BOLD and Blood Volume-weighted fMRI of Rat Cervical Spinal Cord with GE and SE EPI

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[INTRODUCTION] Spinal cord is an important relay of pain pathway. fMRI can indirectly detect the neural activation in central nervous system by detecting the neural activation-induced hemodynamic response (*1*). fMRI results of cervical spinal cord with regard to the spatial extension, in both longitudinal and cross-sectional direction, of neuronal activation induced by noxious forepaw stimulation are inconsistent and inconclusive. Previous cervical spinal cord fMRI experiments were mainly performed using a fast spin echo (RARE) sequence because it is less sensitive to magnetic field inhomogeneities, but compromising fMRI sensitivity (*2*). In this study, we investigate the feasibility of pain fMRI in the cervical spinal cord by BOLD and blood volume-weighted fMRI using gradient echo (GE) and spin-echo (SE) EPI.

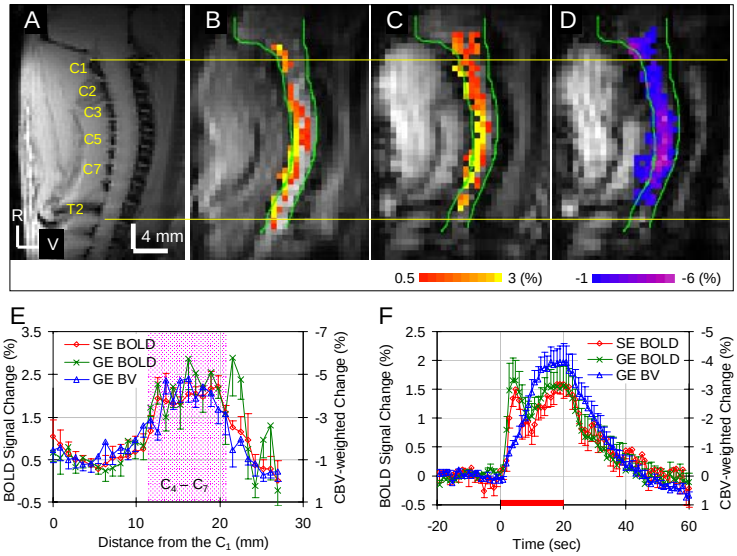

Fig. 1. BOLD and BV-weighted fMRI in the sagittal slice. The corresponding sagittal anatomical image is shown in (A). Noxious stimulation-induced SE BOLD (B), GE BOLD (C) and GE CBV-weighted (D) fMRI data were obtained before (BOLD) and after (BV-weighted) injection of USPIO, and are displayed as relative signal changes. Positive changes (red/yellow) are observed in SE and GE BOLD fMRI, indicating an increase in venous blood oxygenation, while negative changes (blue/violet) are detected in CBV-weighted fMRI, indicating an increase in spinal blood volume. All activations were mainly observed in the dorsal region. Green lines outline the surface of spinal cord in (B) and are overlaid on (C and D). Two horizontal yellow lines indicate the positions of C1 and T2. D: Dorsal; M: Medial; R: Rostral; V: Ventral. (E) shows the activation profiles averaged over animals for noxious stimulation in rostral-caudal direction. Spinal cord corresponding to C1 is at zero, with the caudal direction represented by increasing distances. (F) shows averaged time courses of BOLD and CBV-weighted fMRI (mean ± SEM, n=5). Red bars under the time courses indicate the 20-s stimulation period.

[METHODS] The animal protocol was approved by the Institutional Animal Care and Use Committee of Merck Research Laboratories. All MRI measurements (5 rats) were performed on a 7T/30cm bore Bruker Biospec system. Animals were under the α-chloralose anesthesia. An actively-decoupled 3 cm diameter surface coil positioned above the cervical spinal cord of the rat was used as the RF receiver, while an actively-decoupled 72-mm diameter volume coil was used as the RF transmitter. Anatomical images in two directions (axial and sagittal) were first acquired by a FLASH sequence. From the sagittal image, the 2nd thoracic spinous process was identified and used as a landmark to locate the appropriate vertebral levels (Fig. 1A). Both GE EPI and SE EPI were used for BOLD fMRI and only GE EPI was used for BV-weighted fMRI. Noxious electrical stimulation (2ms, 5mA, 40Hz, known to maximally activate C-fibers) was used. To view the extent of activation in the rostral-caudal direction, fMRI data with single 2mm sagittal slice was acquired to cover the spinal cord at vertebral level from cervical ~C1 to thoracic ~T3 in the rostral-caudal direction and to cover the bilateral dorsal horns in cross-sectional direction. The maximum activation induced by bilateral forepaw stimulation is expected to be detected in this slice. Single-shot GE and SE EPI were used; matrix size = 64 × 64, field of view = 4 cm × 4 cm, gradient echo time (TE) = 11.3 ms, spin echo time (TE) = 35 ms. Each run consisted of 20-**20**-40 image acquisitions (boldface represents stimulation on) with repetition time (TR) =1 sec. To examine the locations of BOLD and CBV-weighted fMRI signals in the cross-sectional direction of the spinal cord by unilateral forepaw stimulation, eight axial images were further acquired in vertebral levels of ~C3 and ~T1. Multiple-slice single-shot GE EPI was used; matrix size = 64 × 64, field of view = 3 × 3 cm^2.

[RESULTS and DISCUSSION] Robust activations were detected in cervical spinal cord in all rats. In GE BOLD fMRI (Fig. 1C), the highest percentage signal changes (yellow pixels) were mainly seen near the spinal cord dorsal surface (green contours). This observation is consistent with previous GE BOLD studies of rat lumbar spinal cord, rat somatosensory cortex (*3*) and cat visual cortex (*4, 5*), where the highest BOLD signal changes were seen in lumbar spinal surface and cortical surfaces. Interestingly, the highest signal changes in SE BOLD fMRI (Fig. 1B) were also mainly seen near the dorsal surface. The high sensitivity of SE BOLD to the spinal surface is probably caused by CSF due to its high diffusion. These results are different from the previous GE BOLD fMRI (*6*) and the SE BOLD fMRI of rat spinal cord (*7*), where the highest BOLD signal changes were seen more towards the interior of the spinal cord. In BV-weighted fMRI (Fig. 1D), the areas of highest signal change (violet pixels) are shifted towards parenchyma. In the rostral-caudal direction, activations of BOLD and BV-weighted fMRI extend from brain stem to T1, with the highest activation located between the vertebrae level C4-C7. To quantitatively analyze the spatial extent of activation in the rostral-caudal direction, profiles of signal changes across vertebral levels were obtained. Averaged results from five animals were plotted as a function of distance from the C1 (Fig. 1E) with the largest signal changes occur at the level of the vertebrae C4 to C7, which roughly corresponds to spinal cord segments C4-C8 (*8*). Time courses of fMRI activations are shown in Fig. 1F. Interestingly, there are humps at the initial response of both GE and SE BOLD signals, which are not seen in the BV response. These humps are most likely caused by arterial blood pressure increase due to an autonomic response to noxious stimulation, picked up by BOLD because of its sensitivity towards deoxyhemoglobin density change in larger draining veins. Fig. 2 shows the activation maps in one axial slice by these three fMRI methods. The activation mainly locates in the ipsilateral dorsal horn, with the highest activation of both GE and SE BOLD in and near the spinal surface. Our results show that the noxious stimulation-induced activation in cervical spinal cord can be robustly detected by GE BOLD, SE BOLD, and GE BV-weighted fMRI with EPI sequence.

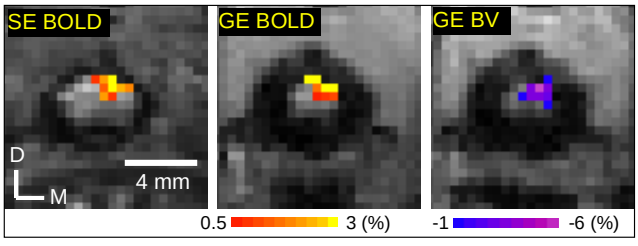

Fig. 2. BOLD and BV-weighted fMRI in axial direction induced by unilateral (right) hindpaw stimulation. The significant positive signal changes (red/yellow) in these GE and SE BOLD maps and negative signal changes in BV-weighted fMRI were observed in ipsilateral dorsal region of spinal cord. D: Dorsal; M: Medial.

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