Functional cortical reorganization in cases of cervical spondylotic myelopathy and changes associated with surgery

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OBJECTIVE The physiological mechanisms underlying the recovery of motor function after cervical spondylotic myelopathy (CSM) surgery are poorly understood. Neuronal plasticity allows neurons to compensate for injury and disease and to adjust their activities in response to new situations or changes in their environment. Cortical reorganization as well as improvement in corticospinal conduction happens during motor recovery after stroke and spinal cord injury. In this study the authors aimed to understand the cortical changes that occur due to CSM and following CSM surgery and to correlate these changes with functional recovery by using blood oxygen level–dependent (BOLD) functional MRI (fMRI).

METHODS Twenty-two patients having symptoms related to cervical cord compression due to spondylotic changes along with 12 age- and sex-matched healthy controls were included in this study. Patients underwent cervical spine MRI and BOLD fMRI at 1 month before surgery (baseline) and 6 months after surgery.

RESULTS Five patients were excluded from analysis because of technical problems; thus, 17 patients made up the study cohort. The mean overall modified Japanese Orthopaedic Association score improved in patients following surgery. Mean upper-extremity, lower-extremity, and sensory scores improved significantly. In the preoperative patient group the volume of activation (VOA) was significantly higher than that in controls. The VOA after surgery was reduced as compared with that before surgery, although it remained higher than that in the control group. In the preoperative patient group, activations were noted only in the left precentral gyrus (PrCG). In the postoperative group, activations were seen in the left postcentral gyrus (PoCG), as well as the PrCG and premotor and supplementary motor cortices. In postoperative group, the VOA was higher in both the PrCG and PoCG as compared with those in the control group.

CONCLUSIONS There is over-recruitment of sensorimotor cortices during nondexterous relative to dexterous movements before surgery. After surgery, there was recruitment of other cortical areas such as the PoCG and premotor and supplementary motor cortices, which correlated with improvement in dexterity, but activation in these areas was greater than that found in controls. The results show that improvement in dexterity and finer movements of the upper limbs is associated with recruitment areas other than the premotor cortex to compensate for the damage in the cervical spinal cord.

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KEY WORDS cervical spondylotic myelopathy; functional magnetic resonance imaging; cortical plasticity

Cervical spondylotic myelopathy (CSM) is a chronic progressive disease caused by degenerative changes in the spine that results in nerve root and cord compression by osseocartilaginous elements, and spondylotic is the most common cause of neural compression.25 Surgery is universally accepted to be better than conservative management with reference to avoiding further neurological deterioration or achieving some functional recovery,2,21 although some studies have raised doubts.17,34 Various poor prognostic factors for surgery have been de-
fined in cases of CSM—an older age, abnormal cervical curvature, multisegmental compression, long duration of symptoms, greater number of comorbidities, decreased signal intensity on T1-weighted images, increased signal intensity on T2-weighted images, and cord atrophy on preoperative MR images, to name a few.6,16,25,30,36,37 The physiological mechanisms underlying the recovery of motor function after CSM surgery are poorly understood.

Neuronal plasticity allows neurons in the brain and spinal cord to compensate for injury and disease and to adjust their activities in response to new situations or changes in their environment. Two of the most commonly discussed mechanisms by which functional recovery occurs after decompression are synaptic changes and dendritic sprouting in the cortical and spinal cord neurons.12,13 Rapid cortical and subcortical changes occurring after spinal cord injury (SCI) or myelitis have been demonstrated on functional imaging.1 Cortical reorganization as well as improvement in corticospinal conduction occurs during motor recovery after stroke, and this has been proved by studies using transcranial magnetic stimulation (TMS).3,7,31,39 Similar functional reorganization of cortical motor functions has been proved in macaque monkeys.35 Not many studies have correlated the postoperative motor improvement with plasticity.39 Some studies have shown adaptive changes in bilateral primary motor cortex (M1), supplementary motor area (SMA), premotor area (PMA), cingulate motor area, parietal cortex, and contralateral primary somatosensory cortex (SI) in cases of SCI.8–11,27–29,33,40 and cervical compressive myelopathy due to spondylosis.13,14,23,38 In this study we aimed to understand the cortical changes that occur due to CSM and following CSM surgery and to correlate these changes with functional recovery by using functional MRI (fMRI). We hypothesized that the recovery of normal activation patterns might coincide with clinical improvement.

Methods

Patient Selection

Twenty-two patients having symptoms related to cervical cord compression due to spondylotic changes were selected for the study between 2010 and 2013. Eleven patients had multiple-level disc osteophyte complex with canal stenosis, 8 had single-level prolapsed intervertebral disc, and 6 had multiple-level cervical ossified posterior longitudinal ligament. Inclusion criteria were an age 18–70 years, symptoms for at least 2 months–4 years, weakness of the upper extremities, right handedness, and spine MRI showing 1 or more levels of cervical spinal stenosis and cord compression. Exclusion criteria were previous cervical spine surgery, compromised cognitive function or other neurological or musculoskeletal disease, and an inability to tolerate and meet the safety criteria for repetitive fMRI studies. Twelve age- and sex-matched healthy controls were also recruited for the study. The National Institute of Mental Health and Neurosciences Ethics Committee approved the study. Informed written consent was obtained from all participants or their legal custodians.

Clinical Evaluation and Imaging

All CSM patients were assessed with the modified Japanese Orthopaedic Association (mJOA) scale to record the severity of myelopathy. Patients underwent cervical spine MRI and blood oxygen level–dependent (BOLD) fMRI using a standard paradigm. After a preoperative imaging diagnosis was rendered, patients underwent anterior or posterior decompressive surgery. Postoperatively patients underwent rehabilitation programs and physiotherapy. Patients were monitored up to 6 months after surgery, and the mJOA score was documented. The BOLD fMRI was performed at 6 months using the same motor paradigm. All healthy controls also underwent fMRI with the same paradigm.

Motor Task

All subjects were instructed to keep their right wrist straight and tap their 4 fingers to their thumb at a constant self-regulated pace.14 In all cases, an examiner ensured proper execution of the task during imaging. A block design in which a motor task was alternated with a rest period was used. There were a total of 100 dynamics, and every 10 dynamics of activity was alternated with 10 dynamics of rest, beginning with rest. Healthy volunteers also performed an identical task during fMRI.

Imaging Protocol

Both patients and healthy controls underwent baseline imaging, and the patients also underwent imaging 6 months after surgery. We performed 3-T MRI (Philips Medical Systems) with a 32-channel head coil. Functional images were acquired using a T2*-sensitive spin-echo echo planar imaging sequence sensitive to BOLD contrast. After obtaining the fMR images, we performed 3D high-resolution T1-weighted imaging to facilitate the localization of fMRI activation. Anatomical and functional images were processed using Statistical Parametric Mapping 8 (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing involved the reorientation of functional and structural images followed by slice timing correction and realignment of functional images.

A hypothesis-driven general linear model (GLM) was used to perform group analyses. Group activation maps were created for each of the 3 groups (control, preoperative, postoperative) using a threshold of p < 0.005 with Bonferroni correction, which provides stringent protection against false-positives by scaling the p value by 1/N, where N is the number of pixels in the functional data set. Based on the results of Curt et al.,10 a minimum cluster size of 48 mm3 was set to confidently differentiate between likely artifacts and significant regions of activation. For all functional activation maps, the volume of activation (VOA), maximum t value (tmax), and Talairach coordinates of the center of gravity (COG) of the VOA were recorded. Anatomical localization of the functional brain activations was performed using the Talairach Client (www.talairach.org) after converting Montreal Neurological Institute (MNI) coordinates into Talairach coordinates using GingerALE (http://www.brainmap.org/ale/).

Results

In 4 patients, preoperative fMRI showed poor or no activation. In 1 patient, x-axis movement was more than 5
mm. Hence, 17 patients with CSM (16 males, mean age 51.76 ± 10.67 years) were eligible for analysis in this study. These patients presented with a duration of symptoms ranging from 2 months to 4 years. Twelve patients underwent decompressive laminectomy, and 5 patients underwent an anterior cervical approach and decompression. Spinal implants were not used in any patients. The mean overall mJOA score improved in patients following surgery; mean upper-extremity, lower-extremity, and sensory scores improved significantly (Table 1).

Although our primary intent was to calculate the degree of clinical improvement with the amount of increase/decrease in VOA, it was not possible given our small sample size. Thus, the mean VOA was calculated in different groups using the software and compared with each other. In the control group, the mean VOA was 529 mm³ in the left S1, 190 mm³ in the cerebellum, and 13 mm³ in the right S1. In the patients, preoperatively, the VOA was 1001 mm³ in the left S1, 266 mm³ in the cerebellum, and 394 mm³ in the right S1. In the patients postoperatively, the VOA was 924 mm³ in the left S1, 341 mm³ in the cerebellum, and 39 mm³ in the right S1. The VOA in the contralateral S1 was higher in the patients both preoperatively and postoperatively than that in the controls. The VOA in the cerebellum was higher in the patients both preoperatively and postoperatively than those in the control group.

In the postoperative group, activations increased and were noted only in the primary motor, medial prefrontal, cingulate, and cerebellar cortices, as well as diffusion tensor imaging changes in cortical and brainstem motor areas. Functional changes can be modifications in neuronal activity or synaptic efficacy or increases in astrocytic activity. Presently many modalities, such as fMRI, PET, electroencephalography, TMS, and magnetic encephalography, permit monitoring of brain activation while movement is taking place.

There is evidence that SCI results in the reorganization of motor areas in the brain. Increased activation in secondary brain areas as well as a distinct spatial shift in activation compared with that in controls has been demonstrated. Patients with complete SCI exhibit morphological changes such as reduced gray matter volume in the primary motor, medial prefrontal, cingulate, and cerebellar cortices, as well as diffusion tensor imaging changes in cortical and brainstem motor areas. With the advent of functional imaging, various reorganization patterns were recognized. In a review by Kokotilo et al., nearly half of the included studies documented a significant increase in activation magnitude in motor areas. Some studies found a distinct spatial shift in activation, with a majority showing a posterior shift in activation and 4 studies demonstrating a shift in activation toward deafferentation. With the advent of functional imaging, various reorganization patterns were recognized. In a review by Kokotilo et al., nearly half of the included studies documented a significant increase in activation magnitude in motor areas. Some studies found a distinct spatial shift in activation, with a majority showing a posterior shift in activation and 4 studies demonstrating a shift in activation toward deafferentation.

In some early studies, postoperative cord expansion was proposed as a good indicator of recovery and was related to “intracord plasticity,” though the researchers did not use electrophysiology or functional brain imaging. In one of the earliest studies in which functional imaging was used to assess cortical reorganization in CSM, Holly et al. demonstrated expansion of the cortical representation of the affected extremity (involvement of adjacent motor territories, the SMA, and bilateral cortical recruitment) before surgery in 4 patients, and surgical decompression resulted in improvements in neurological function and reorganization of the representational map.

In a larger study by Dong et al., which included 8 patients with CSM and 6 healthy control volunteers, the authors quantitatively captured reduced activation in the contralateral M1, S1, and dorsal PMA for dexterous fin-
ger movements—though not for less complex wrist movements before surgery—followed by a progressive increase toward the activation pattern of healthy controls, as functional gains in the upper extremity proceeded after surgical decompression. The reduced pinch-related activation and the normal amount of wrist extension–related activation in contralateral M1 and S1 before surgery suggest that the coordinated finger pinch task demands greater integrity of the corticospinal tract. They postulated that contralateral hemisphere changes during dexterous pinch movements might suggest that some nonpermanently damaged axons within descending motor and ascending sensory pathways have the potential for reversibility of a conduction block. Thus, more cortical sensorimotor neurons were recruited postsurgery as a result of enhanced corticospinal conductivity, and by halting the progression of corticospinal tract injury, cortical sensorimotor reorganization evolved to compensate for lost axons.

In a study by Duggal et al., fMRI was performed in 12 patients prior to decompression and 6 months following surgery. These authors demonstrated that spinal cord compression results in an increased VOA within the PrCG and a loss in VOA within the PoCG in comparison with those in controls. Following decompression, there were varying degrees of increased activation in both the PrCG and PoCG, suggesting cortical recruitment and regional reorganization.

In their study involving 7 patients, Hrabálek et al. performed fMRI in 12 patients prior to decompression and 6 months following surgery. These authors demonstrated that spinal cord compression results in an increased VOA within the PrCG and a loss in VOA within the PoCG in comparison with those in controls. Following decompression, there were varying degrees of increased activation in both the PrCG and PoCG, suggesting cortical recruitment and regional reorganization.

In their study involving 7 patients, Hrabálek et al.24
performed preoperative and 6-month postoperative fMRI studies with the task paradigm of wrist flexion and extension. Postoperatively, the anteroposterior cervical spinal canal distance increased by 40%, the cross-sectional area of the spinal canal by 37%, and cross-sectional areas of the spinal cord by 36%. Functional MRI revealed significant activation in the dorsal MI and adjacent secondary motor and sensory areas, bilaterally in the SMAs, anterior cingulum, primary auditory cortex basal ganglia, thalamus, and cerebellum. After surgery, the cortical activations decreased in most areas. There was a statistically significant decrease in activation of the right parietal operculum and posterior temporal lobe.

In a case report by Tam et al., although no preoperative fMRI studies were available, postdecompression fMRI detected increased cortical activation in the MI during finger tapping with concomitant improvement in motor function. Significant activation was also seen in the ipsilateral culmen of the cerebellum, contralateral medial frontal gyrus, and contralateral inferior parietal lobule. Postoperatively, the patient demonstrated 2 VOAs in the contralateral PrCG and 1 VOA in the ipsilateral PrCG without any activation in the PoCG.

In a recent study, Zhou et al. studied functional connectivity strength (FCS) via resting-state functional connectivity (rsFC) MRI of the sensorimotor network. Patients with CSM showed significantly decreased FCS in the operculum-integrated regions, which exhibited reduced rsFC around the rolandic sulcus. They also showed increased FCS in the premotor, primary somatosensory, and parietal-integrated areas, which primarily showed an enhanced rsFC pattern. Altered FCS was associated with worsening JOA scores.

Green et al. performed TMS and motor function testing 1 month prior to and 4 months after surgery for CSM. They showed that the sum amplitude of motor evoked potentials (sMEPs) and number of focal points at which MEPS were elicited (N) were significantly greater in CSM patients than in controls. Patients with mixed upper and lower limb dysfunction had significantly increased grip strength and reduced sMEPs and N after surgery. Patients with only lower limb dysfunction did not show significant reduction in sMEPs or N after surgery. No significant differences in Hoffmann's reflex parameters obtained from the flexor carpi radialis muscle or in central motor conduction time (CMCT) changes were noted after surgery. These authors proved that the compensatory expansion of motor cortical representation occurs largely at the cortical rather than the spinal levels, with a tendency to normalization after surgery.

In our study there was an increase in VOA in the PrCG compared with that in controls. This finding can be explained as the over-recruitment of sensorimotor cortices during nondexterous relative to dexterous movements occurring before surgery. After surgery, other cortical areas such as the PoCG and the premotor and supplementary motor cortices were recruited. The SMA is involved in the preparation and execution of practiced movement sequences and is strongly influenced by attention, performance, and other components of the movement, which had actually improved after surgery in our cases, as reflected by improved upper limb mJOA scores. Dorsal premotor cortex is proved to be involved in the recovery of dexterity after stroke and SCI, possibly through corticospinal and corticorubral projections to spinal motor neurons in the midcervical segments. Regarding the posterior shift of activation toward the PoCG, previous studies have already documented the posterior spread of activation with the recovery of limb motor function or increased VOA following injury.

Given the existing literature, we can accept that there is compensatory expansion and increased cortical representation of the hand area preoperatively. However, postoperatively, the tendency to normalization of motor representation is less well understood and inconsistent. Patients with CSM form a heterogeneous group with different levels of impairment with different degrees of cord compromise and may have different natural histories if they go untreated. Additionally, the extent of synaptic transmission and reorganization depends on time after the initial insult and variable degree of residual spinal cord atrophy. There is no uniformity in the timing of imaging in relation to surgery, and different authors have used different tasks for fMRI, which makes it additionally difficult to come to any conclusion. All reported studies have identified altered cortical sensorimotor activation patterns together but have not attempted to make distinctions between the motor and sensory responses separately. Somatosensory cortical atrophy can occur in patients with chronic disease, so the VOA may provide incorrect values in comparison with those in healthy controls as the basal brain volume levels are not matched.

Another explanation for the increase in S1 activity during dexterous movements and behavioral improvement postoperatively may be that corticospinal axons originat-

### Table 2. Total VOA in the left sensorimotor cortices in different groups

<table>
<thead>
<tr>
<th>Group</th>
<th>VOA (mm³)</th>
<th>t_max</th>
<th>Talairach Coordinates (x,y,z)</th>
<th>COG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1072</td>
<td>14.03</td>
<td>−30.41, −28.77, 50.58</td>
<td>BA4</td>
</tr>
<tr>
<td>Preop</td>
<td>4305</td>
<td>11.59</td>
<td>−33.18, −25.96, 50.8</td>
<td>BA4</td>
</tr>
<tr>
<td>Postop</td>
<td>2945</td>
<td>15.64</td>
<td>−35.97, −28.74, 50.49</td>
<td>BA3</td>
</tr>
</tbody>
</table>

### Table 3. Volume of activation in different groups in different areas

<table>
<thead>
<tr>
<th>Group</th>
<th>BA Gyrus</th>
<th>VOA (mm³)</th>
<th>t_max</th>
<th>Talairach Coordinates (x,y,z)</th>
<th>COG (x,y,z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Lt PrCG</td>
<td>418</td>
<td>14.03</td>
<td>−30.41, −28.77, 50.58</td>
<td>BA4</td>
</tr>
<tr>
<td></td>
<td>Lt PoCG</td>
<td>654</td>
<td>11.62</td>
<td>−49.73, −25.09, −42.5</td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>Lt PrCG</td>
<td>5998</td>
<td>12.60</td>
<td>−36.02, −20.88, −56.64</td>
<td></td>
</tr>
<tr>
<td>Postop</td>
<td>Lt PoCG</td>
<td>1473</td>
<td>15.64</td>
<td>−35.97, −28.74, 50.49</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lt PrCG</td>
<td>736</td>
<td>7.61</td>
<td>−2.6, −9.35, 52.89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lt PMA &amp;</td>
<td>736</td>
<td>7.62</td>
<td>−46.82, −26.85, 31.57</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ing from SI are more posterior and medial than those of MI and less vulnerable to compression. Reorganization after injury and surgery may be correlated to a patient’s functional recovery, but there may be multiple confounding factors, such as rehabilitative physiotherapy, that produce more sensory activation and thereby increase coactivation of the sensory cortex. A more conclusive study must incorporate a larger number of patients with similar clinical features and duration of symptoms, demonstrate the central motor conduction time, and correlate TMS studies with areas of fMRI activation before surgery and periodically in the postoperative period. Resting-state fMRI may be an effective platform to explore neuronal functional connectivity and may help in further understanding plasticity without any confounding factors associated with task-related imaging.

Conclusions

There is an increase in VOA during movements in cases of CSM to compensate for weakness and loss of dexterity compared with controls. Postoperatively, though the compression is relieved, there is cortical reorganization with the recruitment of PMA and SMAs in an attempt to gain dexterity and coordination. The reorganization signifies dynamic cortical plasticity in response to surgery.

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Cortical plasticity in cervical spondylotic myelopathy

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Author Contributions
Conception and design: Bhagavatula, Shukla, Saligoudar. Acquisition of data: Shukla, Sadashiva, Saligoudar, Prasad. Analysis and interpretation of data: Sadashiva, Saligoudar, Prasad. Drafting the article: Bhagavatula, Sadashiva, Saligoudar, Bhat. Critically revising the article: Bhagavatula, Shukla, Sadashiva, Bhat. Reviewed submitted version of manuscript: Bhagavatula, Shukla, Saligoudar, Prasad, Bhat. Approved the final version of the manuscript on behalf of all authors: Bhagavatula. Statistical analysis: Sadashiva, Prasad. Administrative/technical/material support: Bhagavatula, Shukla, Saligoudar, Prasad, Bhat. Study supervision: Bhagavatula, Shukla, Saligoudar, Prasad, Bhat.

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