Regional Gray Matter Changes Are Associated with Cognitive Deficits in Remitted Geriatric Depression: An Optimized Voxel-Based Morphometry Study

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Background: We aimed to investigate structural abnormalities in first-episode remitted geriatric depression (RGD) with optimized voxel-based morphometry (VBM) in closely matched patients and healthy control subjects and examine the relationship of performances on neuropsychological tests with regional gray matter volumes.

Methods: Nineteen subjects with first-episode RGD and 16 well-matched healthy control subjects were recruited for this study, and neuropsychological tests and magnetic resonance imaging were conducted on the subjects. The differences in regional gray matter volume were determined between these two groups by optimized VBM.

Results: The volumes of right superior frontal cortex, left postcentral cortex, and right middle temporal gyrus were significantly smaller in patients with RGD relative to healthy control subjects. However, patients with RGD had larger left cingulate gyrus volume compared with healthy control subjects. There was a significant negative correlation between left cingulate gyrus volume and Rey Auditory Verbal Learning Test delayed recall raw score in patients with RGD.

Conclusion: These results reveal that RGD is associated with gray matter changes of certain brain regions hypothesized to influence cognition and might thus be involved in the psychopathology and pathophysiology of cognitive impairment in RGD.

Key Words: Cognitive deficit, gray matter, magnetic resonance imaging (MRI), remitted geriatric depression, voxel-based morphometry

Cognitive impairment is common in late-life depression (LLD). There have been many follow-up studies of older depressed adults with varying degrees of cognitive impairment, although the findings have been mixed, including marked or mild improvement in cognitive function and persistence of cognitive impairment or deterioration after the remission of depressive symptoms (1). Late-life depression with cognitive impairment has increased risk of conversion to dementia, and it might be a preclinical stage of dementia (2).

Despite increasing evidences for roles of structural and functional brain impairments in the etiology of LLD, the relationship between selective regional brain volume differences and cognitive deficits remains unclear. Previous morphometric magnetic resonance imaging (MRI) studies using region-of interest (ROI) analyses have revealed that elderly patients with major depressive disorder showed volume reduction in the prefrontal cortex (3), anterior cingulate cortex (3), hippocampus (4), and head of the caudate nucleus (5).

Voxel-based morphometry (VBM) is a user-independent, fully automated method of analysis that allows for unbiased exploration of brain structures without a priori specification of ROIs and can thus identify potentially unsuspected brain structure abnormalities (6). At present, however, VBM studies in patients with major depressive disorder are few (7,8). Only one study has addressed the association between structural alterations and cognitive dysfunction in unipolar depression (9), and no VBM study in patients with remitted geriatric depression (RGD) has investigated the relationship between cortical volume alterations and cognitive performances.

In this study, we hypothesize that gray matter abnormalities of some brain regions detected by VBM are correlated with cognitive deficits, and the abnormalities might be neuroimaging markers of cognitive deficits in the RGD patients.

Methods and Materials

Subjects
A total of 19 patients (9 men and 10 women; average age 67.1 ± 7.2 years) were recruited from the Affiliated Brain Hospital of Nanjing Medical University, China, from January 2007 to June 2007. All patients were interviewed in a semi-structured interview included in the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Clinician Version (10), by two trained and senior psychiatrists (Y.Y. and J.Y.). They met the following inclusion criteria: 1) met the major depressive disorder in DSM-IV criteria and remitted for more than 6 months before the enrollment; 2) in their first depressive episode, and the age of onset was over 60 years; 3) Hamilton Depression Rating scale (HDRS) scores were lower than 7, and Mini-Mental State Examination (MMSE) scores were higher than 24; 4) duration of illness was < 5 years, and the medication-free period for all subjects was longer than 3 month before the assessment; 5) absence of another major psychiatric illness, including substance abuse or dependence; 6) absence of primary neurological illness, including dementia or stroke; 7) absence of medical illness impairing cognitive function; 8) no history of receiving electroconvulsive therapy; and 9) T2-weighted MRI did not show any major white matter changes.
Table 1. Clinical Demographic and Neuropsychological Data Between RGD Patients and Healthy Control Subjects

<table>
<thead>
<tr>
<th>Items</th>
<th>RGD (n = 19)</th>
<th>Mean</th>
<th>SD</th>
<th>Healthy Control Subjects (n = 16)</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age, yrs</td>
<td>67.1</td>
<td>7.2</td>
<td>67.7</td>
<td>3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>9/10</td>
<td></td>
<td></td>
<td>8/8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>School Education, yrs</td>
<td>12.6</td>
<td>4.3</td>
<td>13.1</td>
<td>4.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Age at Onset, yrs</td>
<td>64.6</td>
<td>5.8</td>
<td></td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Duration of Illness, yrs</td>
<td>3.7</td>
<td>2.4</td>
<td>2.8</td>
<td>1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDRS</td>
<td>3.1</td>
<td>2.3</td>
<td>2.8</td>
<td>1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>27.9</td>
<td>2.6</td>
<td>28.1</td>
<td>1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVLT Delayed Recall (raw score)</td>
<td>5.9</td>
<td>2.9</td>
<td>9.4</td>
<td>1.6*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Making Test A (sec)</td>
<td>147.5</td>
<td>127.5</td>
<td>72.9</td>
<td>25.0*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Making Test B (sec)</td>
<td>264.0</td>
<td>197.5</td>
<td>121.4</td>
<td>35.5*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clock Drawing Test</td>
<td>8.7</td>
<td>2.2</td>
<td>9.1</td>
<td>1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span Test</td>
<td>11.5</td>
<td>3.5</td>
<td>13.2</td>
<td>2.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RGD, remitted geriatric depression; HDRS, Hamilton Depression Rating Scale; MMSE, Mini Mental State Exam; RAVLT, Rey Auditory Verbal Learning Test.

*p < .01, with Independent-sample t test, compared with RGD.

*p < .05, with Independent-sample t test, compared with RGD.

matters such as infarction or other vascular lesions. All patients received antidepressant medication: 11 patients received selective serotonin reuptake inhibitors, and 8 received serotonin and noradrenaline reuptake inhibitors. Sixteen well-matched healthy control subjects had also been recruited from the community, including 8 men and 8 women with average age of 67.7 (± 3.8) years. Healthy control subjects had no history of psychiatric disorder. They also met the inclusion criteria 3, 5, 6, 7, 8, and 9. All subjects gave written informed consent after the procedure had been carefully explained and after they had the opportunity to ask any questions they wanted. The research was approved by the Research Ethics Committee of Southeast University. All subjects were all unequivocally and naturally right-handed and of Han Chinese race.

Neuropsychological Test

All subjects received a cognitive battery with standardized administration by two psychiatrists (Y.Y. and J.Y.). The neuropsychological battery consists of Rey Auditory Verbal Learning Test (RAVLT), Trail Making Test A and B, Clock drawing test, and Digit span test. Table 1 contains descriptive demographic and neuropsychological data for the two groups.

MRI Data Acquisition

Subjects were scanned with a General Electric 1.5 Tesla scanner (General Electric Medical Systems, Milwaukee, Wisconsin) with a homogeneous birdcage head coil. High-resolution T1-weighted axial images covering the whole brain were acquired with a three-dimensional spoiled gradient echo (SPGR) sequence: repetition time = 9.9 ms; echo time = 2.1 ms; flip angle = 15°; acquisition matrix = 256 × 192; field of view = 240 mm × 240 mm; thickness = 2.0 mm; gap = 0 mm; number of excitations = 1.0.

Image Data Analysis

Structural data analysis and atrophy measurements were performed with optimized voxel-based morphometry (6). All anatomical data were processed with VBM5 toolbox (http://dbm.neuro.uni-jena.de/vbm) with the SPM5 software package (http://www.fil.ion.ucl.ac.uk/spm). The toolbox used segmentation algorithm from SPM5 and the extension of Hidden Markov Random Field approach. It has been demonstrated to be superior to previous SPM versions (6). The VBM5 toolbox was employed for the structural imaging analysis. During the preprocessing a modulation was performed on the gray matter images to compensate for the effect of spatial normalization. After the described procedure, statistical analysis was carried out with the voxel-wise comparison of the gray volume between RGD and healthy control subjects. A height threshold at p < .001 and an extent threshold more than 80 mm³ (a cluster size equal to 1 × 1 × 1 mm³) were employed at the group-difference t map to detect the local changes in brain volume.

Statistical Analyses

The statistical analyses were conducted with SPSS 10.0 software (SPSS, Chicago, Illinois). Independent-sample t test and χ² test were used to compare demographic data, HDRS scores, and performances of neuropsychological tests between two groups. In addition, we extracted the mean volumes of the clusters that had shown differences between the RGD patients and healthy control subjects. Mean volume measurements were calculated with a semi-automated imaging analysis program developed by us. Correlations between mean volumes of the clusters and the performances of neuropsychological tests in the RGD patients were calculated by Pearson correlation. Two-tailed levels of significance (p < .05) were used. The data were presented as mean (SD).

Results

No significant differences in age, gender distribution, years of education, scores for HDRS, MMSE, Clock drawing test, and Digit span test were observed between the RGD patients and healthy control subjects (all p > .05). However, the RGD patients performed significantly worse in the delayed recall of RAVLT,
A well-matched healthy subjects (13). We believe this finding of left postcentral gyrus was also found to be associated with episodic memory function. The finding has potential conflicts of interest.

Discussing the major finding of the present study is that the patients with RGD have significantly smaller volumes of right superior frontal gyrus, left postcentral gyrus, and right middle temporal gyrus and larger volume in left cingulate gyrus than age-matched healthy subjects.

Our findings of smaller regional gray matter volumes were consistent with previously studies of LLD (3,11). Decreased gray matter in these areas might suggest neuronal apoptosis or a loss of neuropil (12). Interestingly, the grey matter volume reduction of left postcentral gyrus was also found to be associated with RGD. The finding is unusual. This brain region is not typically implicated in mood disorders, although a recent study found that subjects with bipolar disorder exhibited significantly decreased cortical thickness in bilateral postcentral cortices compared with well-matched healthy subjects (13). We believe this finding warrants further investigation to clarify its significance.

Another major finding shows that the RGD patients have significantly worse function of episodic memory (indicated by RAVLT delayed recall) and executive function (indicated by Trail Making Test A and B (sec) when compared with the control group (p < .001, p < .05, and p < .05, respectively) (Table 1).

Optimized VBM analyses showed that RGD subjects had significantly smaller volumes in right superior frontal cortex (Brodmann area [BA] 6), left postcentral cortex (BA 3), and right middle temporal gyrus (BA 21) (Figure 1, Table 2) than healthy control subjects. Contrarily, larger volume in RGD subjects, compared with healthy control subjects, was found in left cingulate gyrus (BA 24) (Figure 1, Table 2).

In addition we found a significant negative correlation between left cingulate gyrus volume and RAVLT delayed recall raw score (r = −.526, p = .056) in patients with RGD. No significant correlations were found between the change of gray matter volume and duration of disease in RGD patients.

**Discussion**

The major finding of the present study is that the patients with RGD have significantly smaller volumes of right superior frontal gyrus, left postcentral gyrus, and right middle temporal gyrus and larger volume in left cingulate gyrus than age-matched healthy subjects.

Our findings of smaller regional gray matter volumes were consistent with previously studies of LLD (3,11). Decreased gray matter in these areas might suggest neuronal apoptosis or a loss of neuropil (12). Interestingly, the grey matter volume reduction of left postcentral gyrus was also found to be associated with RGD. The finding is unusual. This brain region is not typically implicated in mood disorders, although a recent study found that subjects with bipolar disorder exhibited significantly decreased cortical thickness in bilateral postcentral cortices compared with well-matched healthy subjects (13). We believe this finding warrants further investigation to clarify its significance.

Another major finding shows that the RGD patients have significantly worse function of episodic memory (indicated by RAVLT delayed recall) and executive function (indicated by Trail Making Test A and B) than the healthy control subjects. This is consistent with earlier reports that remitted depression had persistence of cognitive impairment (14,15). Our previous research demonstrated that cognitive deficits were associated with white matter integrity abnormality and resting state dysfunction of central brain regions in RGD patients (16,17). Interestingly, we find that the larger volume in left cingulate gyrus is negatively associated with episodic memory function. The finding has raised two possible explanations. One is that increased gray matter volume might be related to preapoptotic osmotic changes or hypertrophy, marking area of early neuronal pathology (12). Another explanation is that it might be associated with neuronal overgrowth or a deficit in the normal pruning process during neurogenesis and neural maturation after one successful course of antidepressant treatment (18,19). Therefore, we tentatively speculate that larger volume in the left cingulate gyrus might be involved in the psychopathology and pathophysiology of episodic memory in RGD, and it is perhaps the important early-stage neuroimaging marker of RGD subjects who might convert to Alzheimer’s disease.

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