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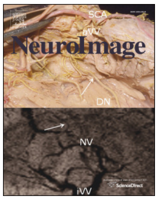

Lateralization of cervical spinal cord activity during an isometric upper extremity motor task with functional magnetic resonance imaging

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ABSTRACT

The purpose of this study was to use an isometric upper extremity motor task to detect activity induced blood oxygen level dependent signal changes in the cervical spinal cord with functional magnetic resonance imaging. Eleven healthy volunteers performed six 5 minute runs of an alternating left- and right-sided isometric wrist flexion task, during which images of the cervical spinal cord were acquired with a reduced field-of-view T2*-weighted gradient-echo echo-planar-imaging sequence. Spatial normalization to a standard spinal cord template was performed, and average group activation maps were generated in a mixed-effects analysis. The task activity significantly exceeded that of the control analyses. The activity was lateralized to the hemicord ipsilateral to the task and reliable across the runs at the group and subject level. Finally, a multi-voxel pattern analysis was able to successfully decode the left and right tasks at the C6 and C7 vertebral levels.

Introduction

In humans, the execution of skilled voluntary movements results primarily from descending excitatory inputs from the contralateral cortical motor areas through the crossing fibers of the corticospinal tract to the motoneurons in the anterior horn of the spinal cord ipsilateral to the movement (Jenny and Inukai, 1983; Lemon and Griffiths, 2005). Shortly after the introduction of the blood oxygen level dependent contrast (BOLD), studies demonstrating the feasibility of using functional magnetic resonance imaging (fMRI) to non-invasively detect motor-related brain activity were published (Bandettini et al., 1992; Joliot et al., 1999; Kim et al., 1993; Kwong et al., 1992; van Gelderen et al., 1995). The characteristic finding from these studies was the robust lateralization of the activity to the contralateral motor and sensory cortices, which is consistent with our understanding of the brain regions involved in the execution of voluntary skilled movements (Cincotta and Ziemann, 2008).

Following the success of the early brain fMRI studies, several independent groups have attempted to use fMRI to detect motor-related spinal cord activity. The development of spinal cord fMRI, however, has been slower than brain fMRI due to several technical difficulties with the imaging of the spinal cord and the analysis of functional spinal cord images (Fratini et al., 2014; Stroman et al., 2014). Despite these challenges, the field has continued to progress, and spinal cord fMRI has been used to detect motor-related activity during several different motor tasks including repetitive finger flexion and extension (Bouwman et al., 2008; Yoshizawa et al., 1996), repetitive squeezing of a ball (Giulietti et al., 2008; Stroman et al., 1999, 2001; Stroman and Ryner, 2001), repetitive fist clenching (Backes et al., 2001; Ng et al., 2006), repetitive elbow flexion and extension (Madi et al., 2001), repetitive wrist extension and flexion (Madi et al., 2001), repetitive finger abduction and adduction (Madi et al., 2001), holding weights in a flexed arm position (Madi et al., 2001), repetitive tongue movements to activate the infrahyoid muscles (Komisaruk et al., 2002), pedaling (Kornelsen and Stroman, 2004, 2007), repetitive thumb to finger apposition (Maieron et al., 2007; Ng et al., 2008; Vahdat et al., 2015), and repetitive finger tapping (Govers et al., 2007; Xie et al., 2009).

As in the brain, lateralization of the activity to the ipsilateral motor (anterior horn) and sensory (posterior horn) areas of the spinal cord during the execution of skilled voluntary movements should be expected with spinal cord fMRI. However, the lateralization of spinal cord activity has not been reliably shown in the previous motor studies. In fact, only a few of the spinal cord fMRI motor studies quantitatively assessed the laterality of the activity (Bouwman et al., 2008; Govers et al., 2007; Maieron et al., 2007; Ng et al., 2008; Stroman et al., 1999; Xie et al., 2009; Yoshizawa et al., 1996). Of these studies, only three statistically assessed the degree of laterality across the subjects, and

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Abbreviations: BOLD, blood oxygen level dependent; MR, magnetic resonance; MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging; SPACE, sampling perfection with application optimized contrast using different flip angle evolutions; FMRIB, Oxford Center for Functional MRI of the Brain; FSL, FMRIB's Software Library; PNM, physiological noise modeling.

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only Maieron et al. (2007) detected significant lateralization of the activity to the ipsilateral hemicord across the subjects (Bouwman et al., 2008; Maieron et al., 2007; Ng et al., 2008).

The shortfall of reported lateralization of the spinal cord activity in the previous studies may be due to the complexity of the motor tasks employed (e.g., repetitive thumb to finger apposition). The motor tasks required the coordinated reciprocal activation and relaxation of multiple muscle groups and likely produced an influx of neural activity from multiple cutaneous, joint, and muscle afferents. Thus, the resulting fMRI signal in the spinal cord was likely a complex summation of multiple motor, interneuronal, and sensory processes, which may have impeded the detection of task-related signal changes and the localization of activity within the spinal cord. In contrast, a less complex isometric motor task may allow for more robust signal detection in the spinal cord as the motoneuron activity and sensory inputs should remain more stable over a block of activation.

The purpose of this study was to use an isometric left- and right-sided wrist flexion task in order to minimize the complexity of the neural signal and robustly detect and localize the fMRI signal in the spinal cord. In order to determine that the signal being detected is physiological in origin and not artifactual, we test whether the activation rate exceeds the false positive rate, examine the anatomical specificity of the activity, and determine the reliability of the signal. Additional advancements with this study include the use of reduced field-of-view imaging and spatial normalization to a standard template (Cohen-Adad et al., 2014; Rieseberg et al., 2002).

Material and methods

Participants

Eleven healthy volunteers (5 male and 6 female; average age ± one standard deviation (SD) 27.7 ± 1.9 years) were studied. Subjects reported no neurological or musculoskeletal diseases or contraindications to MRI. Each subject provided written informed consent, and the entire study protocol was approved by the Northwestern University's Institutional Review Board.

Data acquisition

Imaging was performed with a 3.0 T Siemens (Erlangen, Germany) Prisma magnetic resonance (MR) scanner equipped with a 64-channel head/neck coil (anterior and posterior neck coils were used (24 channels) and head coils 1–4 were turned off). Subjects were placed supine on the scanner bed. A SatPad™ cervical collar was used to increase the magnetic field homogeneity across the cervical spine and to reduce bulk motion during scanning (Maehara et al., 2014). For the functional images, thirty-one transverse slices of the cervical spinal cord were acquired with a $T2^*$-weighted gradient-echo echo-planar-imaging sequence using ZOOMit selective field-of-view imaging ($TR = 2500$ ms, $TE = 30$ ms, flip angle $= 80°$, acquisition matrix $= 128 \times 128$, field-of-view $= 128 \times 128$ mm^2, in-plane resolution $= 1 \times 1$ mm^2, slice thickness $= 3$ mm, discarded 2 dummy volumes) (Pfeuffer et al., 2002; Rieseberg et al., 2002). The imaged volume spanned from the inferior endplate of the third cervical vertebra to the superior endplate of the first thoracic vertebra. For registration of the functional images to standard space, a high-resolution T2-weighted structural image of the entire cervical spine and upper thoracic spine was acquired using a single slab 3D turbo spin echo sequence with a slab selective, variable excitation pulse (SPACE, $TR = 1500$ ms, $TE_{eff} = 115$ ms, echo train length $= 78$, flip angle $= 90°/140°$, resolution $= 0.4 \times 0.4 \times 0.8$ mm^3) (Lichy et al., 2005; Mugler et al., 2000).

During functional imaging, the subjects performed an alternating left- and right-sided upper extremity isometric motor task. Rigid plastic resting hand splints were used to immobilize the wrist and hand bilaterally. When prompted by visual instructions presented during scanning, the subjects were trained to produce and maintain a constant flexion force at the left or right wrist of about 50% of their maximum force output. The subjects performed six 15 s trials of left wrist flexion and six 15 s trials of right wrist flexion per run. The order of the trials was pseudorandomized, each trial was separated by a varying duration rest period for a total time of 5 min per run, and each subject performed six runs. A 5 min task free (resting state) run was also collected for control purposes. Throughout imaging, the subjects were instructed to remain still and not produce any other movements. Subject performance was observed by the study personnel throughout each run.

Motion correction

Image preprocessing and statistical analyses were performed using the Oxford Center for fMRI of the Brain's (FMRIB) Software Library (FSL) (Jenkinson et al., 2012; Smith et al., 2004). Motion correction was performed using FMRIB's Linear Image Registration Tool with spline interpolation and a normalized correlation cost function (Jenkinson et al., 2002). To exclude areas of non-rigid motion outside of the vertebral column, a manually drawn binary mask of the vertebral column was used to weight the reference image. For the first phase of motion correction, the images across the runs were realigned to the first image of the first run with three-dimensional rigid body realignment. To correct for slice independent motion due to the non-rigidity of the cervical spine and physiological motion from swallowing and the respiratory cycle, a second phase of motion correction was performed in which a two-dimensional rigid realignment was performed independently for each axial slice using the mean image from the first phase of motion correction as the reference image (Cohen-Adad et al., 2009; Weber et al., 2014). The average temporal signal to noise ratio (tSNR) across the spinal cord was calculated for each phase of motion correction and compared using two-tailed paired t-tests.

Physiological noise modeling

The cardiac and respiratory cycles are significant sources of noise in spinal cord fMRI and can confound signal detection. To account for this noise, respiratory signals, cardiac signals, and MRI triggers were collected during scanning (sampling rate = 400 Hz, PowerLab 8/30, ADInstruments Inc., Colorado Springs, CO, US), and slice specific voxelwise noise regressors were generated using FSL's physiological noise modeling (PNM) tool, which uses a model-based approach similar to the retrospective image correction (RETROICOR) of physiological motion effects as described by Glover et al. (Brooks et al., 2008; Glover et al., 2000). In brief, a cardiac phase and respiratory phase were assigned to each slice, and the cardiac and respiratory signals were then modeled using a Fourier series (sine and cosine terms) with the principal frequency and the next three harmonics (16 regressors). Multiplicative terms were included to account for the interaction of the cardiac and respiratory cycles (16 additional regressors). A cerebrospinal fluid (CSF) regressor was also generated from the raw CSF signal surrounding the spinal cord using a manually drawn CSF mask. In total, the physiological noise was modeled with 33 regressors, which has been recommended for spinal cord fMRI (Kong et al., 2012). This model does not include the motion parameters as noise regressors, so the effect of including the motion parameters as noise regressors was also explored to control for task-related motion.

Spatial normalization

Spatial normalization from native space to standard space was performed using the open-source Spinal Cord Toolbox (Cohen-Adad et al., 2014). The structural images of the cervical spine were cropped to include the C2 to T1 vertebrae. The C2 and T1 vertebrae were manually identified, and a vertebral landmarks mask was generated. The functional images were registered to the structural image using a non-

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