ORIGINAL ARTICLE

Grey matter volume changes over the whole brain in amyotrophic lateral sclerosis: A voxel-wise meta-analysis of voxel based morphometry studies

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Abstract
Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease with selected both upper and lower motor neuron involvement. Although some inconsistent results exist, both pathological studies and many structural neuroimaging studies have revealed brain volume changes in ALS. To provide an objective overview of structural changes in ALS, a voxel-wise meta-analysis was performed in published voxel based morphometry (VBM) studies. A systematic search of VBM studies was applied in ALS. Five studies met the inclusion criteria, comprising 84 ALS patients and 81 normal controls. A voxel-wise meta-analysis was performed on the retrieved VBM studies using signed differential mapping. Descriptive analysis showed that 25% of ALS patients had right precentral gyrus atrophy (2373 voxels). Group analysis demonstrated regional grey matter loss over the whole brain in the right precentral gyrus \( p = 7.96 \times 10^{-4} \). Sensitivity analysis showed good sensitivity (157 voxels). In conclusion, right precentral grey matter atrophy was a common finding and prominent feature of brain structural changes in ALS.

Key words: Amyotrophic lateral sclerosis, precentral gyrus, meta-analysis, voxel based morphometry

Introduction
Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease with selected both upper and lower motor neuron involvement (1,2). Pathological changes in cerebral cortical regions in ALS were confirmed as selective involvement of the motor cortex in a post mortem study (3). With the development of advanced computed neuroimaging, a novel automatic in vivo brain structural measurement technique, voxel-based morphometry (VBM) (4), has been developed, which provides a feasible and effective tool for brain structure research.

In ALS, VBM studies showed that grey and white matter volume decreased widely, especially in the motor cortex (5,6), frontal and temporal regions (6–8), corpus callosum (9) and amygdala (10). However, one study found no volume reduction in primary motor cortices in ALS patients (11). These results were inconsistent to some extent and may be associated with many factors, including covariates, matching, sample size (12), image resolution (13), normalization template (14), threshold masking (15), imaging protocol (16), registration (17,18), full width half-maximum (FWHM) (19,20) and statistical model (21). Other impact factors included some different clinical variables such as disease duration, cognitive state, and functional rating scores, etc. Although the inconsistency existed, individual VBM study revealed brain structural changes, especially subtle changes over the whole brain in ALS. Voxel-wise meta-analysis could further integrate VBM findings or other functional neuroimaging studies, and obtain consistent results across different studies. Also, it has been used in obsessive-compulsive disorder (22), swallowing (23), emotional faces processing (24), etc. This analysis has been increasingly used to summarize functional neuroimaging results, and it can powerfully localize the active region or structural change region in neuroimaging studies. Meta-analysis methods mainly included kernel density analysis (KDA) (25), activation likelihood estimate (ALE) analysis (26), and multilevel kernel
density analysis (MKDA) (27). A novel voxel-wise meta-analysis technique, signed differential mapping (SDM) (22), is a quantitative meta-analysis method, combining various positive features of ALE and MKDA, and has been successfully used for meta-analysis in obsessive-compulsive disorder (28).

To our knowledge, no voxel-wise meta-analysis on VBM studies in ALS has been reported. The aim of this study was to determine grey matter volume changes over the whole brain in ALS patients using SDM, and to identify possible specific aggregate changes in ALS.

Materials and methods

Search strategy

A focused search strategy was designed as follows: in patients with ALS, brain structural changes over the whole brain were analyzed using voxel-based morphometry. The databases included Medline and PubMed. The first search expression included ‘amyotrophic lateral sclerosis’ and ‘motor neuron disease’. The second search expression included ‘voxel-based’, ‘voxel-wise’, ‘morphometry’, and ‘voxel based morphometry’. This search strategy was performed on Medline and PubMed, and the operator AND was used between different concepts and operator OR was used between similar concepts. In addition, retrospective search and Google Scholar were also applied.

Studies were included in this project if they met the following criteria: 1) VBM over the whole brain; 2) available peak coordinate for VBM; 3) sporadic ALS.

Studies were excluded from the project if they were in line with exclusion criteria: 1) non-whole brain analysis; 2) not using VBM; 3) familial ALS; 4) not listing the coordinate in the article.

Voxel-wise meta-analysis of VBM

Voxel-wise meta-analysis was performed in the included VBM studies using signed differential mapping (SDM) (http://www.sdmproject.com/) (28). Descriptive analysis, group analysis and sensitivity analysis were carried out. In a pre-processing step, a relatively wide full width at half-maximum (FWHM, 25 mm) was used in order to account for different sources of spatial error, coregistration mismatch in the studies, and the size of the cluster or the location of the peak within the cluster. The statistical threshold was set to a \( p \)-value of <0.001 without correction for false discovery rate (FDR).

Results

Included VBM studies

Up to April 2010, a total of 52 articles were selected, including 39 articles without brain morphometry...
research and 13 articles with brain morphometry research. Of the 13 articles, five were included according to the inclusion criteria, and eight articles met the exclusion criteria (three not using VBM and five not listing the coordinate in the article). The included five VBM studies (6,11,29–31) included 84 ALS patients (mean age 51.6 years, F: M = 7: 13) and 81 normal controls (mean age 51 years, F: M = 1: 1). The ALS patients had mean disease duration of 27.5 months; 24 patients had bulbar onset and 60 patients had limb onset. The clinical details are shown in Table I.

The technique details of the included VBM studies are described in Table II. MR scanners used in all the included studies were 1.5 T MR systems, and analysis software included Statistical Parametric Mapping 2 (SPM2) (four studies) and Analysis of Functional NeuroImages (AFNI) (one study). The VBM preprocessing procedure basically included three steps: normalization, segmentation, and smoothing. The smoothing kernel was 8–12 mm FWHM and one study’s smoothing kernel was not available. The statistical threshold was $p < 0.001-0.0025$, and one study $p < 0.05$ (FDR corrected).

**Descriptive analysis**

All the included coordinates are shown in Figure 1. It showed that the significant clusters of the included VBM studies were mainly located in bilateral precentral gyri, frontal, temporal lobe, and left occipital and insula lobe.

Descriptive analysis of quartiles was conducted with the included studies (Table III). Quartiles25 showed that 75% of studies detected atrophy of bilateral cingulate gyri and left inferior parietal lobe. Quartiles50 showed that 50% of studies detected right precentral gyrus atrophy (4795 voxels), right lentiform nucleus atrophy (68 voxels), and left middle frontal gyrus atrophy (6282 voxels). Quartiles75 showed that 25% of studies detected right precentral gyrus atrophy (two clusters, 2373 voxels), and other volume loss clusters located in the bilateral frontal lobe (especially right frontal lobe). From the descriptive analysis of quartiles, it was found that 25%–50% of studies detected right precentral gyrus atrophy in ALS patients.

**Group analysis (regional difference in grey matter over the whole brain)**

Group analysis was applied between ALS and control. Regional grey matter volume loss was mainly located in the right precentral gyrus ($11$ voxels, $p = 0.00796$, BA 4), and no other regions were found to have grey matter volume loss (Table IV, Figure 2).

**Sensitivity analysis**

Jackknife sensitivity analysis showed regional grey matter volume loss in right precentral gyrus (two clusters, 157 voxels) and left insula (one cluster, 18 voxels) (Table IV). The regional pattern of grey matter atrophy in the right precentral gyrus had a good reproducibility and it occurred in three of five included VBM studies.

**Discussion**

This meta-analysis used SDM (28) technique to summarize the results across published VBM studies on ALS. All the included VBM studies were papers published in peer-reviewed journals, followed the same inclusion criteria, and showed the peak cluster coordinates of grey matter volume deficit. The aim of this meta-analysis was to provide a grey matter volume deficit mapping of ALS compared with healthy controls.

In this study, a novel voxel-wise meta-analysis technique was adopted to detect grey matter atrophy pattern. Compared with an individual VBM study, this technique established consistent VBM results from the included studies, and it also developed

<table>
<thead>
<tr>
<th>Study</th>
<th>MRI scanner</th>
<th>Software</th>
<th>VBM process</th>
<th>Smoothing</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al.</td>
<td>1.5 T (GE,</td>
<td>SPM2</td>
<td>Normalize to common template, segmented grey and white matter voxels value were multiplied by the Jacobian determinants</td>
<td>12mm</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td></td>
<td>Milwaukee, WI)</td>
<td></td>
<td></td>
<td>FWHM</td>
<td>(uncorrected)</td>
</tr>
<tr>
<td>Thivard et al.</td>
<td>1.5 T (GE,</td>
<td>SPM2</td>
<td>Classic normalize, segment (with Hidden Markov Random Field approach), and smooth</td>
<td>10mm</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td></td>
<td>Milwaukee, WI)</td>
<td></td>
<td></td>
<td>FWHM</td>
<td>(FDR corrected)</td>
</tr>
<tr>
<td>Ellis et al.</td>
<td>1.5 T (GE,</td>
<td>AFNI</td>
<td>Using a computational algorithm to remove the extracerebral tissues, and manually segmenting the grey matter, white matter and CSF, then using AFNI software to infer difference in tissue distribution between groups</td>
<td>N/A</td>
<td>$p &lt; 0.0025$</td>
</tr>
<tr>
<td></td>
<td>Milwaukee, WI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mezzapesa et al.</td>
<td>1.5 T (GE)</td>
<td>SPM2</td>
<td>Generation of customized and prior probability maps (GM, WM, and CSF); then original images were normalized to the same stereotactic space and partitioned into GM, WM and CSF</td>
<td>12mm</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FWHM</td>
<td>(uncorrected)</td>
</tr>
<tr>
<td>Grosskreutz et al.</td>
<td>1.5 T (GE,</td>
<td>SPM2</td>
<td>Creating a customized template followed by normalization and segmentation with modulation of Jacobian determinants</td>
<td>8mm</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td></td>
<td>Milwaukee, WI)</td>
<td></td>
<td></td>
<td>FWHM</td>
<td>(uncorrected)</td>
</tr>
</tbody>
</table>
some hypotheses derived from studies of brain-damaged patients (32). SDM has been successfully used in the study of obsessive-compulsive disorder, and it has stricter selection criteria with regard to the reported peak coordinates and used a 25-mm FWHM adapted from that of ALE and preferred to that of MKDA (28). In this study, voxel-wise meta-analysis was conducted by using SDM, and the negative coordinates were used to reconstruct the signed differential mapping.

Table III. Regional grey matter deficit of ALS at different quartiles.

<table>
<thead>
<tr>
<th>Quartiles</th>
<th>Talairach coordinates</th>
<th>SDM value</th>
<th>Number of voxels</th>
<th>Cluster location</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartiles25</td>
<td>−60,−22,26</td>
<td>−1.000</td>
<td>28153</td>
<td>Left inferior parietal lobule</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>−4,−28,22</td>
<td>−0.174</td>
<td>32</td>
<td>Left posterior cingulate</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>6,−6,26</td>
<td>−0.092</td>
<td>13</td>
<td>Right cingulate gyrus</td>
<td>24</td>
</tr>
<tr>
<td>Quartiles50</td>
<td>36,−24,54</td>
<td>−0.763</td>
<td>4795</td>
<td>Right precentral gyrus</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>−36,34,34</td>
<td>−0.607</td>
<td>6282</td>
<td>Left middle frontal gyrus</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>18,−4,−4</td>
<td>−0.093</td>
<td>68</td>
<td>Right lentiform nucleus Medial globus pallidus</td>
<td></td>
</tr>
<tr>
<td>Quartiles75</td>
<td>−36,24,30</td>
<td>−0.273</td>
<td>507</td>
<td>Left middle frontal gyrus</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>24,40,32</td>
<td>−0.195</td>
<td>197</td>
<td>Right superior frontal gyrus</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>50,−2,6</td>
<td>−0.194</td>
<td>2360</td>
<td>Right precentral gyrus</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>30,−6,44</td>
<td>−0.166</td>
<td>92</td>
<td>Right middle frontal gyrus</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>40,−18,38</td>
<td>−0.103</td>
<td>13</td>
<td>Right precentral gyrus</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>34,26,34</td>
<td>−0.095</td>
<td>13</td>
<td>Right middle frontal gyrus</td>
<td>9</td>
</tr>
</tbody>
</table>

∗Continued voxels (> 10) was considered significant (SDM value < −0.001). BA: Brodmann area.
By reviewing all the included VBM studies of ALS, it was found that ALS was not only a motor neuron disease (MND) but also a multisystem disease. ALS involved the bilateral precentral gyri as well as other brain regions. After descriptive analysis of quartiles, it was revealed that 25%–50% of VBM studies detected right precentral gyrus atrophy, and 25% detected frontal lobe (bilateral middle frontal and right superior frontal gyrus) atrophy. Group analysis further showed that only right precentral gyrus demonstrated atrophy, which should be a specific grey matter atrophy pattern for ALS according to this voxel-wise meta-analysis. Moreover, sensitivity analysis showed that right precentral gyrus atrophy had good sensitivity and reproducibility. Thus, right precentral gyrus atrophy may be a relatively common and specific finding in ALS, and more attention should be paid to this region in ALS patients, which may provide more information for clinical evaluation. Post mortem study (3) revealed the absence of Betz cells from layer 5 of the precentral cortex and the remaining pyramidal cells were significantly smaller than those seen in normal controls; in vivo brain structural volume changes could be effectively assessed by using VBM, and voxel-wise meta-analysis of VBM could be used to summarize the results of different laboratories and obtain consistent findings, and thus it should be more conclusive than individual VBM study.

This meta-analysis study showed only the right precentral gyrus volume deficit, and this atrophy pattern presented asymmetry in ALS. The selective right precentral gyrus atrophy may be associated with neuronal degeneration in this area. Reasons for right precentral gyrus atrophy in ALS remain unknown, but the phenomenon is of great interest and further clinical study and structural asymmetry (33) study are needed to elucidate the underlying mechanism(s).

A limitation of our study is that the number of included VBM studies was relatively small as ALS is an uncommon disease. Future studies needed to carry out further VBM studies should be of larger sample size.

In summary, voxel-wise meta-analysis of VBM studies revealed that right precentral gyrus atrophy may be a specific grey matter volume deficit pattern for ALS.

Table IV. Group analysis and sensitivity analysis for VBM studies on ALS.

<table>
<thead>
<tr>
<th>Group analysis</th>
<th>Talairach coordinates</th>
<th>SDM value</th>
<th>p-value ($\times 10^{-4}$)</th>
<th>Number of voxels $^*$</th>
<th>Cluster location</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>36,–24,54</td>
<td>–0.525</td>
<td>7.96</td>
<td>11</td>
<td>Right precentral gyrus</td>
<td>4</td>
</tr>
<tr>
<td>Jackknife sensitivity analysis</td>
<td>36,–24,54</td>
<td>–0.653</td>
<td>5.17</td>
<td>41</td>
<td>Right precentral gyrus</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>36,–24,54</td>
<td>–0.653</td>
<td>2.02</td>
<td>116</td>
<td>Right precentral gyrus</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>–42,12,–2</td>
<td>–0.575</td>
<td>5.90</td>
<td>18</td>
<td>Left insula</td>
<td>13</td>
</tr>
</tbody>
</table>

$^*$Continued voxels ($>10$) was considered significant (SDM value $<-0.001$). BA: Brodmann area.

Figure 2. Regional grey matter volume loss in right precentral gyrus in ALS compared with normal control. The cluster representing atrophy of the right precentral gyrus (BA 4) is rendered on the template.
Acknowledgement

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References