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fMRI of the Lumbar Spinal Cord During a Lower Limb Motor Task

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This study applied spinal fMRI to the lumbar spinal cord during lower limb motor activity. During active ankle movement, activity was detected in the lumbar spinal cord motor areas and sensory areas bilaterally. During passive ankle movement, activity was detected in the motor and sensory areas in lower lumbar spinal cord segments and motor activity in higher lumbar spinal cord segments. Spinal fMRI detects patterns of activity consistent with known physiology and can be used to reliably assess activity in the lumbar spinal cord during lower limb motor stimulation. This study affirms spinal fMRI as an effective tool for assessing spinal cord function and increases its potential as a clinical tool. Magn Reson Med 52: 411–414, 2004. © 2004 Wiley-Liss, Inc.

Key words: Spinal fMRI; spinal cord; motor; human; imaging

Previous work with functional MRI of the spinal cord (spinal fMRI) has shown that it is a reliable tool for assessing condition and localizing activity in both healthy and injured spinal cords (1–4). To date, spinal fMRI has proven to be useful in investigating sensory and motor activity in the cervical spinal cord and sensory activity in the lumbar spinal cord. The present study is the first to apply spinal fMRI to the lumbar spinal cord during lower limb motor activity.

Spinal fMRI reveals neuronal function indirectly by way of changes in blood flow and blood oxygen levels that occur near metabolically active gray matter, as with conventional fMRI of the brain (5–7). Blood oxygen-level dependant contrast is linked to the metabolic activity that occurs in active neuronal tissues. When neuronal firing rates increase, nerve cell bodies take up more oxygen. To compensate, an overabundant increase in blood supply to neurons occurs, resulting in a decrease in the concentration of deoxygenated hemoglobin. Deoxygenated hemoglobin in blood acts as an MR contrast agent that causes the MR signal to decay quickly. At the time of recording, the MRI signal is stronger from metabolically active areas because the signal has not decayed as quickly as in the adjacent less active tissues. The MR image intensity increases as the spiking rate increases (8). However, the more dominant contrast mechanism in spinal fMRI is due to signal enhancement from extravascular water protons (SEEP), which is more closely related to the blood flow increase to the active neural tissues (9–11). When blood flow increases, the intravascular pressure also increases, particularly on the arterial side of the capillary system. This pressure change alters the normal fluid balance and increases movement across blood vessel walls into extracellular space, resulting in a slight increase of water protons near active neural tissues. This is a normal physiological process and serves to compensate for the absence of lymphatics in the central nervous system. Spinal fMRI is able to detect both primary neuron activity as well as interneuron activity in spinal cord gray matter. The sensitivity to primary neuron and interneuron activity allows for mapping of sensory and motor activity as well as reflex activity.

With spinal fMRI, stimulation of specific dermatomes has been shown to map to the corresponding spinal cord segments, and different types of sensory stimulation have mapped to the analogous gray matter regions (1,2,4). Previous work has focused on imaging of the cervical spinal cord during sensory and motor stimulation of the hands, as well as lumbar spinal cord imaging during sensory stimulation of the lower leg. Results have shown activity in the cervical cord dorsal horn and the lumbar cord dorsal horn, and these areas correlate with sensory stimulation of the hand and lower leg, respectively. In a study involving a motor task and sensory stimulation of the hand, spinal fMRI also proved reliable in displaying laterality and spread of activity in the spinal cord (4). Signal intensity changes in the lumbar cord have also been observed to depend on the temperature of cold stimulation, and have shown marked differences between innocuous and noxious cold stimulation (1,3). Recently, the spinal fMRI method has been applied to the study of injured spinal cords (1,3,12). These results are in agreement with known physiology and electrophysiology (13). Spinal fMRI is therefore able to detect neuronal activity in the appropriate spinal cord segments as well as specific gray matter areas in healthy spinal cords, and can demonstrate areas of impaired and preserved activity in spinal cord injured patients.

The implications that follow from the findings are not only important for understanding normal sensory/motor function and reflexes, but also for comprehending impaired function. The information attained by spinal fMRI regarding spinal cord condition is invaluable for designing and assessing rehabilitation programs and for evaluating potential recovery of function in those with either incomplete or complete injuries. In addition, spinal fMRI can provide information that self-report techniques are unable to acquire, such as where the cord is preserved. Significantly, this information can be obtained despite a patients' inability to report a sensation or produce a movement. The purpose of the present study was to test the efficacy of

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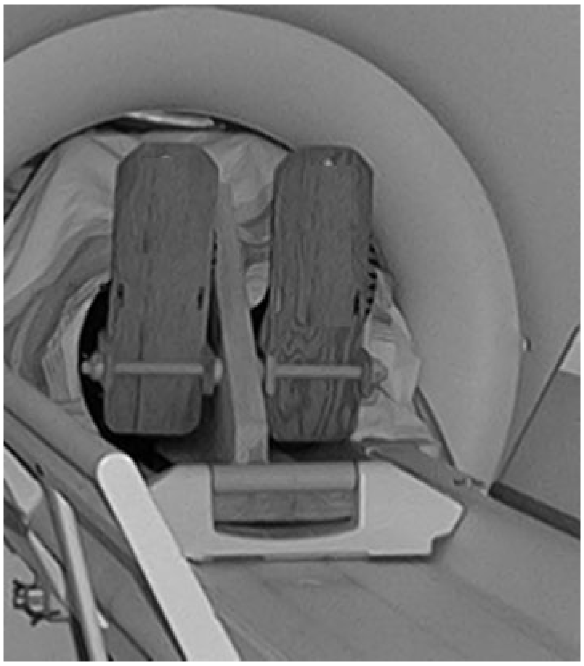

FIG. 1. MR compatible pedaling device; in place in the magnet with a healthy volunteer positioned for imaging.

spinal fMRI during motor stimulation of the lower limbs and further establish spinal fMRI as a valuable clinical and research tool by expanding the repertoire of stimuli and responses that can be assessed.

SUBJECTS AND METHODS

Six healthy subjects (five male, one female) were studied in a 1.5 T GE (Milwaukee, WI) Signa Horizon LX clinical MR system. Subjects were supine on a GE phased-array spine receiver coil, with their feet secured to an MR-compatible pedaling device specifically designed for the study. The device consisted of two pedals with adjustable straps over the toes and over and below the ankle, which was secured on a base designed to fit the MR bed (Fig. 1). The device allowed for alternating rhythmic flexion and extension movements of the ankles. The device was custom-made to assist in keeping the movements alternate and equal. Placing a cushion under the knee stabilized the thighs and reduced movement of the upper body, thereby minimizing motion effects. The study was reviewed and approved by our institute's Human Research Ethics Board and informed consent was obtained from all participants before entering the magnet room.

Spinal fMRI was carried out in a block design with two stimulation periods. During active pedaling the subjects moved the pedals with their feet in the alternating pedaling motion. During passive pedaling, the experimenter moved the pedals manually while the subject was asked to relax and let their feet be moved by the pedals. Each subject completed two series of active pedaling and one series of passive pedaling in each study. Images were acquired repeatedly during alternating rest and stimulation periods, resulting in a total of 56 time points recorded.

Functional time course data were obtained using single-shot fast spin-echo imaging with sets of eight contiguous slices from approximately the 3rd sacral spinal cord segment (S3), and spanning the entire lumbar spinal cord, up to the 1st lumbar spinal cord segment (L1). This required a repetition time of 11 sec. The single-shot fast spin-echo method employed for this study was a product sequence developed by GE, without any modification. The matrix was 128 × 128 with an echo time of 42.3 msec and an echo train length of 72 with the eighth echo at *k*-space center. Slices were oriented transverse to the spinal cord and the thickness was adjusted so that every second slice was aligned with either the intervertebral discs or centers of the vertebrae, spanning the entire lumbar cord. Adjusting the slice thickness accordingly resulted in a slice thickness range of 7.0–7.5 mm. Spatial saturation pulses were applied to eliminate signal from surrounding areas to avoid aliasing and to reduce motion artifacts arising from regions anterior to the spine. A reference image was obtained with the first subject to ensure that the same extent of the spinal cord was being imaged with all subsequent subjects.

Custom-made analysis programs written in MatLab software (MathWorks, Natick MA) were used to analyze the individual's data using a correlation method with a p-threshold of 0.05. Images were registered to reduce the effects of motion by means of rigid-body translation and rotation. However, only a small subregion of the images spanning the spine was used for the registration process to avoid influence from changes in the surrounding muscle tone. A region of interest (spinal cord white and gray matter) was outlined manually for each slice. The correlation between the time-course for each pixel and a box-car reference paradigm was then used to create individual activation maps, as in previous studies (1,3,4).

After all studies had been completed the individual activation maps were superimposed to generate combined activation maps of the 12 active runs and six passive runs from the six subjects. The resulting maps were thresholded to indicate activity only where it was duplicated in two or more series, and these activations were color-coded to indicate level of overlap. The signal intensity changes were calculated and time courses were plotted.

RESULTS

During active pedaling, activity was detected in the lumbar spinal cord ventral horn and dorsal horn bilaterally (Fig. 2). Activity was observed in the left ventral and dorsal regions of spinal cord segments S3 and S2, in the bilateral ventral horns in L5, and in the bilateral ventral and dorsal horns in L4 through L1, with increased activity in L2 and L1. The amount of activity increased at higher levels of the cord. The amount of overlap ranged from a minimum of two (yellow) up to a maximum of five (red) active pixels at one location. The average signal intensity change was 11.9 ± 1.0% (mean ± SEM) averaged over the duration of all active conditions (Fig. 3).

During passive pedaling, activity was detected in the central region and dorsal horn in lower lumbar spinal cord segments and ventral activity was detected in higher lumbar spinal cord segments. Activity was observed in the bilateral dorsal horns in the S3 and S2 spinal cord seg-

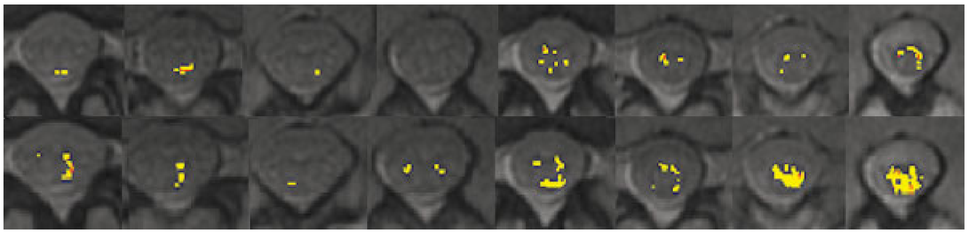

FIG. 2. Combined activity map of the lumbar spinal cord during passive pedaling (top row) showing motor and reflex activity and during active pedaling (bottom row) showing bilateral motor activity and sensory activity. Images are axial and in radiological orientation, with the right side of the body to the left of the image; dorsal is toward the bottom. Eight image slices are shown, spanning from the 3rd sacral spinal cord segment (S3) on the left, moving rostrally along the spinal cord, reaching the 1st lumbar spinal cord segment (L1) on the right.

ments, in the right ventral and central regions of the spinal cord segment L4, and in the bilateral ventral horns in the L3 through L1 spinal cord segments, with increased activity in L1. More activity was observed at higher spinal cord segments than in lower spinal cord segments for both active and passive maps. The average signal intensity change was 12.4 ± 1.1% averaged over the duration of all passive conditions.

DISCUSSION

The observed activity corresponds well with known spinal cord physiology. Movement of the ankle flexor and extensor muscles corresponds to myotomes that innervate the spinal cord at levels S1, L5, and L4. With alternating movements of antagonistic muscle groups there is reflex activity, which is relayed to other areas of the spinal cord by interneurons. This activity is seen in the central region of the spinal cord gray matter. Active pedaling involved use of the motor area as indicated by the bilateral activation of the ventral horns. This activity was seen in the lumbar spinal cord segments L5 and L4, as would be expected during active movement of the ankles. Dorsal horn activity also occurred as proprioceptive information was relayed to the spinal cord during motion.

Passive pedaling incurred sensory activity in the dorsal horn due to proprioception and central region activity due to reflexes relayed by interneurons at lower lumbar segments. Higher segments revealed ventral horn activity, which could be accounted for by reflexes. The increased activity at higher ventral levels could also be due to the subjects' tensing their thigh muscles while attempting to remain motionless as their feet were moved for them. Passive movements generated less activity overall, but the locations of the activity remained true to the physiology. The findings are reliable in that there is overlap in up to five activated pixels in locations consistent with the physiological response expected during the performed motor task from the six subjects.

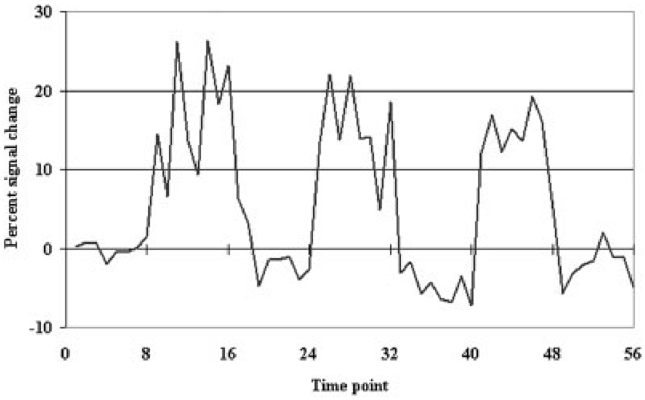

FIG. 3. Average signal intensity time course averaged across all active regions in six healthy subjects. The subjects performed a rhythmic alternated ankle flexion task during time points 9–16, 25–32, and 41–48, and rested otherwise.

The average signal intensity changes were notably higher than that observed in previous spinal fMRI studies with thermal sensory stimulation, in which values of ~8% have been reported (1–3,12). The values obtained in this study after initial analysis were observed to be 15.4 ± 1.3% and 18.3 ± 1.4% for active and passive motion, respectively. The signal intensity changes were lower when voxels identified as apparent activity that were at edge of the spinal cord, and therefore were presumed to be due to motion, were set apart from the analysis (2,3). Areas of apparent activity that were clearly the result of motion were readily identifiable based on their location and relatively high signal intensity changes. After eliminating these identifiable false activations, the signal changes observed with passive and active motion were much more similar, and these were still significantly higher than with sensory stimulation observed in previous studies. Average signal intensity changes were reduced to 11.9 ± 1.0% and 12.4 ± 1.1% when the presumed motion associated voxels were removed for active and passive motion, respectively. This would suggest that the elevated signal changes initially observed in the present study may have been due to motion effects. However, different average signal changes were observed when comparing the dorsal activity and the ventral activity after excluding the motion-induced activations. During active motion the average signal changes were 13.3 ± 1.8% for dorsal activity and 10.7 ± 1.0% for ventral activity, $P = 0.2$ (two-tailed Student's *t*-test). During passive motion, the average signal changes were 14.7 ± 2.1% for dorsal activity and 10.6 ± 1.1% for ventral activity, $P = 0.07$. Although these values likely contain residual motion effects, comparing overall dorsal activity to overall ventral activity revealed significantly different signal changes. Given that the areas of activity are mere millimeters apart in the spinal cord and are induced by the same stimuli, they should be affected equally by noise and motion. The overall signal changes were 13.8 ± 1.4% for dorsal regions and 10.7 ± 0.7% for ventral regions, for active and passive tasks combined ($P = 0.04$). The signal changes are therefore significantly different in the dorsal and ventral areas and are both significantly higher than the signal changes observed in studies with thermal stimulation. This suggests that the signal changes are indeed larger with a motor task than with sensory stimulation, and that the difference is not artifactual or due only to the task-related motion. This higher signal change seen with a motor task could originate from a greater change of neuronal activity with a motor task than with sensory stimulation. In consideration of spinal cord neuroanatomy, this could be accounted for by a larger number of neurons involved, a greater difference in spiking rate, or, based on the work of Logothetis et al. (8), greater afferent input to the gray matter with motor activity than with sensory.

CONCLUSIONS

This initial motor study demonstrates that the problems associated with motor-related tasks can be overcome and spinal fMRI can be used to reliably assess the activity in the lumbar spinal cord during lower limb motor stimulation. In spite of the effects of motion, we were able to detect consistent areas of motor and sensory activity which correspond well with spinal cord neuroanatomy. The effects of motion were identified primarily at the high-contrast boundaries at the edge of the spinal cord. Fortunately, spinal cord gray matter does not extend to the edge of the spinal cord, and with the imaging methods we employ there is very little contrast between white and gray matter. Motion effects arising at gray/white boundaries are therefore expected to be very small, with a very low probability of contributing to the identification of false-positive activations. The observed spatial characteristics of the individual and combined activity maps serve to demonstrate the reliability of our results. We propose that motion contributions to the data can be assessed at the cord boundaries, and may be used in future motor studies as a quality assurance marker, without significantly degrading the spinal fMRI results. Nonetheless, the signal changes observed with edge regions excluded were larger than observed with sensory stimulation in previous studies. This difference is presumed to have some contribution from task-related motion, but we conclude that the signal changes we have observed are accurate to within less than ±2% standard error. The signal changes observed with active and passive motor tasks (~12%) are therefore significantly higher than with thermal stimulation (~8%) employed in previous studies, and so are presumed to be due to a larger degree of neuronal activity with the motor task. This difference will be more readily investigated in future studies with spinal cord-injured subjects.

The data reported here conclude the basic spinal cord physiological testing that was required to affirm spinal fMRI as an effective tool for assessing spinal cord function. Spinal fMRI has now been proven successful at identifying sensory, motor, and reflex activity in both the cervical and lumbar spinal cord.

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