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Cervical spinal cord BOLD fMRI study: Modulation of functional activation by dexterity of dominant and non-dominant hands

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The objective of this study was to investigate the effect of dexterity on the magnitude of signal changes in functional magnetic resonance imaging (fMRI) in the cervical spinal cord with unilateral finger-tapping. Right-handed healthy volunteers were investigated with blood oxygenation level-dependent (BOLD) fMRI. Spinal cord BOLD functional MR images were acquired from 10 healthy right-handed volunteers who performed four sessions of unilateral finger-tapping tasks: left sequential (LS), right sequential (RS), left interleaved (LI), and right interleaved (RI) tasks. Our results from the difficulty measurement test showed that finger-tapping in interleaved order was more difficult than in sequential order. For the functional activation, seven out of 10 subjects had activation in all four fMRI sessions (two of the subjects who showed no detectable activation had problems in volume registration). The mean contrast value of the activation area inside the entire cervical spinal cord was significantly higher in performing LS than RS tasks. The increase in the mean contrast value was because the less skilled and competent right hemisphere required additional processing power for doing the left hand task than the left hemisphere required in doing the right hand task. The analysis of the interleaved finger-tapping tasks did not show any significant difference in the results. This was probably because the interleaved task was similarly challenging for both hands, and required high dexterity. Therefore, differences in activity between the left and right hands were less apparent. Our results showed the modulation of activation intensity in the spinal cord by the dexterity.

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Keywords: BOLD fMRI; Dexterity; Functional activation; Spinal cord

Introduction

Contralateral activations found in the brain were revealed in 1973 by Brinkman and Kuypers (1973), who showed that right hand movements are associated with neural activity in the left motor cortex, while left hand movements are associated with neural activity in the right motor cortex. The action potential carrying the motor information travels along the white matter tract from the contralateral motor cortex of the cerebrum down to the midbrain, pons, and medulla oblongata, at which the neuronal fibers cross to the ipsilateral side and finally reach the spinal cord. Therefore, contralateral activations in the brain and ipsilateral activations in the spinal cord are both present.

The advances of magnetic resonance imaging (MRI) and positron emission tomography (PET) enable the investigation of tissue structure *in vivo*. Functional MRI (fMRI) and PET enable functional mapping of different activities in the central nervous system (CNS). Since the findings of Brinkman and Kuypers, (1973), researchers have been investigating the relationship between task complexity, dexterity, handedness, and functional activation of both ipsilateral and contralateral hemispheres (Jancke et al., 1998; Kawashima et al., 1993; Kim et al., 1993; Li et al., 1996; Rao et al., 1993; Singh et al., 1998; Wexler et al., 1997). It has been found that stronger brain functional activation is associated with left hand rather than right hand movement in right-handed individuals (Jancke et al., 1998; Kim et al., 1993). It has been suggested that right-handed individuals expend more effort performing with their non-preferred hand (Jancke et al., 1998), which means that the less skilled and competent system expends more effort (the anatomical studies of Amunts et al., 1996, cited in Jancke et al., 1998) and therefore provides more fMRI signals. The functional organization difference in the brain in response to task complexity has also been documented. It has been found that more functional areas are activated in the brain during complicated motor tasks than during simple tasks (Rao et al., 1993; Wexler et al., 1997). On the other hand, an ipsilateral activation

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component has been reported in brain fMRI studies with unilateral finger motion (Li et al., 1996; Singh et al., 1998). It shows that the activation induced in unilateral finger movement is not restricted to the contralateral cortex. This finding has also recently been confirmed in the cervical spinal cord using blood oxygenation level-dependent (BOLD) fMRI (Maieron et al., 2007). The recruitment of the ipsilateral cortex has also been shown to be more pronounced when participants use their non-dominant hand in fMRI (Singh et al., 1998) and PET (Kawashima et al., 1993) studies.

In the past 20 years, BOLD (Ogawa et al., 1990a,b) and signal enhancement by extravascular protons (SEEP)-weighted (Stroman et al., 2002) fMRI have been introduced for imaging the human cervical spinal cord. The present study was focused on BOLD fMRI. Previous studies have shown that BOLD fMRI is feasible in the spinal cord at both 1.5 T and 3 T, and the activation areas detected have good localization at the segmental level (Govers et al., 2007; Madi et al., 2001; Maieron et al., 2007; Stroman et al., 1999; Stroman and Ryner, 2001; Yoshizawa et al., 1995). Although it has been shown that BOLD fMRI can be affected by the draining veins, especially at the surface of the spinal cord (Govers et al., 2007), modulation of activation can still be detected during upper limb movement (Madi et al., 2001; Maieron et al., 2007). It has been shown that there is a linear relationship between the applied force and the BOLD signal amplitude during isometric exercise (Madi et al., 2001), and that there is also a movement rate-dependent increase in spinal fMRI signals (Maieron et al., 2007). All these studies have shown that spinal BOLD fMRI is a reliable and sensitive tool for studying the modulation of functional activity in the spinal cord.

In the current study, we investigated the effect of dexterity on the BOLD activation intensity in the cervical spinal cord in right-handers. This was examined in the context of finger-tapping tasks in both sequential and interleaved order. Our hypothesis is that the modulation of the functional signal observed in the brain is also reflected in the spinal cord. Since the spinal cord is the output station of the CNS, by studying the modulation of the functional signal in the cervical spinal cord, functional activation for a specific task can be assessed directly.

Materials and methods

Subjects

Ten right-handed healthy volunteers were recruited for this study. All were male, aged between 18 and 25 years, and had normal cervical spinal cords, without any history of disease or injury. The subjects included did not have any special training leading to different dexterity (none of the subjects knew how to play musical instruments and their typing speed was medium). Each subject gave fully informed consent prior to participating in the experiments. The protocol was approved by the Research Ethics Committee of the institution in which the study was carried out. For screening, sagittal T2-weighted and T1-weighted images were acquired before the fMRI study to ensure that the subjects recruited did not have abnormal MR signals in the spinal cord or any stenosis arising from the intervertebral discs or vertebrae.

Scanning

Subjects were in the supine position in a 3 T MR system (Philips Achieva), and a multi-element spine coil was used to image the neck region enclosing the C1 to C7 vertebral levels. BOLD functional MR images were acquired with a single-shot gradient-echo echo planar imaging (GE-EPI) sequence. Thirteen axial slices were acquired with each one placed at either vertebral or disc level from C1 to C7. The imaging parameters were as follows: field of view (FOV), 80 mm; rectangular FOV (RFOV), 45%; scan percentage, 80%; matrix size, 80; voxel size, $1 \times 1.33 \times 5$ mm^3; slice thickness, 5 mm; phase-encoding direction, anterior/posterior; flip angle, 45°; repetition time (TR), 2.5 s; echo time (TE), 15 ms; EPI factor, 29; number of averages (NEX), 3; and acquisition time per volume, 7.5 s (for 3 NEX). Spatial suppression pulse was used to suppress the anterior and posterior regions outside the FOV.

Exercise paradigm

There were altogether four fMRI sessions for each subject to complete: left sequential (LS), right sequential (RS), left interleaved (LI), and right interleaved (RI) finger-tapping. In order to describe the sequential tasks (LS and RS) and interleaved tasks (LI and RI), each digit was given a number, starting with the thumb as 1 and ending with the little finger as 5. LS and RS tasks required the thumb to touch the digits sequentially in the order of 2, 3, 4, and 5, whereas LI and RI tasks were in the order of 4, 2, 3, and 5. In order to have a relatively objective measure of the task difficulty and to verify that finger-tapping in the interleaved order was more difficult than in the sequential order, the task difficulty was measured for each subject before scanning. This consisted of measuring the time for each subject to do each of the four tasks for 20 cycles at their maximum speed.

The exercise paradigm used in the fMRI studies was a block design consisting of four cycles of alternating rest and motor periods, acquiring 10 scans for each motor or rest period. The subjects were instructed to perform all the tapping tasks at a constant rate of 1 Hz in a self-paced manner. All subjects' motor performances were monitored visually during the entire fMRI scans to ensure that the motor task was performed properly.

Post-processing

The data were processed by means of a 2D rigid-body registration with three degrees of freedom to reduce any effect of bulk motion. This was carried out with the Automated Image Registration software (Woods et al., 1998). The resliced data sets were then analyzed using SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, London, UK). A box-car function was used to model the hemodynamic response. Statistical maps SPM{t} were then generated for all the subjects (uncorrected $P < 0.001$). In order to investigate the ipsilateral and contralateral components of functional activation, as well as the entire cervical spinal cord, binary masks for the left and right sides of the spinal cord and the binary mask for the entire cord were created manually. It has been shown that activation detected by spinal BOLD fMRI may have a problem of “absence of activation” at the expected spinal level in some cases (Govers et al., 2007); therefore, when calculating the intersubject mean for the percentage signal change, contrast value and activation volume of the activation areas in different vertebral levels, segments with no detectable activation were excluded. The mean contrast value, percentage signal change, and activation volume in the entire spinal cord, as well as on the ipsilateral and contralateral sides, were obtained.

Statistical analysis

The non-parametric Wilcoxon signed-rank test for paired samples was performed to detect any significant difference in the mean contrast value and the mean percentage signal change of the activation areas of the entire cervical spinal cord, between the LS and RS and between the LI and RI tasks. This statistical test was used in this study because the samples were paired and a normal distribution could not be assumed with the limited number of samples. The mean activation volume was not put in the statistical test due to the "absence of activation" problem mentioned (Govers et al., 2007), which could have adversely affected the results. For the investigation of the ipsilateral and contralateral activation components, the non-parametric Wilcoxon signed-rank test for paired samples was again used to detect any significant difference on the ipsilateral and contralateral components between LS and RS and between LI and RI. All the statistical tests were carried out in three different spinal cord vertebral ranges (first test C1–C7, second test C1/C2–C7, and third test C5–C7). The reason for carrying out the tests on C1/C2–C7 and C5–C7 is given in the discussion. The statistical tests were conducted using the software SPSS Rel. 13.0 (SPSS, Chicago, IL, USA).

Results

For the difficulty measurement test, the time for doing 20 cycles of the interleaved tasks (LI and RI) was significantly longer than for the sequential tasks (LS and RS), using the Wilcoxon signed-

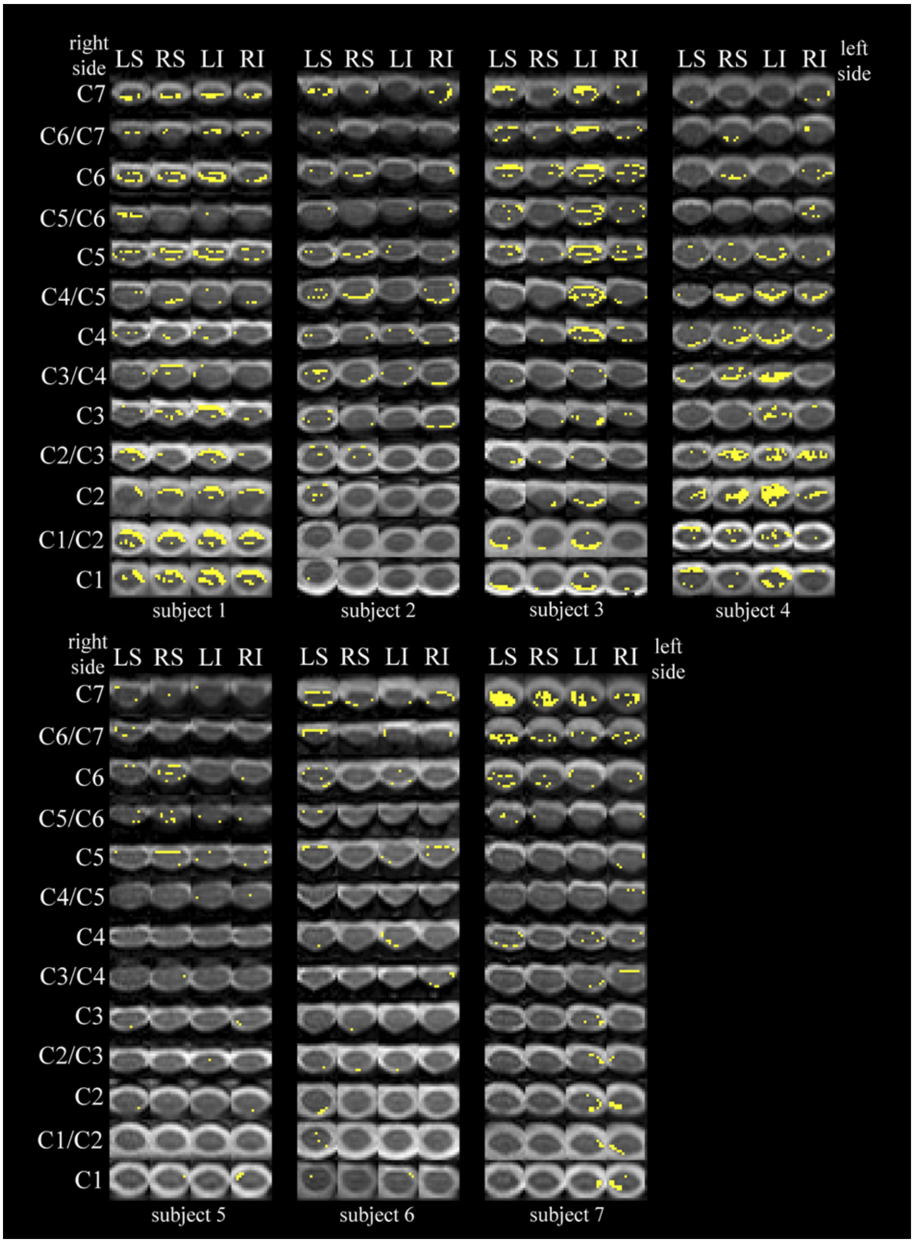
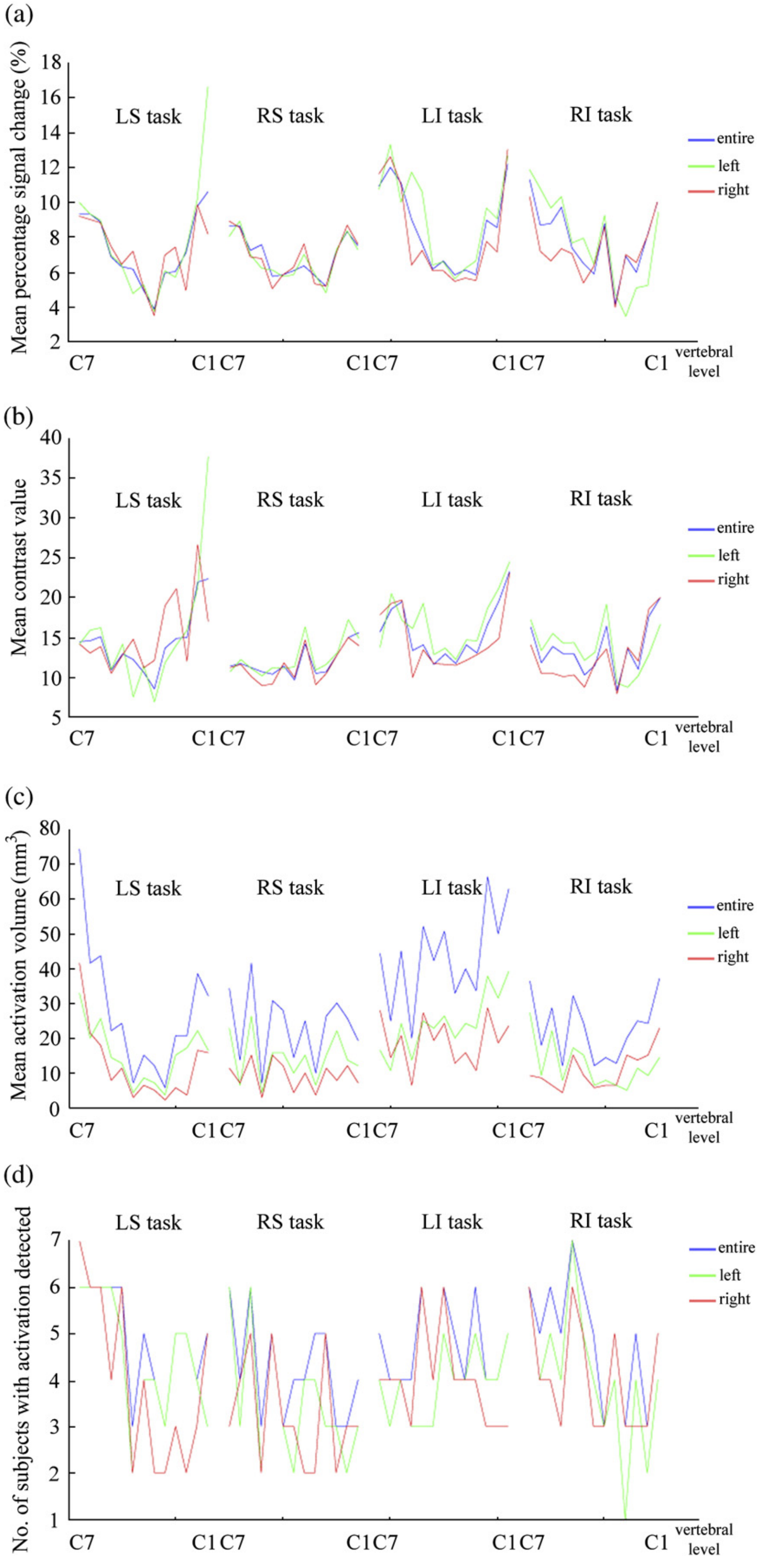


Fig. 1. Masked activation maps (uncorrected $P<0.001$) of all subjects who had activation detected in four unilateral finger-tapping tasks overlaid on the echo-planar imaging (EPI). The yellow patches in the spinal cords are the activation regions detected. (LS—left sequential; RS—right sequential; LI—left interleaved; RI—right interleaved).


(a)
Mean percentage signal change (%)
18
16
14
12
10
8
6
4
2
LS task
RS task
LI task
RI task
entire
left
right
C7
C1 C7
C1 C7
C1 C7
C1
vertebral level
(b)
Mean contrast value
40
35
30
25
20
15
10
5
LS task
RS task
LI task
RI task
entire
left
right
C7
C1 C7
C1 C7
C1 C7
C1
vertebral level
(c)
Mean activation volume (mm^3)
80
70
60
50
40
30
20
10
0
LS task
RS task
LI task
RI task
entire
left
right
C7
C1 C7
C1 C7
C1 C7
C1
vertebral level
(d)
No. of subjects with activation detected
7
6
5
4
3
2
1
LS task
RS task
LI task
RI task
entire
left
right
C7
C1 C7
C1 C7
C1 C7
C1
vertebral level

rank test for paired samples ($P<0.001$). This implies that tapping the fingers in interleaved order was more difficult than in sequential order.

For the fMRI studies, seven out of the 10 subjects recruited exhibited BOLD activation in all four fMRI sessions. When the translation and rotation parameters from the registration process were investigated, it was found that the maximum in-plane (x, y) translations among the seven subjects who had activation detected were 3.28 and 4.87 mm, and the maximum rotation was 2.10°. However, among the three subjects who had no activation detected, two showed abnormal bulk motion parameters (maximum translation >1 cm) in at least one of the four fMRI sessions, due to volume mis-registration in some of the fMRI dynamics. Fig. 1 shows the masked activation maps of all seven subjects. Functional activity was seen inside the spinal cord. Activation on both the ipsilateral and contralateral sides was observed in all seven subjects. Fig. 2 shows the properties of the activation signal at different vertebral levels. Figs. 2a–c shows the mean percentage signal change, mean contrast value, and activation volume of the activation areas at different vertebral levels across subjects, while Fig. 2d shows the number of subjects with activation detected at different vertebral levels during different tasks. For the comparison between left hand and right hand tasks (Fig. 3), the Wilcoxon signed-rank test showed that the mean contrast value of the activation areas in the LS task was significantly higher than that in the RS task (Fig. 3a, Table 1), while there was no significant difference between the LI and RI tasks (Fig. 3a). There was a trend toward an increase in the mean contrast value on the ipsilateral side in the LS task (Table 1), although it did not pass the statistical threshold. Although the percentage signal change showed a trend similar to contrast value, it was not statistically significant.

Discussion

Our results showed that the functional activation induced in unilateral finger-tapping tasks could be detected inside the cervical spinal cord by using BOLD fMRI. Both ipsilateral and contralateral activations were detected in all seven subjects who had activation seen inside the spinal cord. This was consistent with our previous study (Ng et al., 2006) and the most recent studies (Maieron et al., 2007). It was found that the mean contrast value of the entire cervical spinal cord in the LS task was significantly higher than in the RS task, while there was no significant difference between the LI and RI tasks (Fig. 3a). There was a trend that the higher mean contrast value in LS was due to an increase in contrast value of the ipsilateral components (Fig. 3b).

In finger-tapping, the corticospinal tract and different extrapyramidal tracts (the rubrospinal, vestibulospinal, and reticulospinal tracts) are involved in the conduction of the motor information action potential (Govers et al., 2007). These tracts run down to the gray matter of the ipsilateral cervical spinal cord and synapse at the level of the exiting nerve root (Govers et al., 2007). The sensory feedback consists of proprioceptive activation rather than tactile stimulation (Jansma et al., 1998). The lateral spinothalamic tract transmits the proprioceptive impulses to the brain. The fibers ascend one level before they synapse on the ipsilateral side in the substantia gelatinosa (Govers et al., 2007). The dorsal and ventral spinocerebellar tracts also pass on proprioceptive information from the joints, tendons, and muscle spindles. These fibers synapse immediately on the ipsilateral side and then run toward the cerebellum, mostly on the ipsilateral side (Govers et al., 2007).

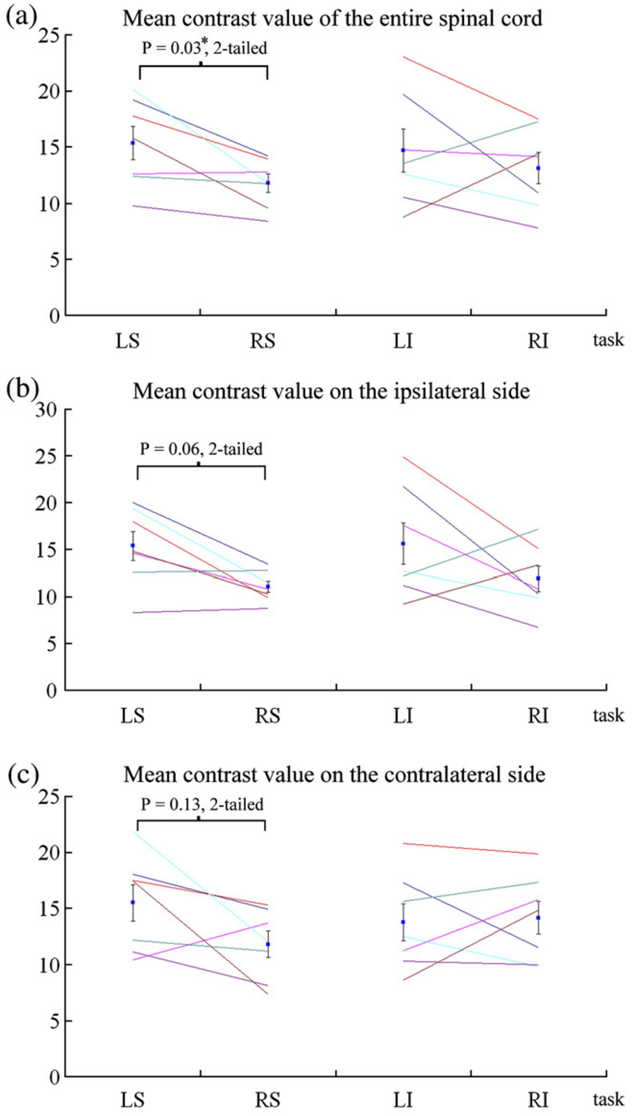


Fig. 3. Mean contrast value comparison of the activation areas in (a) the entire cervical spinal cords, (b) on the ipsilateral side, and (c) on the contralateral side from C1/C2 to C7 vertebral levels in seven subjects. The intersubject mean with standard error is also shown (LS—left sequential; RS—right sequential; LI—left interleaved; RI—right interleaved; * means significant difference using non-parametric Wilcoxon signed-rank test for paired samples). Tapping the fingers in an interleaved order (LI and RI) is more difficult than in a sequential order (LS and RS) from the difficulty measurement test mentioned.

Fig. 2. Properties of the activation signal in different vertebral levels from C1 to C7 across subjects. (a) Mean percentage signal change; (b) mean contrast value; (c) mean activation volume; (d) number of subjects with activation detected in the entire cervical spinal cord and on the left and right hand sides in different finger-tapping task. (LS—left sequential; RS—right sequential; LI—left interleaved; RI—right interleaved). It was shown that tapping the fingers in an interleaved order (LI and RI) is more difficult than in a sequential order (LS and RS) from the difficulty measurement test mentioned.

Table 1

P-value from the activation intensity comparison between the mean contrast value in the left sequential (LS) task and right sequential (RS) task using Wilcoxon signed-rank test for paired samples at three different spinal cord vertebral ranges (* means significant)

Vertebral ranges	C1–C7	C1/C2–C7	C5–C7
Entire spinal cord	0.03* (two-tailed)	0.03* (two-tailed)	0.02* (two-tailed)
Ipsilateral side	0.06 (two-tailed)	0.06 (two-tailed)	0.09 (two-tailed)
Contralateral side	0.09 (two-tailed)	0.13 (two-tailed)	0.13 (two-tailed)

Therefore, fMRI signals are expected in the gray matter on the ipsilateral side at a vertebral level between C5 and T1. When considering the segmental localization of our results, >85% of subjects had activation detected between C5 and C7 in the LS, RS, and RI tasks (Fig. 2d), which is consistent with current knowledge of neuroanatomy. This region also has a high percentage signal change, as indicated in Fig. 2a. The LI task was less consistent with the other three tasks, and the peak was absent in C5–C7 (Fig. 2d), which may be due to the problem of “absence of activation” (Govers et al., 2007) in some of the subjects (Fig. 1). This problem was suggested to occur with BOLD fMRI in the spinal cord (Govers et al., 2007). On the other hand, a small peak was observed at the C3–C4 level (Fig. 2a) in some of the subjects. This peak at C3–C4 has been reported previously (Govers et al., 2007; Stracke et al., 2005), and has been suggested to be caused by the existence of an interneuronal system at this level (Stracke et al., 2005).

Conventional neuroanatomy and previous spinal BOLD fMRI studies (Stroman et al., 1999; Stroman and Ryner, 2001; Yoshizawa et al., 1995) have shown that activation induced by unilateral hand movement localizes mainly on the ipsilateral side, with little on the contralateral side. The contralateral activation is suggested to be due to the involvement of reflex arc pathways in the spinal cord (Stroman and Ryner, 2001). However, in a recent spinal fMRI study (Maieron et al., 2007) and our current study, both ipsilateral and contralateral activation exists in unilateral finger-tapping. The discrepancy may be due to the use of different tasks. In the earlier studies mentioned, simple hand gripping (Yoshizawa et al., 1995) and bulb squeezing (Stroman et al., 1999; Stroman and Ryner, 2001) were used. However, in the recent study by Maieron et al. (2007) and our current study, more complex movement of digits was involved. A larger number of interneurons may discharge during movements of either hand (Maieron et al., 2007), which results in a higher degree of interhemispheric interaction (Kobayashi et al., 2003; Matsunami and Hamada, 1984) for facilitatory and inhibitory effects to suppress mirror movement by the corticospinal pathway, in anticipatory postural control or in bimanual coordination (Maieron et al., 2007). On the other hand, it has also been reported that the draining veins, particularly those located at the surface of the spinal cord, can contribute to BOLD signals, which can hinder the localization capability and give rise to artifactual fMRI signals (Backes et al., 2001; Govers et al., 2007). The contralateral activation near the spinal cord boundary could be attributed to the draining vein effect in some of our cases.

There are limitations in our experiments. Firstly, the cross-sectional diameter of the spinal cord is very small (~10 mm). Also, the spinal cord is subjected to considerable magnetic field inhomogeneity because of the large susceptibility difference among tissues. This problem becomes more severe with gradient-echo-based BOLD fMRI, due to the absence of the 180° refocusing pulse. Thus, it is difficult to obtain detailed information of functional localization in BOLD fMRI (Govers et al., 2007; Stracke et al., 2005). Secondly, physiological motion arising from blood and cerebrospinal fluid flow and breathing can decrease the sensitivity of fMRI. Recently, it has been found that the physiological motion artifacts can be minimized by utilizing cardiac triggering information (Stroman, 2006). The other limitation of this study was that it was difficult to provide an objective measure of the difficulty of the tasks. Although in this study the time for doing 20 cycles of each finger-tapping task at maximum speed was used to quantify the difficulty level of the sequential and interleaved tasks, we realized that it was not a perfect index to measure the difficulty, as the tapping rate used (maximum speed) was different from that of the exercise paradigm in the fMRI study (self-paced at 1 Hz). However, we think that it provides a general idea that tapping the fingers in an interleaved order is more difficult than in a sequential order.

In Figs. 2a and b, an abnormally high BOLD signal was detected at C1. The mean percentage signal change was as high as 16.6%. This high signal change, also observed by Backes et al. (2001) is suggested to either originate from large veins or to be due to the difference in BOLD effects in the brain and spinal cord (Backes et al., 2001). Therefore, in order to minimize the possible effect from large veins, statistical tests for comparing the contrast value and percentage signal change between LS and RS and between LI and RI tasks have been conducted in three different spinal cord vertebral ranges. The first test covered all the slices (C1–C7). The second one omitted C1 (C1/C2–C7), and the third test covered only the segments where synaptic activities are expected to take place (C5–C7). The observation that the mean contrast value of activation areas in the LS task was significantly higher than that in the RS task (Fig. 3a, Table 1) means that there is more functional-hemodynamic coupling in the LS than in the RS tasks. This implies more intensive neuronal activity in sequential finger-tapping tasks using the non-dominant hand than using the dominant hand. It also appears as if the increase in neuronal activity was due to an increase in the activity on the ipsilateral side (Fig. 3b, Table 1). All these results are related to the dexterity of the subjects. It has been suggested that the superiority of the dominant hand lies not in its greater strength but in its greater skill (Geschwind, 1975; Singh et al., 1998). For right-handed subjects, the left hand is less skilled and competent than the right hand. The non-dominant right motor cortex has less processing capacity to control left hand tasks than the dominant left motor cortex has to control right hand tasks. Additional processing demands are required when using the left hand rather than the right hand (anatomical studies of Amunts et al., 1996, cited in Jancke et al., 1998). Therefore, more neuronal input was involved, providing a stronger fMRI signal (higher contrast value) on the ipsilateral side of the spinal cord in the LS than in the RS task. It was originally expected that the comparison of the contrast value between the LI and RI tasks would have similar results as the LS and RS tasks. However, our results showed that it was not statistically significant (Fig. 3). It was probably due to the higher difficulty level in the interleaved task than in the sequential task, as shown in the difficulty measurement test. Therefore, the interleaved task was similarly challenging for both hands, and required high dexterity. Due to the limited sample size in this study, no significant difference in the mean contrast values between the LI and RI tasks could be obtained. On the other hand, the sequential task was less challenging for the right hand than the left, and therefore differences in activity were apparent. For the analysis of the percentage signal change, no task comparison showed a significant difference. This may be due to the fact that the contrast value was the parameter estimated directly in the generalized linear model, and it provided a better estimation for the activation intensity than the mean percentage signal change did. Due to the limited sample size mentioned, there was only a trend toward an increase in the percentage signal change in the sequential task by using the non-dominant rather than the dominant hand.

Conclusion

Our spinal BOLD fMRI results showed that the functional activation intensity in the sequential finger-tapping task using the non-dominant left hand was significantly higher than that for the dominant right hand in right-handed individuals. The increase in activation intensity arose from the fact that the non-dominant hand was less skilled and competent, and thus required additional processing power for doing the finger-tapping task, which produced a stronger fMRI signal. There were no significant differences between the right and left hands with the more difficult (interleaved) task, because the task was similarly challenging for both hands, and required high dexterity. Therefore, differences in activity were less apparent.

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