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Cortical reorganization in patients with cervical spondylotic myelopathy

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Abstract

Object—Recent investigations have demonstrated that the cerebral cortex can reorganize as a result of spinal cord injury and may play a role in preserving neurological function.

Reorganization of cortical representational maps in patients with cervical spondylotic myelopathy (CSM) has not been previously described. The authors sought to determine the feasibility of using functional magnetic resonance (fMR) imaging in patients with CSM to investigate changes in the cortical representation of the wrist and ankle before and after surgical intervention.

Methods—Four patients with clinical and imaging evidence of CSM were prospectively enrolled in this study. The patients underwent preoperative neurological examination, functional assessment, cervical imaging, and brain fMR imaging. The fMR imaging activation task undertaken was either wrist extension or ankle dorsiflexion, depending on whether the patient's primary impairment was hand dysfunction or gait difficulty. The cohort then underwent further evaluations at 6 weeks and 3 and 6 months postoperatively. In addition, five healthy volunteers underwent fMR imaging at two different time points and served as controls.

In the healthy volunteers fMR imaging demonstrated areas of focal cortical activation limited to the contralateral primary motor area for the assigned motor tasks; the activation patterns were stable throughout repeated imaging. In comparison, in patients with CSM fMR imaging demonstrated expansion of the cortical representation of the affected extremity. Surgical decompression resulted in improvements in neurological function and reorganization of the representational map.

Conclusions—The findings of this preliminary study demonstrate the potential of fMR imaging to assess changes in cortical representation before and after surgical intervention in patients with CSM. A future study involving a larger cohort of patients as well as the stratification of patients with CSM, based on the aforementioned factors that influence cortical adaptation, will allow a more detailed quantitative analysis.

Keywords

cervical myelopathy; cortical mapping; cortical reorganization; function

Cervical spondylotic myelopathy is the most common form of acquired myelopathy; it commonly presents with hand dysfunction and gait difficulty^{9,31}. The signs and symptoms of CSM are primarily caused by damage to nerve fibers within the cervical spinal cord, in particular those in the lateral corticospinal tract. Not surprisingly, the overwhelming majority of clinical and laboratory investigations into the pathogenesis of CSM have focused on spinal column or cord abnormalities^{9,10, 12,14,17,26–29}. In contrast, the function of the cerebral cortex within the affected motor network has been largely understudied and represents a potential area of novel investigation.

One of the most studied adaptive mechanisms of the central nervous system is the ability of the cerebral cortex to reorganize following neuronal loss and axonal injury. Simply stated, areas of the cortex that normally are not primarily involved in the performance of a specific task may be recruited to participate in control of that function. This dynamic compensatory mechanism likely represents an adaptive remodeling response designed to preserve neurological function. Although the majority of functional neuroimaging studies have demonstrated this neuroplasticity in cerebral pathological conditions, the results of recent laboratory investigations have demonstrated that cortical reorganization can occur in response to injury to ascending and descending fiber tracts within the spinal cord^{4,7,11,19–23}.

In this article we describe a novel method of assessing cortical representational maps for hand and foot activity in patients with CSM by using fMR imaging. In the pilot study described, we investigated the cortical plasticity in patients with CSM as a result of chronic spinal cord injury, as well as subsequent reorganization following decompression surgery. It is hoped that continued study will provide additional insights into the adaptive responses of the cerebral cortex in patients with CSM and the role of the cerebral cortex in the pathophysiology of this disorder.

Materials and Methods

Four patients with signs and symptoms of CSM were recruited into the study. Cervical spine imaging demonstrated evidence of cervical stenosis and/or spinal cord injury related to CSM. Exclusion criteria included the following: 1) previous cervical spine surgery; 2) age younger than 18 or older than 85 years; 3) clinical or radiological evidence of stroke or other neurological disease; 4) presence of a cardiac pacemaker or other non-MR imaging-compatible implant; 5) musculoskeletal or degenerative joint disease, or another medical cause for weakness or pain affecting the hand and gait; and 6) severe claustrophobia.

Before surgery, each patient in the study underwent baseline neurological examination, MR imaging of the cervical spine, and fMR imaging of the brain. Patients who presented with gait difficulty underwent a formal gait analysis. The patients underwent surgery within 2 weeks after the fMR imaging study was performed. All surgeries were performed by one surgeon (L.T.H.) and consisted of anterior or posterior decompression procedures. The

patients underwent repeated fMR imaging, neurological examination, and gait analysis (if applicable) 6 weeks and 3 and 6 months postoperatively. A minimum of two postoperative fMR imaging sessions was performed in each of the study patients in addition to the one pre-operative study. A cervical spine MR imaging study was performed 3 months postoperatively, and each case was graded using the modified Japanese Orthopaedic Association Scale² at each time point. Five healthy age-matched volunteers were included in the study as controls; they underwent neurological evaluation and serial fMR imaging at two time points. The Office for the Protection of Research Subjects at the University of California at Los Angeles approved the protocol and consent form for this study.

Gait Analysis

Gait analysis was performed using the Intelligent Device for Energy Expenditure and Activity (IDEEA, MiniSun), an integrated system of lower-extremity accelerometers that acquires spatiotemporal data while study participants walk in the laboratory or community²⁴. After the accelerometer had been properly attached and calibrated, the participants were asked to walk approximately 200 feet through an unobstructed hallway. They were instructed to walk at their usual and fastest speeds while maintaining their safety, each time over a tiled floor for 30 meters. The middle 10 strides were manually analyzed because in all participants the walking speed reached a plateau. The parameters studied included walking speed, cadence, and stride length, as well as single-limb and double-limb support and swing times.

Functional MR Imaging Activation Tasks

Two different fMR imaging activation tasks were used in the acquisition of pilot data: ankle dorsiflexion and wrist extension. The wrist extension and ankle dorsiflexion paradigms⁸ represent the two most commonly encountered impairments and disabilities in CSM: hand function and gait. Wrist extension is critical for hand prehension and is associated with finger extension, which is also highly represented by the M1. Ankle dorsiflexion is similarly represented and is a critical movement for walking in humans; dorsiflexion occurs during swing and on heel strike.

The participants attended a 1-hour preimaging training session before each fMR imaging session. During preimaging training, the participants were given detailed instructions regarding the performance of the activation tasks and were allowed to practice the tasks until they were able to perform the tasks correctly. This decreased the likelihood that the imaging data would be adversely affected by activation of undesired muscle groups or excessive head motion.

For the wrist extension task, each study participant's wrist and forearm were placed on a molded plastic form. Visual cues were presented to the participant to inform him or her when to rest and when to extend the wrist. No visual feedback was provided about the quality or extent of wrist extension, but an attached device extended over the participant's fingers provided tactile feedback when wrist extension reached approximately 15°. The imaging paradigm consisted of 30 seconds of rest followed by alternating 30-second periods of extension and rest, providing a total imaging session length of 4 minutes and 30 seconds.

During each 30-second extension period, participants performed 10 extensions, each consisting of 1 second of extension, 1 second of return to rest position, and 1 second of rest.

The ankle dorsiflexion task was performed using the same protocol as the wrist extension task. An ankle-foot orthosis articulated at the ankle joint allowed 10° of dorsiflexion. Visual cues were again used to initiate periods of activity and rest. In both wrist extension and ankle dorsiflexion tasks, the associated devices could be attached to the left or right side.

Structural Images

Structural and functional images were acquired using a 1.5-tesla imaging system optimized for head imaging (Sonata, Siemens) at the University of California at Los Angeles Brain Mapping Center. Each imaging session began with a series of three reference images. Scout images were acquired in the sagittal plane to locate the anterior and posterior commissures. A high-resolution anatomical gradient-echo T₁-weighted series (TR 1970 msec, TE 4.38 msec, TI 1100 msec, flip angle 15°, and matrix 256 × 256° covering the entire brain was used to identify those slices containing ROIs within the sensorimotor network. A set of high-resolution T₁-weighted spin echo images was then acquired using the following parameters: 25 contiguous axial slices parallel to the anterior commissure-posterior commissure plane; 4-mm thickness with a 1-mm gap, TE 15 msec, TR 600 msec, flip angle 90°, and matrix 256 × 256. The high-resolution spin echo MR images served as a template for functional image rendering and image registration.

Functional MR Imaging

A set of functional images was acquired using echo planar T₂-weighted image volumes with BOLD contrast enhancement. The following parameters were used for the functional images: 25 axial slices with a 4-mm thickness and a 1-mm gap coplanar with the T₁-weighted spin echo images described earlier, 3 × 3 × 4-mm voxels; matrix 64 × 64, TR 2500 msec, TE 60 msec, and flip angle 80°. A total of 108 volumes was acquired.

Functional MR Imaging Data Analysis

Preprocessing—The FSL (FMRIB Software Library, version 3.3; <http://www.fmrib.ox.ac.uk/fsl>) was used for the fMR imaging data analysis²⁵. The following preprocessing procedures were applied before statistical analysis. Images were corrected for the participant's head motion by using MCFLIRT (Motion Correction using FMRIB's Linear Image Registration Tool). All functional volumes were aligned to the middle volume of the time series to correct for misalignment and residual head motion. The EPI time series were spatially smoothed using a gaussian kernel of 6 mm full-width-half-maximum. Next, MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) was used to identify individual components of the fMR imaging time series data. Components clearly related to motion artifact or physiological noise (for example, sagittal sinus pulsation) were excluded from further analysis¹. Functional images were aligned to the standard Montreal Neurological Institute template space in a three-step process using FLIRT (FMRIB's Linear Image Registration Tool)¹⁵¹⁶. First, the middle reference image of the EPI time series was registered using seven-parameter rigid-body transformation to the coplanar T₁-weighted spin echo imaging. In addition, a weighting

volume was used to deemphasize the areas of EPI-related signal loss on the orbitofrontal and temporal regions. This T₁-weighted image was then aligned to the participant's T1 volume image using 12-parameter affine transformation. Finally, the participant's T1 volume image was aligned to the Montreal Neurological Institute template by using 12-parameter affine transformation.

The BOLD Analysis—A task-specific effect was estimated using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction. A t-test was performed to construct a task-specific voxel-by-voxel activation map for each individual. The statistical threshold was set at a cluster-level Z value greater than 3.1 with a spatial extent at a probability value less than 0.01 (corrected for multiple comparisons according to random field theory). To quantify dynamic changes in fMR imaging activation in key brain areas, an ROI analysis was performed for within-participant and between-session comparisons at the individual level.

Regions of Interest—We selected four pairs of ROIs including the bilateral M1, the dorsal premotor area, the primary sensory cortex, and the SMA. The M1 was defined as the cortex lying within the anterior bank of the central sulcus and the posterior half of the precentral gyrus located superior to the dorsal surface of the lateral ventricles. In addition, the M1 was further divided into medial and lateral portions (M1med and M1lat) at a point approximately 20 mm from the interhemispheric fissure. The dorsal premotor area was defined as the anterior half of the precentral gyrus and the area extending anteriorly less than 10 mm from the precentral sulcus and superior to the dorsal surface of the lateral ventricle. The SMA was defined as the cortex on the banks of the interhemispheric fissure, extending approximately 10 mm anteriorly from the border of the M1 (roughly covering the medial extent of Brodmann area 6). The primary somatosensory area included the postcentral gyrus superior to the dorsal surface of the lateral ventricles.

In addition to a whole-brain voxel-wise analysis of an individual patient's fMR imaging time series, intraparticipant across-session comparisons were made to capture dynamic changes in the aforementioned key brain areas across time. To make these comparisons, an in-house software tool was used to extract task-related activations, including spatial extent (absolute voxel counts) and magnitude (percentage signal change), within each ROI from each activation map, which are generated from different fMR imaging sessions. The temporal evolution of motor task-related activations was evaluated at the individual level.

Results

In each healthy volunteer we found areas of focal cortical activation limited to the contralateral M1 for both the ankle dorsiflexion (Fig. 1 left) and wrist extension (Fig. 1 right) paradigms. Ankle dorsiflexion provided particularly focused activation (Fig. 2), and the patterns for both paradigms were highly conserved across healthy volunteers. Furthermore, the activation patterns for each individual volunteer showed little change in magnitude or location over the two designated time points.

Compared with the healthy volunteers, the patients with myelopathy had significant abnormalities in cortical activation that corresponded to the location of their disability (Table 1). The first patient (Case 1) presented with progressive gait difficulty; preoperative fMR images obtained during ankle dorsiflexion demonstrated a significantly larger representation than that observed in healthy volunteers. A second patient (Case 2) suffered from progressive hand incoordination; preoperative fMR images obtained during wrist extension showed a large area of activation that incorporated cortical regions located posterior and medial to those of healthy volunteers. The third patient (Case 3) suffered from progressive gait difficulty; preoperative fMR images obtained during ankle dorsiflexion demonstrated bilateral activation in the leg representation areas. The fourth patient (Case 4) presented with declining hand function; fMR images demonstrated an increased amount of dorsal premotor activity.

In each patient subjective and objective neurological improvements were achieved postoperatively, and fMR images demonstrated marked changes in the patterns of cortical representation (Figs. 3 and 4). Gait analysis showed marked improvements in walking speed, stride length, and cadence in the patients with walking difficulties (Table 2). Postoperative cervical spine MR imaging demonstrated satisfactory decompression of the spinal cord in each case. Following surgical decompression, distinct focusing patterns of cortical activation were demonstrated in two patients at each time point, as the area of activation incrementally decreased and began to resemble those of the healthy volunteers. In two patients we found patterns of shifting activation along with additional recruitment followed by focusing of the activation at later time points.

Discussion

Functional MR Imaging

Functional MR imaging is a novel technology that can be used to map areas of brain function as voluntary movement produces neuronal activation in the cortical representation accompanied by changes in cerebral blood flow and oxygen extraction. This imaging modality has emerged as a powerful tool for mapping cerebral reorganization over time and in relation to functional gains and declines in the use of upper and lower extremities^{7,8}. To our knowledge, the present study is the first in which this technology has been used with activation paradigms that can explore a range of behaviors in patients with CSM.

The results of previous studies have validated the ability of fMR imaging to yield reproducible results. Yoo et al.³⁰ evaluated fMR imaging signal changes in study participants every 8 weeks over a 1-year period, and consistent activation patterns were found in the M1, SMA, and pre-motor areas throughout the sessions. Results from another study, in which a well-controlled motor task was performed while monitoring handgrip force and surface electromyography, revealed that the signal-to-noise ratio varied among trials, but the average value across trials displayed no significant intersession difference¹⁸.

Cerebral Cortical Reorganization in Patients With Spinal Cord Injury

The presence of an intact corticospinal tract pathway is not required to activate the M1 as patients with complete traumatic spinal cord injury are able to activate motor areas corresponding to body parts located caudal to the level of spinal cord injury by attempting or imagining movement^{4,23}. Compared with healthy volunteers, patients with complete spinal cord injury are commonly found to have an expansion or shift in the location of cortical activation while attempting to move the affected extremity.

A similar phenomenon of increased areas of cortical activation and recruitment has been described in patients with incomplete spinal injury and residual function of the affected limb. In contrast to patients with complete spinal cord injury, patients with incomplete spinal cord injury have, according to a few published examples^{7,11}, been found to show further cortical reorganization back toward more normal activation patterns as neurological function improves. If a large percentage of axons from the motor network have been damaged, that activation may fall below the magnitude and extent seen in healthy participants. For instance, the authors of fMR imaging studies involving patients with a spinal cord injury that causes impairment of gait function demonstrated that M1 representation for the foot expanded into the proximal leg and paraspinal representation⁷. As control of lower-extremity function improved through rehabilitation, the extent of cortical activation decreased and resembled that of normal healthy volunteers. Electroencephalograms and dipole source analysis were used to map cortical potentials during finger and toe movements in patients with incomplete spinal cord injury¹¹. The motor potentials were mapped posterior to the central sulcus in the majority of patients compared with normal controls. It was postulated that this represented greater participation of the primary sensory area in driving motor control. A small subset of patients underwent repeated study 6 months later, and recovery of neurological function was associated with a change in the site of the cortical motor potential to the anterior location found in healthy controls.

Mechanisms of Cerebral Cortical Reorganization Following Spinal Cord Injury

The exact mechanism by which cortical reorganization occurs following spinal cord injury is complex and not completely understood; however, it is believed that it occurs through one or two broad processes: synaptic modification of preexisting connections and/or the development of new circuitry. Horizontal intracortical axons and dendrites interconnect different movement representations of the M1 and likely serve an important role in neuroplasticity²⁰. Rapid representational shifts can be observed in regions that have a high density of these fibers, whereas reorganization is restricted in areas that have a smaller concentration¹³. The results of laboratory investigations in monkeys have demonstrated that γ -aminobutyric acid exerts inhibitory influences on these interconnections to maintain standard cortical representations⁶. This inhibitory influence can be interrupted by a loss of afferent or efferent fibers, which facilitates cortical reorganization through the disinhibited connections. Long-term potentiation is a synaptic activity-dependent mechanism involving motor skill learning and represents another manner in which adaptations via synaptic strengthening can occur⁷.

The development of new circuitry relies on the growth of dendritic or axonal arbors as well as on physiological remodeling. This can be manifested by the development of new horizontal connections within the cerebral cortex. Collateral sprouting from undamaged spinal cord fibers may also occur as a means to evolve alternative synaptic connections with spinal motor pools. Rapid representational plasticity demonstrated on fMR imaging, perhaps map adaptations that occur in less than 1 or 2 months, more likely suggests physiological rather than morphological adaptations, but additional work in animal models of injury are needed to assess mechanisms of change⁵.

Functional Neuroimaging in Patients With CSM

The finding that patients with CSM have changes in cortical representation as a result of progressive spinal cord injury and subsequent reorganization following surgical decompression has not been previously described. In the present study, patients with CSM were found to have areas of expanded cortical representation for the affected limb when compared with healthy controls. This included involvement of adjacent motor territories, the SMA, and bilateral cortical recruitment. It is our belief that in some patients with CSM, neurological function is preserved by reorganization and recruitment of new pathways in an analogous fashion to that of patients with stroke or cervical myelitis, in whom the motor cortex ipsilateral to the moving hand and other nodes of the distributed motor network are used to optimize residual neurological function^{3,22}. This may explain one mechanism by which patients with CSM who have a distinct evidence of corticospinal tract injury are able to perform motor activities with little or mild neurological deficits. Other patients with CSM manifest a more progressive or even rapid neurological deterioration; this may be related to a loss of cervical descending fibers that exceeds adaptive capacity or injury to newly developed compensatory pathways by the disease process.

All the patients with CSM achieved neurological improvement and manifested significant changes in cortical representation after undergoing surgery. In contrast, as demonstrated in previous studies^{18,30}, fMR imaging activation patterns in healthy volunteers showed stability throughout repeated imaging. Surgical decompression may induce cortical reorganization by allowing recovery of conduction in injured but not permanently damaged axons. This may result in increased activation (recruitment) or decreased extent of activation (focusing, perhaps through an increase in synaptic efficacy), depending on the availability of cortical neuron pools and the ability of existing corticospinal projections to activate spinal motor pools. After the initial representational changes take place following surgical decompression, continued reorganization and neurological recovery can occur secondary to activity-dependent mechanisms related to task practice and learning. Although there was some variation in the evolution of the cortical representational maps, in each study patient eventual focusing of the activation pattern was demonstrated after a period of wide recruitment. Such variation is to be expected. The participants had different levels of motor function and different rates of deterioration before they came to surgery. The decision to perform decompression was in part related to a recent, more rapid decline, perhaps because previously spared descending fibers became involved in the injury and cortical compensatory mechanisms failed.

Conclusions

Patients with CSM may manifest a spectrum of cortical adaptations over time related both to axonal loss and impaired corticospinal tract conduction as the disease progresses and to recovery of conduction following decompression. A variety of factors is likely to influence this response, including severity of the spinal cord injury, mechanism of pathology, duration and rate of progression of symptoms and impairments, age, and timing and success of surgery. In this preliminary study we demonstrated the potential for using fMR imaging as a physiological assessment to examine patients with CSM for changes in cortical representation before and after surgical intervention. A future study involving a larger cohort of patients, as well as stratification of patients with CSM based on the aforementioned factors that influence cortical adaptation, will allow a more detailed quantitative analysis.

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Abbreviations in this paper

BOLD	blood oxygenation level–dependent
CSM	cervical spondylotic myelopathy
EPI	echo planar imaging
fMR	functional MR
FMRI	Oxford Centre for Functional Magnetic Resonance Imaging of the Brain
M1	primary motor area
MR	magnetic resonance
ROI	region of interest
SMA	supplementary motor area

Fig. 1. Functional MR imaging studies demonstrating the reproducibility of the right ankle dorsiflexion (*left*) and right wrist extension (*right*) paradigms. In each panel the *red* and *blue* areas represent two different imaging studies performed 1 month apart in one healthy volunteer. *Purple* areas show overlaps between the two imaging studies.

Fig. 2. Spatial colocalization of the responses of three healthy volunteers during right ankle dorsiflexion, overlaid in *red*, *green*, and *blue*. Each color represents the activation in one healthy volunteer at one time point. The activation patterns are well conserved in size and location across the volunteers.

Fig. 3.

Case 1. A: Preoperative MR image of the cervical spine demonstrating severe spinal cord compression with signal change. B: Postoperative MR image obtained after laminoplasty was performed, showing alleviation of compression and reexpansion of the spinal cord. C: Preoperative mapping of right ankle dorsiflexion (*red*) revealing a large pattern of activation in the contralateral medial motor area that corresponds to M1 for the ankle as well as the premotor and SMAs. At 6 weeks postsurgery, the activation pattern in M1 has become restricted to a small region of contralateral primary motor and sensory areas and much

smaller portions of the SMA and premotor cortex. This focused pattern persists at 3 months after surgery.

Fig. 4.

Left: Case 2. Preoperative mapping of left wrist extension (*red*) revealing a large pattern of activation including areas dorsal and lateral to the M1 for the wrist. At 3 months postoperatively (*blue*) the activation pattern has decreased in size, followed by further significant focusing of the activation to a small region that corresponds to the area of the wrist at 6 months (*green*). This correlated with improving left hand function. The postoperative image obtained at 6 weeks is not included due to technical errors that occurred during image acquisition. *Right:* Case 3. Preoperative mapping of ankle dorsiflexion showing bilateral activity in the leg representation within medial motor areas. The 6-week postoperative image (*blue*) is similar in the extent of activity, but the pattern has become restricted entirely to the contralateral medial motor cortex. In the 3-month postoperative image (*green*), the activation pattern has increased in the M1s, mostly contralateral to the foot. In addition, there is much more involvement of the bilateral SMAs and dorsal premotor areas, suggesting wide recruitment of motor pools. The 6-month fMR images (*yellow*) demonstrate focusing of the pattern to primarily include the contralateral ankle motor area.

Table 1
Clinical & fMRI imaging characteristics in patients undergoing surgery for CSM*

Case No.	Age (yrs), Sex	Symptom	Preop mJOA	fMRI Activation	Procedure	Postop mJOA
1	47, F	gait difficulty	12	expanded	C3–7 laminoplasty	16
2	43, F	hand dysfunction	15	expanded	C4–5, C5–6 ACDF	17
3	75, M	gait difficulty	13	expanded	C3–6 laminectomy & fusion	16
4	68, F	hand dysfunction	14	expanded	C4–5 laminectomy & fusion	17

* ACDF = anterior cervical discectomy and fusion; mJOA = modified Japanese Orthopaedic Association Scale Score.

Table 2
Preoperative and postoperative gait analysis*

Case & Component	Preop	6 Wks Postop	3 Mos Postop	6 Mos Postop
Case 1				
walking speed (M/min)	66.27	76.69	91.80	104.4
step length (M)	0.62	0.65	0.71	0.775
cadence (steps/min)	106	118	130	134
Case 3				
walking speed (M/min)	68.65	78.78	88.28	86.745
step length (M)	0.63	0.63	0.69	0.69
cadence (steps/min)	109.81	124.98	128.98	125.38

* Gait analysis demonstrates significant improvement postoperatively in walking speed in both patients secondary to increased stride length and cadence.