the motor functional alterations in schizophrenia (SZ) are also associated with structural changes in the related brain areas using functional magnetic resonance imaging (fMRI) and voxel-based morphometry (VBM).

Methods—A sample of 14 right-handed SZ patients and 14 right-handed healthy control subjects matched for age, sex, and education were examined with structural high-resolution T1-weighted MRI; fMRI images were obtained during right index finger-tapping task in the same session.

Results—fMRI results showed reduced functional activation in the motor areas (contralateral precentral and postcentral gyrus) and ipsilateral cerebellum in SZ subjects as compared to healthy

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controls ($n=14$). VBM analysis also revealed reduced grey matter in motor areas and white matter reduction in cerebellum of SZ subjects as compared to controls.

Conclusion—The present study provides an evidence for a possible association between structural alterations in the motor cortex and disturbed functional activation in the motor areas in persons affected with SZ during a simple finger-tapping task.

Keywords

fMRI; BOLD; VBM; Motor task; Schizophrenia

Introduction

Schizophrenia (SZ) is psychotic major mental disorder characterized by disorders of thought, perception, behavior, and social problems specifically delusions, hallucinations, negative symptoms and disorganized speech or behavior [1]. In addition, the disorder results in cognitive impairment reflecting abnormal functioning of brain. Studies have reported deficits in working memory, verbal memory, language, and executive functions in schizophrenics [2–7]. Motor dysfunction is one of the major characteristics of schizophrenia (SZ, [8]). Persons affected with SZ tend to be slow in initiating movements while performing a simple motor task as demonstrated by prolonged reaction time [8]. Previous neuropsychological and functional imaging studies have also shown motor impairments in SZ [9–11]. Several reviews have focused on catatonia [12,13], abnormal involuntary movements and neurological soft signs (NSS; [14,15]), psychomotor slowing [16], motor deficits or neurological abnormalities in antipsychotic naive SZ patients [14,17,18]. Similarly, a recent review on motor symptoms in SZ supports that motor symptoms are closely related to neuro-developmental disturbances of SZ and a distinct syndromal dimension with its own pathophysiology [19]. The available evidence also suggests that populations at risk for SZ have increased rates of motor abnormalities [17]. Delayed motor development in pre-SZ subjects and poor motor skills in the offspring of patients with SZ has been observed. In first-degree relatives, increased rates of neurological soft signs have been reported. It has been suggested that motor abnormalities may constitute markers of vulnerability to SZ. Therefore, studying the underlying neural correlates of motor dysfunction in SZ becomes important.

Advancement in neuroimaging technology is capable of providing both the structural and functional information in brains of SZ patients [20]. Functional magnetic resonance imaging (fMRI) using blood oxygenation level-dependent (BOLD) signal contrast is one of the most versatile and important tools to study non-invasive functional activation in the normal and diseased human brain [21]. A whole brain fMRI finger-tapping study reported that motor-induced cortical, subcortical, and cerebellar brain regions activation in healthy controls was significantly higher than in patients with SZ treated with neuroleptic drugs [9]. Another fMRI study demonstrated hypoactivation of supplementary motor area (SMA), left primary sensorimotor cortex, bilateral lateral premotor, and inferior parietal cortices during a sequential finger opposition task in akinetic neuroleptic-treated schizophrenic patients [22].

Various studies based on voxel-based morphometry (VBM) reported gray matter loss in several brain regions such as thalamus, superior temporal gyrus (STG), frontal gyrus, precentral gyrus, postcentral gyrus, insula, and cerebellum in persons affected with SZ [23–27]. VBM findings showed longitudinal loss of grey matter (GM) volume in patients of first episode SZ using diffeomorphic anatomic registration through exponentiated lie (DARTEL) algebra algorithm automated tool and region of interest (ROI) validation [28]. The same study showed significant GM volume reductions compared with healthy controls in the left STG including Heschl's gyrus and in widespread brain neocortical regions of frontal, parietal, and limbic regions including the cingulate gyrus.

Although functional and structural studies have separately reported the functional and structural alterations associated with SZ, the relationship between these structural and functional alterations remains unclear. There are few earlier studies that have investigated the association between clinical symptoms and structural and functional cerebral deficits in SZ [29,30]. In the present study, we used both fMRI and VBM techniques to investigate whether motor functional alterations in SZ are also associated with structural brain aberrations in related brain regions or in anatomically closely connected areas using a finger-tapping task.

Methods

The study was conducted at the NMR Research Center, Institute of Nuclear Medicine and Allied Sciences (INMAS), Defence Research and Development Organization (DRDO), Delhi, India and was approved by the Institutional Ethics Committee of Post Graduate Institute of Medical Education and Research (PGIMER), Dr. Ram Manohar Lohia Hospital (RMLH), New Delhi, India and the Institutional Review Board, INMAS, DRDO, Delhi, India. After complete description of the study to the participants, written informed consent was obtained from all the participants.

Subjects

A total of 18 right-handed SZ subjects and 14 healthy controls, matched for age, sex, handedness and socio-economic status, underwent MRI scans. Excessive head movement inside the scanner (greater than ± 1.5 mm or $\pm 1.5^\circ$) meant that four of the schizophrenic patients' data had to be discarded, leaving 14 SZ subjects and 14 healthy controls (Table 1). Schizophrenia subjects were recruited from outpatients at Department of Psychiatry, PGIMER-RMLH, New Delhi.

We included patients aged between 25 and 55 years with a DSM-IV diagnosis of SZ, interviewed using the Hindi version of Diagnostic Interview for Genetic Studies (DIGS; [31,32]) after diagnostic review with a board-certified psychiatrist. Patients with history of alcohol/illicit substances or individuals with any neurological disorders that interfered with diagnosis or cognitive evaluations were excluded. All patients were on antipsychotic medications at the timing of MRI acquisition.

The controls were recruited from the local community. They were screened for presence of any psychiatric disorder and those subjects who had no prior psychiatric disorder and had

never used any psychotropic medication, no history of major head injury (loss of consciousness), no mental retardation, or any contraindications on MRI were enrolled. Both patients and controls, on physical and neurologic examinations, revealed no abnormalities. A neuroradiologist examined the MRI scans, which were free of pathology.

Sensorimotor assessment

Sensorimotor dexterity of both controls and patients were assessed using a Hindi version of Penn Computerized Neuro-psychological Battery (CNB; [33]). For sensorimotor assessment, three summary functions were calculated: (a) accuracy (number of correct responses), (b) speed (median reaction time for correct responses), and (c) efficiency (reflects both accuracy and speed). To see whether antipsychotic drug has any effect on motor performance of the SZ patients, the three summary functions obtained above were correlated with duration of antipsychotic drug taken by the patients using SPSS (version 15.0, SPSS, Chicago, IL, USA) statistical software.

Data acquisition

The functional and structural data were collected in the same session on a 3 Tesla whole-body MRI system (Magnetom Skyra, Siemens, Germany) with a 20-channel head and neck coil. Subjects lay in the supine position with their heads supported and immobilized within the head coil using foam ads (vendor provided), to minimize head movement and gradient noise. Thirty-six axial slices parallel to the bicommissural plane through the fronto-parietal cortex covering the whole brain volume using an echo-planar imaging sequence (matrix=64×64, field of view=210 mm, TE= 36 ms, TR=3 s, flip angle=90°, slice thickness=3 mm) were obtained. Block paradigm (BABABABA...) with alternating phases of activation (A) and baseline (B) was chosen. 110 sequential image volumes (belonging to five cycles+one baseline for eliminating T₁ saturation effects and acclimatization of the patient to the gradient noise) were taken. Prior to imaging, shimming was performed to optimize the magnetic field homogeneity.

High-resolution MR images were obtained with a T1-weighted 3D gradient echo sequence [Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE), 160 sagittal slices, slice thickness=1 mm, field of view=256 mm, matrix size=256×256, TR=1,900 ms, TE=2.07 ms, TI=900 ms]. In addition, a T2-weighted turbo spin echo (TE=100 ms, flip angle=150°, field of view=220 mm, matrix size=312×512) scan with 25 axial 4 mm slices and 1.2 mm gap of the whole brain was acquired for neuro-diagnostic evaluation to rule out any other neurological problem.

Task paradigm

In the fMRI experiment, subjects performed a discrete tapping task with the right index finger in which a visual stimulus was given using the fMRI Hardware system by Nordic Neurolab that indicated the required frequency of the tapping. Subjects were instructed to keep their eyes open throughout the scanning series. They were provided instructions and allowed to practice the motor activation task prior to scanning. Subjects tapped their right index finger in air without touching any surface. Entire study comprised of fMRI experiment in which subjects performed the tapping task at tapping rate of 120 taps/min. Five cycles

each of active (right index finger tapping) and rest (baseline) phase, preceded by a rest (baseline) phase of ten measurements, were performed. Each cycle consisted of ten measurements for activation and rest phase, resulting in a total of 110 measurements for complete study. During the experiment, the subject's performance of the task was monitored visually to confirm adherence to the experimental design.

Functional data analysis

fMRI data were processed with Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK, <http://www.fil.ion.ucl.ac.uk/spm>) software package implemented in MATLAB R2008a (Version 7.6.0, MathWorks, Sherbon, MA). The first ten brain volumes (one baseline) of each fMRI data set were discarded to remove the initial transit signal fluctuations and subsequent images were realigned within the session to remove any minor movements. Translational or rotational movement greater than ± 1.5 mm or $\pm 1.5^\circ$, respectively, were not considered for analysis. The T1-weighted high-resolution anatomical images were coregistered to the mean functional images and spatially normalized to the Montreal Neurological Institute (MNI) brain template. The time-course images were normalized using the same normalization parameters and then smoothed with a $6 \times 6 \times 6$ mm³ [full-width at half-maximum (FWHM)] Gaussian smoothing kernel. The EPI images were high-pass filtered (0.008 Hz) to remove low-frequency signal drift. A statistic parametric map (SPM) was generated for each subject under each condition by fitting the stimulation paradigm to the functional data, convolved with a canonical hemodynamic response function. Condition-specific effects at each voxel were estimated using the general linear model [34]. Individual first level contrast images were generated for the motor task versus baseline contrast [familywise error (FWE)-corrected, $p < 0.05$]. One-sample t test in both the groups was performed to generate an average activation map using the contrast images from the single-subject analyses. For the between-group analyses, two-sample t test was performed. Since age and duration of illness might influence the BOLD activation pattern in the two groups, they were added as covariates of no interest in the two-sample t test. The resulting statistical map was set at a combined threshold of $p < 0.001$ for each voxel and a minimum cluster size > 48 voxels for one-sample t test and > 25 voxels for two-sample t test, which resulted in a corrected threshold of $p < 0.05$ as determined by AlphaSim in REST software.

The anatomical representation of the clusters was related to cytoarchitectonic maps as implemented in SPM Anatomy Toolbox [35] which provides a routine, standardized application of probabilistic cytoarchitectonic maps as an anatomical reference for functional activations.

BOLD contrast estimates were also extracted from the 8 mm ROIs defined on the regions showing group differences in two-sample t test using MarsBaR toolbox of SPM (<http://marsbar.sourceforge.net/>).

Structural data analysis

Image processing—Images were processed using Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology) implemented in MATLAB R2008a (version

7.6.0, MathWorks,). All the steps for data processing were followed as described in detail by Ashburner and Friston[36])).¹ In order to improve the registration of the MRI images, DARTEL toolbox for SPM8 was used. Briefly, the anatomical images were firstly reoriented so that the mm coordinate of the anterior commissure matched the origin (0, 0, 0), and the orientation approximated MNI space. Then, T1-weighted images were segmented and classified into GM, white matter (WM), and cerebrospinal fluid (CSF) probability maps using the ‘new-segment’ option implemented in SPM8, which gives both the native space versions and DARTEL imported versions of the tissues. All the GM and WM images were spatially nonlinearly normalized to the population template which was created by GM and WM maps and DARTEL, and then Jacobian modulated. These images were affine transformed to MNI space and, finally, were smoothed with a 10 mm FWHM Gaussian kernel.

Total GM volume, WM volume, CSF volume, and total intracranial volume (TIV) were calculated using a MATLAB script downloaded from the SPM email list.²

Statistical analysis—The GM, WM, and CSF volumes of all the subjects were normalized by dividing the individual value by TIV of the respective subjects (Table 1). Normalized GM (nGM) volume, normalized WM (nWM) volume, normalized CSF (nCSF) volume, and TIV were compared among the two groups using the Student’s independent *t* test.

The normalized, segmented, smoothed, and modulated GM and WM data were analyzed using a voxel-wise SPM. ‘Two-sample *t* test’ analysis with nGM volume or nWM volume of the individual subjects was used to find the regional changes in the GM or WM volumes, respectively. TIV was entered as a global variable to correct for the global brain volume of different subjects. A whole brain analysis was performed, with a significance level of $p < 0.001$, uncorrected for multiple comparisons. Since this threshold might have led to false positive results, in those areas which passed this threshold, a small volume correction (SVC) was further applied, setting the cut-off value for significance at FWE-corrected $p < 0.05$ (at cluster level) and using a 8-mm radius. The anatomical representation of the clusters was related to cytoarchitectonic maps as implemented in the SPM anatomy toolbox [35].

Results

Sensorimotor assessment

Student’s independent *t* test showed significant difference for sensorimotor accuracy ($p = 0.002$), sensorimotor speed ($p = 0.001$) and sensorimotor efficiency ($p = 0.001$) between schizophrenic and control groups (Table 1).

No correlation was obtained between the duration of anti-psychotic drug taken and any of the three summary functions of sensorimotor dexterity.

¹<http://www.fil.ion.ucl.ac.uk/~john/misc/VBMclass10.pdf>

²<http://www.jiscmail.ac.uk/cgi-bin/wa.exe?A2=ind0807&L=SPM&P=R7075&1>

fMRI analysis

Group analysis for right index finger-tapping task showed significant clusters of activation in the contralateral precentral gyrus, postcentral gyrus, SMA, thalamus, putamen, rolandic operculum, insula lobe, and ipsilateral cerebellum in controls (Fig. 1 and Table 2). In SZ subjects, clusters of activation were found in the contralateral precentral gyrus, postcentral gyrus, SMA, rolandic operculum, insula lobe, and ipsilateral cerebellum (Fig. 2 and Table 2). In two-sample t test, SZ subjects showed reduced cluster of activations in contralateral precentral and postcentral gyrus and ipsilateral cerebellum as compared to controls (Fig. 3 and Table 2).

ROI analysis

The contrast estimates of BOLD response as obtained using MarsBaR toolbox in the regions obtained in two-sample t test were significantly decreased in SZ patients as compared to controls (Fig. 4 and Table 3).

VBM analysis

The subject groups did not show any significant differences with respect to age, gender, handedness, and education. Student's t test did not reveal any statistically significant intergroup differences in any of the volumetric parameters, i.e., nGM volume, nWM volume, nCSF volume, and TIV shown in Table 4.

VBM results showed that SZ subjects had significantly reduced grey matter volumes in the contralateral precentral, postcentral gyrus, and middle frontal gyrus as compared to healthy controls (Fig. 5 and Table 5). A significant WM volume reduction was found in ipsilateral cerebellum and inferior temporal gyrus in schizophrenic patients as compared to healthy controls (Fig. 5 and Table 5).

Discussion

The present study aimed to characterize the association between hemodynamic and morphometric measurements to investigate whether motor functional deficits in SZ patients are related to structural abnormalities in specific brain regions. For the purpose, fMRI was carried out in right-handed schizophrenic patients and controls for a finger-tapping task using the dominant hand. Earlier studies have shown that the use of the dominant hand is associated with a greater volume of activation in the contralateral motor cortex [9,37] as well as ipsilateral cerebellum [9]. Our fMRI study showed that schizophrenic patients had relatively less activation in the contralateral motor areas (contralateral precentral and postcentral gyrus) and ipsilateral cerebellum as compared to healthy controls during a simple finger-tapping task. VBM results also showed GM volume loss in the contralateral precentral and postcentral gyrus and WM volume decreases in the ipsilateral cerebellum in patients as compared to controls. Previous neuropsychological studies have also shown motor impairment such as motor dexterity and psychomotor slowing in SZ patients [10,38].

Movement is accompanied by activation of the postcentral gyrus and somatosensory stimuli which activate the precentral gyrus [39]. Since the primary motor cortex (precentral and

postcentral gyrus) is responsible for the direct production of movements via its outputs to the pyramidal tract, any GM or WM loss in this area will produce a motor deficit in the corresponding parts of the body. Our fMRI results showed lesser cluster of activations in these areas in SZ subjects compared to controls, which corroborates a previous fMRI study showing a diminished activation in cortical, subcortical, and cerebellar regions of brain in the SZ subjects as compared to healthy controls using finger-tapping task [9].

The cerebellum also plays an important role in the processing of sensory inputs along with motor coordination. Cerebellar lesions are associated with ataxic movements and sensory dysfunctions [40,41]. The lesser cluster of activation was found in ipsilateral cerebellum and there was a WM volume loss in ipsilateral cerebellum in SZ subjects as compared to controls. These results correlate well with a previous fMRI study which reported diminished activation in cerebellar regions in SZ subjects [9] and VBM studies which showed WM reduction in SZ subjects [42,43]. These findings suggest GM and WM volume reduction in cerebellum might be a cause of motor functional deficits in them.

Besides these results, the present VBM study revealed GM volume loss in contralateral middle frontal gyrus and WM volume loss in the ipsilateral inferior temporal gyrus of persons affected with SZ as compared to controls. These brain regions are mainly involved in attention, problem-solving and decision-making, and high-level visual processing of complex stimuli and memory functions, respectively. Any GM or WM reduction in these areas might be responsible for deficits in attention, memory, and visuospatial ability in SZ subjects. Previous studies reported GM and WM volume loss in left middle frontal gyrus and right inferior temporal gyrus [23,24,43], which are in consistence with our findings. Reichenberg's review [44] also reported that the neurophysiological dysfunction in SZ resulted in severe impairment in attention, executive functions, memory, visuo-spatial ability, and motor speed, a finding reported in several other studies [5,45–47].

It has been suggested that motor deficit might be due to undesirable side effects of the antipsychotic drugs [48,49]; however, there is no consistency in the literature. Some studies have shown that motor deficit was independent of antipsychotics [50]. We also did not find any significant correlation between duration of antipsychotic drugs and sensorimotor dexterity in our patient group.

However, the current study has some limitations also. Our patient sample is relatively small; a greater number of subjects would yield more statistically significant results. Secondly, all of the patients were taking antipsychotic medications. A third group of subjects consisting of first-episode patients without medication history will be helpful to determine the potential effect of pharmacological treatment in SZ.

In conclusion, our findings provide an evidence for a possible association between motor functional deficits and structural alterations in SZ subjects as compared to controls. Thus, a combination of different imaging modalities facilitate in providing comprehensive and complementary information about the disease than a single imaging method.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
a Three-dimensional rendered view and **b** Glass-Brain view showing group analysis of BOLD fMRI activation pattern in the brain of healthy controls corresponding to 120 taps/min

Fig. 2.
a Three-dimensional rendered view and **b** Glass-Brain view showing group analysis of BOLD fMRI activation pattern in the brain of schizophrenic patients corresponding to 120 taps/min

Fig. 3.
a Three-dimensional rendered view and **b** Glass-Brain view showing whole brain activation map for regions that responded less in schizophrenia patients as compared to controls during right index finger-tapping task

Fig. 4. Comparison of mean contrast estimates for motor task versus control condition in Control and Patient group. *LPoG* left postcentral gyrus, *LPG* left precentral gyrus, and right cerebellum (*RC*). Asterisk indicate significant difference between groups ($*p < 0.05$)

Fig. 5. Overlay of the peak cluster on the grey and white matter template provided in SPM8, of **a** grey matter volume loss in contralateral precentral and postcentral gyrus and **b** white matter volume loss in ipsilateral cerebellum in schizophrenic subjects as compared to controls in VBM analysis

Table 1

Demographic and clinical characteristics of subjects

	Schizophrenic patients (mean $\pm$ SD) (N=14)	Healthy controls (mean $\pm$ SD)
Age (years)	34.06 $\pm$ 9.89	32.63 $\pm$ 7.64
Gender (male/female)	8/6	7/7
Handedness (R/L)	10/0	10/0
Years of education	8.6 $\pm$ 4.8	11.3 $\pm$ 3.3
Age of onset (years)	23.9 $\pm$ 8.2	NA
Duration of illness (years)	9.6 $\pm$ 4.3	NA
SANS total score	11.5 $\pm$ 5.2	
SAPS total score	8.3 $\pm$ 3.9	
Antipsychotic equivalent dosage of CPZ (mg/day)	471.4 $\pm$ 370.4	
Duration of antipsychotic drug taken (in weeks)	443.6 $\pm$ 310.6	
Sensorimotor assessment		
(a) Accuracy *	-0.47 $\pm$ 1.23	0.70 $\pm$ 0.22
(b) Speed **	-0.25 $\pm$ 1.00	0.95 $\pm$ 0.67
(c) Efficiency **	-0.68 $\pm$ 1.39	0.94 $\pm$ 0.48

SANS Scale for the Assessment of Negative Symptoms, *SAPS* Scale for the Assessment of Positive Symptoms, *CPZ* chlorpromazine Asterisks indicate significant difference between groups

*
 $p=0.002$

**
 $p=0.001$

Table 2

Cluster volume summary for functional areas of activation in healthy and schizophrenic subjects

Hemisphere	Localization of peak voxels	MNI coordinates	<i>t</i> Value	Cluster size (voxels)
Controls				
L	Precentral gyrus	−36 −13 55	12.39	
L	Postcentral gyrus	−48 −16 −11	10.06	995
L	SMA	−9 −7 55	7.13	
R	Cerebellum (lobule VI)	6 −64 −14	8.07	549
R	Cerebellum (lobule V)	9 −58 −11	7.09	
L	Rolandic operculum	−51 −4 10	9.06	158
L	Insula lobe	−36 2 13	6.63	
Patients				
L	Precentral gyrus	−45 −10 61	12.49	
L	Postcentral gyrus	−54 −16 46	7.41	427
L	SMA	−9 −4 58	6.21	
R	Cerebellum (lobule VI)	9 −76 −38	7.12	235
R	Cerebellum (lobule V)	6 −58 −14	6.86	
L	Rolandic operculum	−45 2 7	6.23	52
L	Insula lobe	−33 −1 16	5.36	
Controls>patients				
L	Postcentral gyrus	−54 −7 25	6.71	47
L	Precentral gyrus	−33 −16 64	5.37	43
R	Cerebellum	12 −73 −35	4.37	21
Patients>controls				
No significant activation				

L Left, *R* Right

Table 3

A summary of group means and SDs of the contrast estimates of BOLD response in three regions obtained in two-sample *t* test in schizophrenia patients as compared to controls.

	LPoG[*]	LPG[*]	Cerebellum[*]
Controls	0.32±0.12	2.68±0.50	0.51±0.26
Schizophrenia	0.08±0.04	1.20±0.15	0.20±0.04

LPoG left postcentral gyrus, *LPG* left precentral gyrus

^{*} Significant difference between two groups (*p* 0.01)

Table 4

Volumetric parameters for two groups (mean±SD)

	TIV (l)*	nGM*	nWM*	nCSF*
Schizophrenia	1.3712±0.13013	0.4595±0.01112	0.3171±0.01134	0.2234±0.01494
Controls	1.4296±0.15453	0.4576±0.00698	0.3209±0.00965	0.2215±0.01029

nGM Normalized grey matter volume, *nWM* normalized white matter volume, *nCSF* normalized cerebrospinal fluid volume, *TIV* total intracranial volume

* TIV, nGM, nWM, and nCSF showed no significant difference between two groups ($p>0.05$)

Table 5

Regions of GM and WM volume changes

Hemisphere	Localization of peak voxels	MNI coordinates	<i>t</i> Value	Cluster size (voxels)
<i>Controls versus schizophrenic subjects contrast</i>				
(A) GM volume changes				
L	Middle frontal gyrus [*]	−26 36 45	5.49	275
L	BA6, Postcentral gyrus [#]	−45 −9 52	3.73	104
L	BA6, Precentral gyrus [^]	−39 −13 57	3.63	
(B) WM volume changes				
R	Inferior temporal gyrus [@]	60 −31 −20	4.43	360
R	Lobule V, cerebellum ^{\$}	9 −43 −26	3.84	429

MNI Montreal Neurological Institute, *BA* Brodmann area^{*} Small volume correction (FWE-corrected), $p < 0.004$ [#] Small volume correction (FWE-corrected), $p < 0.006$ [^] Small volume correction (FWE-corrected), $p < 0.007$ ^{\$} Small volume correction (FWE-corrected), $p < 0.002$ [@] Small volume correction (FWE-corrected), $p < 0.006$