Anatomical Increased/Decreased Changes in the Brain Area Following Individuals with Chronic Traumatic Complete Thoracic Spinal Cord Injury

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ABSTRACT. Objectives: This study aimed to investigate anatomical changes in the brain following chronic complete traumatic thoracic spinal cord injury (ThSCI) using voxel-based morphometry (VBM). That is, it attempted to examine dynamic physical change following thoracic injury and the presence or absence of regions with decreased and increased changes in whole brain volume associated with change in the manner of how activities of daily living are performed. Methods: Twelve individuals with chronic traumatic complete ThSCI (age; 21-63 years, American Spinal Injury Association Impairment Scale; grade C-D) participated in this study. VBM was used to investigate the regions with increased volume and decreased volume in the brain in comparison with healthy control individuals. Results: Decreases in volume were noted in areas associated with motor and somatosensory functions, including the right paracentral lobule (PCL) — the primary motor sensory area for lower limbs, left dorsal premotor cortex, and left superior parietal lobule (SPL). Furthermore, increased gray matter volume was noted in the primary sensorimotor area for fingers and arms, as well as in higher sensory areas. Conclusions: Following SCI both regions with increased volume and regions with decreased volume were present in the brain in accordance with changes in physical function. Using longitudinal observation, anatomical changes in the brain may be used to determine the rehabilitation effect by comparing present cases with cases with cervical SCI or cases with incomplete palsy.

Key words: Spinal cord injury, Voxel-based morphometry, Anatomical change, Brain, Rehabilitation

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The pathological characteristic of spinal cord injury (SCI) is impairment in the neural transmission between the brain and any site below the injury site of the spinal cord through interruption in afferent and efferent fibers. In recent years, studies on SCI using animal models and humans reported that atrophic neuronal changes in the sensory-motor system could occur, in addition to the spinal cord, in brain regions without lesions. Meanwhile, neural restructuring was shown to occur in the cortical area in association with the recovery of motility through rehabilitation following SCI.

Voxel-based morphometry (VBM) is one of the ways to investigate non-invasively anatomical changes in the human brain. Several studies have been reported that used VBM to investigate anatomical changes in the gray matter (GM) and white matter (WM) following SCI. However, the results varied considerably between them. One study reported that no atrophic change was noted in gray matter volume (GMV) in the primary motor area, which is responsible for movement, while other studies reported that the GMV decreased significantly compared to that in healthy control individuals, and no consensus has been reached. The variation in these results may be due to differences in the selection of study participants in terms of site of SCI, time from the injury, injury type (traumatic or non-traumatic), and complete or incomplete injury.

VBM analysis results indicated the degree of motility recovery and associated areas. Anatomical changes in the brain may be used as a biomarker for the prognosis of SCI.
motility recovery following SCI and the development of rehabilitation therapy. Adjusting selection criteria for study participants and investigating morphological changes in the brain following SCI is a study of high clinical significance.

The aim of this study is to investigate morphological changes in the brain of individuals in the chronic complete traumatic thoracic spinal cord injury (ThSCI) using VBM. A notable study on the chronic complete ThSCI using VBM was reported by Wringle et al.\textsuperscript{12}), which revealed volume reduction in the primary motor cortex and cognitive regions (temporal cortex, anterior cingulate cortex, prefrontal cortex, etc.) compared to those in healthy control individuals. However, their report only investigated areas with reduced volume and no results for areas with increased volume were shown. ThSCI undergoes dynamic physical changes in a manner related to activities of daily living. Therefore, we investigated not only the atrophic region of the brain volume but also the region which showed increased brain volume.

**Methods**

**Participants**

Twelve individuals with chronic traumatic complete ThSCI [mean (SD) age was 43 (14) years, range 21 - 63 years, 3 females] were recruited for this study from the Chiba Rehabilitation Center (Chiba, Japan), who fulfilled the following inclusive criteria, over 6 months onset injury, clinically lower limb motor complete, no head or brain region, no seizure, no medial or mental illness, no contraindications (Table 1). Twelve healthy participants participated in the control group [mean (SD) age was 38 (12) years, range 22 - 61 years, 3 females]. Their median age was not significantly different from ThSCI individuals (Mann-Whitney U test, p = 0.01). They had no neurological disease or history of psychiatric diseases. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Commission of Chiba Rehabilitation Center, Japan (Approval number: Medical 30-12). Written informed consent was obtained from all participants.

**MRI acquisition**

All participants were scanned on a 3T MRI scanner (Magnetom Skyra, Siemens Medical Solutions, Erlangen, Germany) operated with a radio frequency body transmit and a 32-channel birdcage head coil. Sagittal high-resolution 3D T1-weighted anatomical images were acquired using a magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence with the following parameters: repetition time (TR) = 2,700 ms, echo time (TE) = 2.33 ms, flip angle (FA) = 7°, slice thickness = 1.0 mm with no gap, matrix size = 256 × 256, field of view (FOV) = 256 mm × 256 mm. The acquisition time was approximately 5 min for this sequence.

**VBM data analysis**

VBM analysis was processed using SPM12 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/), compiled with the MATLAB version R2014a (MathWorks, Natick, MA, United States) with the VBM module. First, every scan was aligned to the anterior commissure manually. T1-weighted MR images were segmented into gray matter, white matter, cerebrospinal fluid, bone, soft tissue, and air/background after bias regularization. Images of gray matter and white matter were spatially normalized to the Montreal Neurological Institute (MNI) space through diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) algorithm\textsuperscript{18,19}). The total amount of GMV and white matter volume (WMV) of each voxel was

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**Table 1. Characteristics of individuals with spinal cord injury.**

<table>
<thead>
<tr>
<th>ID</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Time since injury (days)</th>
<th>Level of lesion</th>
<th>AIS classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>M</td>
<td>181</td>
<td>Th11</td>
<td>A</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>M</td>
<td>184</td>
<td>Th10</td>
<td>A</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>M</td>
<td>252</td>
<td>Th5</td>
<td>A</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>F</td>
<td>301</td>
<td>Th2</td>
<td>A</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>M</td>
<td>180</td>
<td>Th4</td>
<td>A</td>
</tr>
<tr>
<td>6</td>
<td>51</td>
<td>M</td>
<td>298</td>
<td>Th9</td>
<td>A</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>F</td>
<td>225</td>
<td>Th11</td>
<td>A</td>
</tr>
<tr>
<td>8</td>
<td>54</td>
<td>M</td>
<td>229</td>
<td>Th10</td>
<td>A</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>M</td>
<td>244</td>
<td>Th5</td>
<td>A</td>
</tr>
<tr>
<td>10</td>
<td>45</td>
<td>M</td>
<td>201</td>
<td>Th7</td>
<td>A</td>
</tr>
<tr>
<td>11</td>
<td>53</td>
<td>F</td>
<td>282</td>
<td>Th8</td>
<td>A</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>M</td>
<td>192</td>
<td>Th10</td>
<td>A</td>
</tr>
</tbody>
</table>

Mean±SD 43±14 231±43

Gender; M = male; F = female. Level of lesion; Th = thoracic level SCI. AIS classification A; complete - no sensory or motor function is preserved in sacral segments S4-S5. SD = standard deviation.
obtained through modulation. Additionally, the resulting GM and WM images were smoothed with a Gaussian kernel with a full width at half maximum (FWHM) of 8 mm. Finally, the total GMV and WMV was calculated based on the modulated images and total intracranial volume (TIV) was calculated as the sum of GMV and WMV.

**VBM statistical analysis**

GMV and WMV alterations were assessed by comparing SCI with controls, using the standard general linear model (GLM) implementation in SPM12 for independent two-sample t-tests. Age, gender, and TIV were modeled as covariates of no interest. Statistical parametric maps of two different contrasts (Controls > SCI and SCI > Controls) were created by applying a significant threshold of p < 0.001 (uncorrected) and a cluster size of 10 voxels.

**Results**

We have conducted a whole-brain voxel-based analysis of GMV and WMV in healthy control individuals and individuals with ThSCI by using the VBM approach. Compared with healthy controls, individuals with ThSCI had significantly decreased regional GMV in the right paracentral lobe (PCL), left dorsal premotor cortex (PMd), right superior temporal gyrus (STG), left middle frontal gyrus (MFG), left superior parietal lobe (SPL), left amygdala, right parahippocampus, and lower WMV in the right subcortical PCL (Table 2, Fig. 1).

On the other hand, compared to healthy controls, individuals with ThSCI had significantly increased regional GMV in the left primary sensorimotor cortex (SM1), and right precuneus. Furthermore, they had significantly increased regional WMV in the left posterior limb of the internal capsule (ICpost) and right subcortical occipital lobe (OCL) (Table 3, Fig. 2).

**Discussion**

As we compared changes in the cerebral structure of chronic phase ThSCI cases with healthy control individuals, we revealed volume reduction in regions associated with sensory/motor functions such as right PCL — the primary SM1 for lower limbs, left PMd, and left SPL. Additionally, significant volume reduction was observed in cognitive areas such as the right STG, left amygdala, and right parahippocampal gyrus. Furthermore, several regions with increased volume were noted in the ThSCI group.

Individuals with SCI lose motor or sensory functions below the level of the injury site due to degeneration of afferent and efferent motor fibers. Moreover, studies have reported that motor command signals from the brain as well as sensory feedback from the periphery are blocked in the SCI site, causing functional and structural alterations in the brain. In the VBM of the brain, GMV reflects atrophic or increasing changes in functional localization, while WM reflects changes in projective fibers, such as the corticospinal tract and associative fibers.

Several studies reported changes in GMV in the brain of individuals with SCI, demonstrating volume reduction mainly in the primary motor cortex (M1) and primary and secondary somatosensory cortex. Among these studies, a study on complete ThSCI using VBM revealed volume reduction in the SM1 for lower limbs, and similar results were obtained in the present study, in which volume reduction occurred in the same area. Similarly, studies on individuals with hemiplegia following subcortical stroke reported GMV reduction in the SM1 in the injured hemisphere. Anatomical change is believed to occur in the motor region of the brain because of long-term non-use and incompetence of paralyzed limbs following the disease onset. In our study, the non-use of lower limbs by participants, due to paralysis in lower limbs following ThSCI, was associated with reduced GMV in PCL. Similarly, the reduced WMV in the subcortical area of the right PCL is considered to be a result of the decline in fibers that project signals from the PCL, according to the same mechanism as GMV.

With regard to sensory/motor regions, GMV reduction was noted in the PMd and SPL. The PMd is a higher motor area associated with motor preparation, which has been demonstrated to function with the M1 during voluntary movement and represents the somatotopy of lower limbs. Loss of motility in lower limbs is thought to have resulted in the volume reduction in the area corresponding to lower limbs in PMd. In addition, SPL is a higher somatosensory area and it can be inferred that loss of input into the primary sensory region associated with the interruption of afferent fibers caused GMV reduction in the same region as a secondary phenomenon.

In the present study, volume reduction was also observed in cognitive regions. Previous studies reported GMV decline in the prefrontal cortex and limbic system, including anterior cingulate cortex, STG, and amygdala. Likewise, in this study, the volume decline was observed in nearly the same regions. Although change in the emotional aspect following SCI may have contributed to the volume reduction, it is not clear the extent to which the cognitive psychological function contributes to the volume reduction. As areas correlated with the recovery of lower limb motility in incomplete cervical SCI, Villiger et al. reported to have observed positive correlations between the improvement of lower extremity motor score of American Spinal Injury Association impairment scale (LEMS) and GMV in the temporal lobe, hippocampus, and between improvement of Berg balance scale (BBS) and GMV in the temporal lobe. Participants in our study were cases with complete loss of lower limb function and, in agreement with the study of Villiger et al., reduction in GMV was noted in the tempo-
Table 2. Gray matter and white matter volume decreases (e.g., atrophy) at whole brain between individuals with spinal cord injury and healthy control individuals.

<table>
<thead>
<tr>
<th>Anatomical region</th>
<th>Peak MNI coordinates</th>
<th>Cluster size (voxels)</th>
<th>Peak T-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray matter</td>
<td>X</td>
<td>Y</td>
<td>Z</td>
</tr>
<tr>
<td>Paracentral lobe (R)</td>
<td>9</td>
<td>-35</td>
<td>66</td>
</tr>
<tr>
<td>Dorsal premotor cortex (L)</td>
<td>-36</td>
<td>-8</td>
<td>65</td>
</tr>
<tr>
<td>Superior temporal gyrus (R)</td>
<td>66</td>
<td>-3</td>
<td>-3</td>
</tr>
<tr>
<td>Middle frontal gyrus (L)</td>
<td>-47</td>
<td>38</td>
<td>27</td>
</tr>
<tr>
<td>Superior parietal lobe (L)</td>
<td>-29</td>
<td>-53</td>
<td>57</td>
</tr>
<tr>
<td>Amygdala (L)</td>
<td>18</td>
<td>-2</td>
<td>-14</td>
</tr>
<tr>
<td>Parahippocampus (R)</td>
<td>15</td>
<td>0</td>
<td>-18</td>
</tr>
<tr>
<td>White matter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcortical paracentral lobe (R)</td>
<td>12</td>
<td>-35</td>
<td>72</td>
</tr>
</tbody>
</table>

MNI = Montreal Neurological Institute

Fig. 1 Statistical parametric maps (p < 0.001, uncorrected and a cluster size of 10 voxels) showing regions of gray matter and white matter volume decreased in participants with ThSCI compared with healthy control participants. The location of each slice in Montreal Neurological Institute space is shown at the above of each section. Abbreviations: L, left; R, right; PHC, parahippocampus; AMG, amygdala; STG, superior temporal gyrus; MFG, middle frontal gyrus; SPL, superior temporal gyrus; PMd, dorsal premotor cortex; PCL, Paracentral lobe.
Table 3. Gray matter and white matter volume increases at whole brain between individuals with spinal cord injury and healthy control individuals.

<table>
<thead>
<tr>
<th>Anatomical region</th>
<th>Peak MNI coordinates</th>
<th>Cluster size (voxels)</th>
<th>Peak T-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray matter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary sensorimotor cortex (L)</td>
<td>-30 -28 52</td>
<td>26</td>
<td>5.72</td>
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<tr>
<td>Precuneus (R)</td>
<td>8 -48 65</td>
<td>20</td>
<td>3.44</td>
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<tr>
<td>White matter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior limb of the internal capsule (L)</td>
<td>-24 -33 12</td>
<td>84</td>
<td>4.61</td>
</tr>
<tr>
<td>Subcortical occipital lobe (R)</td>
<td>11 -76 14</td>
<td>15</td>
<td>4.40</td>
</tr>
</tbody>
</table>

MNI = Montreal Neurological Institute

Fig. 2  Statistical parametric maps (p < 0.001, uncorrected and a cluster size of 10 voxels) showing regions of gray matter and white matter volume increases in participants with ThSCI compared with healthy control participants. The location of each slice in Montreal Neurological Institute space is shown at the above of each section. Abbreviations: L, left; R, right; PCL, Paracentral lobe; ICpost, posterior limb of the internal capsule; OCL, occipital lobe.

Anatomical reorganization P

Peak MNI coordinates Cluster size (voxels) Peak T-value

Gra

y matter

Primary sensorimotor cortex (L) -30 -28 52 26 5.72

Precuneus (R) 8 -48 65 20 3.44

White matter

Posterior limb of the internal capsule (L) -24 -33 12 84 4.61

Subcortical occipital lobe (R) 11 -76 14 15 4.40

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Fig. 2  Statistical parametric maps (p < 0.001, uncorrected and a cluster size of 10 voxels) showing regions of gray matter and white matter volume increases in participants with ThSCI compared with healthy control participants. The location of each slice in Montreal Neurological Institute space is shown at the above of each section. Abbreviations: L, left; R, right; PCL, Paracentral lobe; ICpost, posterior limb of the internal capsule; OCL, occipital lobe.

Anatomical Changes in Brain Following Thoracic SCI

increases in GMV were observed in the left SM1 and right precuneus in the SCI group. As for WM, volume increases were observed in the left ICpost and OCL subcortical region.

Studies on cervical SCI using VBM reported volume decline in the SM1. On the other hand, there was a volume increase in the left SM1 in this study. It is surmised that volume increases occur in the areas corresponding to fingers and arms in the somatotopy of the SM1. Furthermore, performing task-oriented training that actively use the hemiparetic upper limb in stroke rehabilitation increased GMV in the SM1 in the injured hemisphere. This demonstrated that increased use of the hemiparetic upper limb increased the brain area corresponding to the usage site. Participants in this study were with ThSCI complete palsy and their upper limb functions were normal. Individuals with ThSCI change their mode of conduct in a way that life activities, such as transfer and wheelchair driving, can be performed with upper limbs only. Compared to healthy people or those before injury, situations where use of upper limbs is required have necessarily become more prominent and overuse of upper limbs is thought to have resulted in the increase in GMV of the left SM1. In addition, an increase in WMV was observed in the left ICpost where the corticospinal tract passes through and this is considered to be the result of a similar mechanism as to the one that caused an increase in GMV in the left SM1.

Volume increases were also noted in sensory regions, such as the precuneus and the OCL subcortical region. Since individuals with complete ThSCI have dynamic changes in the sensory input system associated with loss of somatosensory functions below the level of injury, a new body image must be established. Since the OCL is the visual region and the precuneus is considered as a region that constitutes the somatotopic map, it is speculated that to obtain a new body image, these functions compensated the loss of somatic sensation and contributed to the volume increase in both of these regions. The increased gray matter volume in both regions has also been indicated in stroke in VBM studies on both humans and animal models.
In the present study, we observed several regions that increased or decreased asymmetrically. Because of the laterality of the left and right hemispheres in brain function, contrasting changes are not always observed. However, it is reasonable to expect a bilateral appearance in areas such as the primary motor cortex. We believe that clear results can be obtained in a study with a large sample size.

The results of the present study also demonstrated the presence of areas with increased volume in addition to areas with decreased volume in association with ThSpCI-induced changes in physical function. Several limitations of this study should be noted. First, the sample size was relatively small, and the statistical power (p < 0.001, uncorrected) is therefore low. However, the areas that were reduced in this study showed similar results to previous VBM studies in SCI, and we are confident that the findings show differences from healthy subjects. Indeed, this assumption should be verified in the future with larger sample sizes. It is predicted that the affected brains areas that differ between individuals with SCI and healthy individuals will become clearer by increasing the number of cases. Moreover, to reveal changes in the brain structure following SCI, it is necessary to compare ThSCI patients with those who have sustained cervical spinal cord cord injuries and patients with incomplete injury, and to conduct a longitudinal study in the same group. Clarification of the relationship between changes in the brain structure and residual disabilities may be used to determine the rehabilitation effect.

**Conflict of Interest:** The authors declare no conflict of interest.

**References**

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