Brief report

Larger regional white matter volume is associated with executive function deficit in remitted geriatric depression: An optimized voxel-based morphometry study

Yonggui Yuan\textsuperscript{a,b}, Zhijun Zhang\textsuperscript{a,c,*}, Feng Bai\textsuperscript{a}, Hui Yu\textsuperscript{a}, Jiayong You\textsuperscript{b}, Yongmei Shi\textsuperscript{c}, Yun Qian\textsuperscript{a}, Wen Liu\textsuperscript{b}, Tianzi Jiang\textsuperscript{d}

\textsuperscript{a} School of Clinical Medicine, Southeast University, Nanjing 210009, PR China
\textsuperscript{b} Department of Psychiatry, Nanjing Brain Hospital Affiliated to Nanjing Medical University, Nanjing 210029, PR China
\textsuperscript{c} Department of Neurology, Affiliated ZhongDa Hospital of Southeast University, Nanjing, 210009, PR China
\textsuperscript{d} National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing 100080, PR China

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Abstract

Objective: We aimed to investigate structural abnormalities in first-episode remitted geriatric depression (RGD) using optimized voxel-based morphometry (VBM) in closely matched patients and healthy controls, and examining the relationship of performances on neuropsychological tests with regional white matter volumes.

Methods: Forty subjects with first-episode RGD and 36 well-matched healthy controls were recruited for this study and neuropsychological tests and magnetic resonance imaging (MRI) were conducted on the subjects. The differences in regional white matter volume were determined between these two groups by optimized VBM.

Results: The white matter volumes of left inferior parietal lobule and right inferior frontal gyrus were significantly larger in patients with RGD relative to healthy controls. RGD patients performed significantly worse in the delayed recall of RA VLT, Trail Making Test A and B (seconds), and Symbol Digit Modalities Test when compared with the control group (all \( P < 0.01 \)). And there was a significant positive correlation between white matter volume of right inferior frontal gyrus and Trail Making Test A (\( r = 0.319 \), \( P = 0.045 \)) in patients with RGD.

Limitations: This study is cross-sectional, therefore it cannot determine whether increased white matter volume is a state marker or trait marker of RGD.

Conclusion: These results reveal that RGD is associated with larger white matter volumes of left inferior parietal lobule and right inferior frontal gyrus, and the right inferior frontal gyrus may thus be involved in the pathophysiology of executive function in RGD.

Keywords: Remitted geriatric depression; Executive function; White matter; Voxel-based morphometry (VBM); Magnetic resonance imaging (MRI)

1. Introduction

Depressed elderly often exhibit cognitive impairments that are substantial, prevalent, and disabling (Butters et al., 2004). Follow-up studies showed that

* Corresponding author. School of Clinical Medicine, Southeast University, Nanjing 210009, PR China. Fax: +86 25 8328 5132.
E-mail address: zhijunzhang838@yahoo.com.cn (Z. Zhang).

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45% patients with geriatric depression had persistence of cognitive impairment or deterioration after the remission of depressive symptoms (Butters et al., 2004; Bhalla et al., 2006). The patient of geriatric depression with cognitive impairment has increased risk of conversion to dementia, and it might be a preclinical stage of dementia (Kohn and Epstein-Lubow, 2006). Many researches suggest that the importance of genetic predisposition to affective disorders declines in geriatric depression (Baldwin, 2000), and may be replaced by associations with structural abnormalities of the brain (Lesser et al., 1991; Krishnan et al., 1993).

Increasing evidence showed that the abnormalities of microstructural white matter were associated with geriatric depression (Herrmann et al., 2008). Alexopoulos et al. (2008) found that lower fractional anisotropy in distributed cerebral networks was associated with poor antidepressant response of geriatric depression. Some studies also reported that white matter hyperintensities of geriatric depression were related to cognitive decline in various domains, particularly executive skills, attention and mental speed (Lesser et al., 1996; Kramer-Ginsberg et al., 1999; Murata et al., 2001). Therefore, there are no published studies examining the white matter volume alterations and cognitive performances in geriatric depression (RGD). In this study, we hypothesize that white matter abnormalities of some brain regions detected by optimized VBM are correlated with RGD, and the abnormalities might be one of neuroimaging markers of cognitive deficits in the RGD patients.

2. Subjects and methods

2.1. Subjects

A total of 40 patients (15 male and 25 female; average age 70.3 ±4.0 years) were recruited from the Affiliated Brain Hospital of Nanjing Medical University, China, from January 2007 to December 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 (First et al., 1997), by two trained and senior psychiatrists (Y Yuan and J You). The detailed inclusion criteria were described in Yuan et al. (2008). All patients received antidepressant medication: 28 patients treated by selective serotonin reuptake inhibitors and 12 patients treated by serotonin and noradrenaline reuptake inhibitors. Thirty-six well-matched healthy controls had also been recruited from the community, including 18 male and 18 female with average age of 70.5 ±3.8 years. Healthy controls also met the inclusion criteria described in Yuan et al. (in press). All subjects were all unequivocally and naturally right-handed and Han Chinese race. Written informed consent was obtained after a full written and verbal explanation of the study. The research was approved by the Research Ethics Committee of Southeast University.

2.2. Neuropsychological test

All subjects received a neuropsychological battery using standardized administration by two psychiatrists (Y Yuan and J You). The neuropsychological battery consists of Rey Auditory Verbal Learning Test (RAVLT), Rey—Osterrieth Complex Figure Test (CFT), Digit Span Test, Symbol Digit Modalities Test, Trail Making Test A and B, and Clock Drawing Test. Table 1 contains descriptive demographic and neuropsychological data for the two groups.

<table>
<thead>
<tr>
<th>Items</th>
<th>RGD (n=40)</th>
<th>Healthy controls (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years</td>
<td>70.3 ±4.0</td>
<td>70.5 ±3.8</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>15/25</td>
<td>18/18</td>
</tr>
<tr>
<td>School education in years</td>
<td>14.3 ±1.8</td>
<td>14.4 ±3.1</td>
</tr>
<tr>
<td>Mean age at onset in years</td>
<td>64.8 ±4.3</td>
<td>–</td>
</tr>
<tr>
<td>Mean duration of illness in years</td>
<td>3.2 ±1.3</td>
<td>–</td>
</tr>
<tr>
<td>Mean duration of depressive illness prior to remission</td>
<td>2.3 ±1.1</td>
<td>–</td>
</tr>
<tr>
<td>Mean period of exposure to antidepressants</td>
<td>2.1 ±0.9</td>
<td>–</td>
</tr>
<tr>
<td>Mean duration between remission and the scan</td>
<td>0.9 ±0.3</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviations: RGD, remitted geriatric depression; HDRS, Hamilton Depression Rating Scale; MMSE, Mini Mental State Exam; RAVLT, Rey Auditory Verbal Learning Test; CFT, Rey–Osterrieth Complex Figure Test. *P<0.01 statistical significance between RGD and healthy controls.
2.3. MRI data acquisition

Subjects were scanned using a General Electric 1.5 Tesla scanner (General Electric Medical Systems, USA) with a homogeneous birdcage head coil. High-resolution T1-weighted axial images covering the whole brain were acquired using a 3D spoiled gradient echo (SPGR) sequence: repetition time=9.9 ms; echo time=2.1 ms; flip angle (FA)=15°; acquisition matrix=256×192; field of view=240 mm×240 mm; thickness=2.0 mm; gap=0 mm; number of excitations=1.0.

2.4. Image data analysis

Structural data analysis and atrophy measurements were performed with optimized VBM. All anatomical data were processed using 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. The VBM5 toolbox was employed for the structural imaging analysis. During the preprocessing a modulation was performed on the white matter images to compensate for the effect of spatial normalization. Following the described procedure, statistical analysis was carried out with the voxel-wise comparison of the white matter volume between RGD and healthy controls. A height threshold at \( P < 0.001 \) and an extent threshold more than 100 mm\(^3\) (a cluster size is 1.0 mm × 1.0 mm × 1.0 mm) were employed to the group-difference t map to detect the local changes in brain volume.

2.5. Statistical analyses

The statistical analyses were conducted with SPSS 10.0 software (SPSS Inc., Chicago, IL, USA). Independent-sample t-test and chi-square 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 controls. Mean volume measurements were calculated using a semi-automated imaging analysis program developed by Dr. W Zhu at Institute of Automation, Chinese Academy of Sciences. 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 (\( P < 0.05 \)) were used. The data were presented as mean (standard deviation).

3. Results

No significant differences in age, sex distribution, years of education, scores for HDRS, MMSE, CFT delayed recall, Digit Span Test and Clock Drawing Test were observed between the RGD patients and healthy controls (all \( P > 0.05 \)). However, the RGD patients performed significantly worse in the delayed recall of RAVLT, Trail Making Test A and B (seconds), Symbol Digit Modalities Test when compared with the control group (all \( P < 0.01 \)) (as shown on Table 1).

Optimized VBM analyses showed that RGD subjects had significantly larger white matter volumes in left inferior parietal lobule (IPL) and right inferior frontal gyrus (IFG) (Fig. 1, Table 2) than healthy controls. No region of significantly smaller white matter volume was identified in RGD subjects as compared with the controls.

There was a significant positive correlation between white matter volume of right IFG and Trail Making Test A (\( r = 0.319, P = 0.045 \)) in patients with RGD. But a significant negative correlation was found between white matter volume of left IPL and Trail Making Test A (\( r = -0.336, P = 0.045 \)) in the healthy controls. No

Fig. 1. Results from an optimized voxel-based morphometry (VBM) analysis, showing that RGD subjects had larger white matter volumes in the left inferior parietal lobule (a) and right inferior frontal gyrus (b) than healthy controls at a threshold of \( P_{\text{uncorrected}} < 0.001 \), extent threshold = 100 mm\(^3\). The study compared 40 RGD subjects with 36 healthy controls. Color scale: 0–4 represents Z score.
significant correlations were found between the changes of white matter volume and duration of disease, duration of depressive illness prior to remission, period of exposure to antidepressants, and the duration between remission and the scan in RGD patients.

4. Discussion

The major finding of the present study is that the patients with RGD have significantly larger white matter volumes of left IPL and right IFG than age-matched healthy subjects. Interestingly, we find that the larger white matter volume in right IFG is related to the impairment of executive function in RGD patients; however, the white matter volume in left IPL is positively associated with executive function in the healthy controls.

Two possible factors might underlie the negative association between the white matter volume of right IFG and the executive function. Firstly, the increased white matter volume may be related to preapoptotic osmotic changes or hypertrophy, marking area of early neuronal pathology (Adler et al., 2005). Secondly, the increased white matter volume might be also associated with certain neuronal overgrowth or a deficit in the normal pruning process during neurogenesis and neural maturation after one successful course of antidepressant treatment (Lavretsky et al., 2005; Adler et al., 2007). Additionally, our previous DTI research demonstrated that executive function was associated with white matter integrity abnormality of the right superior frontal gyrus in RGD patients (Yuan et al., 2007). Therefore, the abnormalities of microstructural white matter in the right frontal lobe might be involved in the pathophysiology of executive function in RGD.

Another major finding shows that the RGD patients exhibit several impaired component of cognition, including episodic memory (indicated by RAVLT delayed recall), psychomotor speed (indicated by Symbol Digit Modalities Test) and executive functioning (indicated by Trail Making Test A and B). The results are consistent with the previous reports (Butters et al., 2004; Bhalla et al., 2006; Lee et al., 2007). Our findings suggest that a broad range of cognitive impairments still persist after the remission of depression. However, the present study is a cross-sectional case control study but not a follow-up study. It remains unclear whether these cognitive deficits will continue in a degenerative fashion and whether these individuals are at greater risk for developing a frank dementia (Bhalla et al., 2006). In further study, we will undertake the follow-up research in late-life geriatric depressive patients to further elucidate the possible mechanism of cognitive impairment of RGD.

5. Conclusion

Our optimized VBM study indicates that RGD is associated with larger white matter volumes of left IPL and right IFG, and the right inferior frontal gyrus may thus be involved in the pathophysiology of executive function in RGD. Further work is needed to determine how these white matter abnormalities contribute to cognitive function of RGD.

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Conflict of interest

No conflict declared.

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<table>
<thead>
<tr>
<th>Brain region</th>
<th>Cluster size (mm³)</th>
<th>Z score</th>
<th>Puncorrected</th>
<th>x, y, z (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left inferior parietal lobule</td>
<td>137</td>
<td>3.57</td>
<td>0.000</td>
<td>−54, −43, 21</td>
</tr>
<tr>
<td>Right inferior frontal gyrus</td>
<td>206</td>
<td>3.47</td>
<td>0.000</td>
<td>27, 30, −3</td>
</tr>
</tbody>
</table>

Abbreviations: RGD, remitted geriatric depression; VBM, voxel-based morphometry; BA, Brodmann’s area; the threshold was set at P<0.001 (SPM random effects analysis; uncorrected); cluster size is more than 100 mm³, Z scores are expressed as the maximum with each area (MaxZ). Local maxima are separated by a minimum of 12 mm. RGD subjects, n=40, healthy controls, n=36.
References


