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Functional exploration of the human spinal cord during voluntary movement and somatosensory stimulation

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Abstract

Demonstrations of the possibility of obtaining functional information from the spinal cord in humans using functional magnetic resonance imaging (fMRI) have been growing in number and sophistication, but the technique and the results that it provides are still perceived by the scientific community with a greater degree of scepticism than fMRI investigations of brain function. Here we review the literature on spinal fMRI in humans during voluntary movements and somatosensory stimulation. Particular attention is given to study design, acquisition and statistical analysis of the images, and to the agreement between the obtained results and existing knowledge regarding spinal cord anatomy and physiology.

A striking weakness of many spinal fMRI studies is the use of small numbers of subjects and of time-points in the acquired functional image series. In addition, spinal fMRI is characterised by large physiological noise, while the recorded functional responses are poorly characterised. For all these reasons, spinal fMRI experiments risk having low statistical power, and few spinal fMRI studies have yielded physiologically relevant information.

Thus, while available evidence indicates that spinal fMRI is feasible, we are only approaching the stage at which the technique can be considered to have been rigorously established as a viable means of noninvasively investigating spinal cord functioning in humans.

Keywords: Spinal cord; fMRI; Human

The present paper discusses published studies investigating the spinal cord function in humans using functional magnetic resonance imaging (fMRI). The experimental paradigms used in human spinal fMRI include motor tasks and somatosensory stimulation (using acupuncture, tactile and thermal stimuli). In several cases, the thermal stimulation, either hot or cold, was sufficiently intense to be considered as noxious. The aims of the studies include demonstrating and characterizing data acquisition and processing techniques, determining the anatomic localization of the functional response to a specific task or stimulus and, in a minority of cases, examining the dependence of the intensity and the spatial extent of the response on task or stimulation demand/duration. Our aim was not to provide a comprehensive review of the literature, but rather to highlight and discuss those aspects of study design, technique, statistical analysis, adherence to practices of neurophysiological assessment and consistency of results with knowledge from other sources, that most lend credence to the field of spinal fMRI, or are likely to be seen by the neuroscience community as a source of concern.

1. The problems with functional assessment of spinal cord using fMRI

Blood oxygen level-dependent (BOLD) fMRI has gained a primary role in modern neuroscience, because it allows non-invasive detection and localization of the brain's hemodynamic responses to sensory, motor and cognitive tasks [1]. The availability of a similar technique for the functional investigation of the spinal cord would be extremely attractive in both basic and clinical research.

There are several reasons to expect that the function of the spinal cord could be successfully explored using BOLD fMRI. First, the metabolic signal changes, at least during

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nociceptive stimuli, are larger in the spinal cord than in the brain [2]. Second, the small veins draining blood from the spinal cord grey matter tend to run perpendicular to the axis of the cord [3]. This orientation is optimal for BOLD effect in conventional MR scanners, as the cord runs parallel to the static magnetic field of the scanner [4]. Third, the grey matter of the spinal cord, where the synaptic activity that relates to the observed BOLD response takes place, is largely surrounded by white matter, while the larger draining veins are positioned peripherally, at the cord surface. Thus, the white matter may protect the BOLD signal arising in the gray matter from partial volume effects with both the cerebrospinal fluid (CSF), which is heavily prone to motion-related signal variations, and from the confounding BOLD signals arising in the distal draining veins [5].

These theoretical advantages are counterbalanced, however, by several factors that make the collection of functional MR images of the spinal cord difficult to achieve. The spinal cord has a relatively deep location, a small cross-section and a long rostro-caudal extent; these anatomical properties lead to inefficient MR signal reception. The surrounding vertebral structures and the conformation of the head, neck and body impose significant magnetic field inhomogeneities that can lead to image distortion and signal loss. In addition, the spinal cord lies in close proximity to the heart and the lungs that are strong sources of physiological noise [6-8]. It is unsurprising then, that a large amount of experimental effort has been devoted to addressing these difficulties rather than to investigating spinal cord physiology per se (see the reviews of Stracke et al., Giove et al. and Stroman for detail on the technical aspects of spinal fMRI [3,9,10]).

The BOLD fMRI response in the healthy brain is an indirect measure of neural activity, related to synaptic function [11,12]. Applying BOLD fMRI to the spinal cord assumes that a similar relationship between a change in neuronal activity and BOLD signal change is present in the spinal cord. Invasive studies have previously demonstrated mechanisms of stimulus induced alteration of spinal synaptic activity, and activity modulated changes in glucose metabolism and blood flow [13,14]. Recent experiments conducted using hypercapnia suggest that the vasoreactive aspect of this coupling is present in the human spinal cord and leads to BOLD signal changes [15]. In a rat model, experiments by Zhao et al. have further compared the locations of spinal cord blood volume and BOLD contrast changes during noxious and non-noxious electrical stimulation [16,17]. As yet, however, direct exploration of the relationship between neural activity and BOLD signal change [or equally the signal enhancement by extravascular protons (SEEP) response described in the following section] in the spinal cord is lacking.

2. Developments in image acquisition

The earliest reports of spinal fMRI in humans are notable for their use of a simple, long echo time, BOLD sensitive fast low-angle shot (FLASH) sequence [18,19]. The experimental paradigm used by Yoshizawa et al. [18] consisted of two blocks of repetitive hand clenching and two of rest, with each block lasting nine minutes. The C7-C8 spinal segments were covered using three axial slices, with a very poor temporal resolution (133 s for the three slices). In a subsequent report, Stroman et al. [19] introduced breath-holding, volume shimming and excitation pulses adapted to reduce the motion effects arising from the CSF, to a FLASH acquisition during a hand squeeze motor task. In this latter study, the temporal resolution was improved (11 s), but only a single slice was acquired (sagittal in the ipsilateral or contralateral hemicord, and axial at the C7 vertebra in separate measurements).

All four subjects in the Yoshizawa et al. [18] study showed task-induced responses (average signal change 4.8%), and good reproducibility was found over three repeated scans performed in one subject. In three subjects, the observed activity was largely ipsilateral to the moving hand, and distributed in the dorsal and ventral quadrants of the cord; in one subject, equally intense signal changes were detected on both the ipsilateral and the contralateral side of the cord. When the activation maps were coregistered across subjects, a common active region was seen in the grey matter ipsilateral to the active hand. The study by Yoshizawa et al. represented a promising start, and it still stands as the best example of intersubject reproducibility in spinal fMRI.

In the study by Stroman, 14 of the 21 subjects showed activation between C6 and T1 in both sagittal acquisition (1/1 contralateral, 13/20 ipsilateral) and the axial slice at C8. The remaining seven showed no task-related response. The sites of activity detected in the sagittal acquisition were centered on the C7 vertebra. All but one subject showed activity in either the ipsilateral, or both the ipsilateral and contralateral sides in the axial acquisition. The average observed signal change was 7%.

The slow acquisition associated with BOLD-sensitive FLASH imaging is not well suited to experimental designs where habituation of the response is expected, or where multiple tasks/stimuli are to be performed/delivered. It follows that, apart from the two reports above, reports on fMRI of the spinal cord have all made use of fast imaging techniques. The gradient echo echo-planar imaging (EPI) acquisition technique commonly and successfully used in brain fMRI can, however, be severely affected by image distortions and signal losses induced by the inhomogeneous magnetic field within the spinal cord. These effects can be minimized through the use of turbo spin-echo imaging or spin-echo EPI, at the cost of reducing BOLD sensitivity relative to gradient-echo EPI.

Comparisons of spin-echo and gradient-echo BOLD fMRI in the spinal cord have not yielded consistent findings. Bouwman et al. [20] compared sagittal turbo spin-echo and gradient-echo EPI acquisitions, during voluntary finger movement. In defining their imaging sequences, the choice of echo time (TE) was based on a joint optimization of the signal amplitude and the contrast

to noise ratio (CNR),[1] leading to the use of echo times about two-thirds of those considered optimal from a CNR viewpoint alone. They observed motor-related signal changes for gradient-echo EPI that were about double those of TSE. In an earlier report, however, Stroman et al. [21] obtained the conflicting result that the spinal responses using spin-echo acquisition were slightly greater than those found using a gradient-echo EPI sequence; at odds with both the theoretical description of the BOLD effect and the findings of several brain fMRI studies [22–24]. Neither study took account of the differences in physiological noise and in signal to noise ratio (SNR) between the sequences being compared, leaving grounds for uncertainty in characterizing BOLD sensitivity in spinal fMRI.

In a further series of spin-echo EPI experiments, Stroman et al. [21,25] have observed a non-zero intercept value on interpolating the functional response back to TE=0, leading to the suggestion of an TE-independent functional response that they have christened SEEP [26,27]. Spin-echo based acquisitions [usually turbo spin echo (TSE)], have been used aiming to obtain fMRI signals dependent on the SEEP effect in isolation (i.e., with long TR, and short TE, or low magnetic field strength where BOLD effects are negligible) [21,28], or coupled with BOLD enhancement (using moderate to long echo times) for stronger contrast [29,30]. Being based on spin-echo acquisitions, SEEP-sensitive studies are comparatively immune to distortion and signal losses due to imperfect shimming and susceptibility effects within the spinal cord. Moreover, the SNR obtained is high, allowing high resolution imaging to be performed. These features make SEEP attractive for potential use in spinal fMRI. While the SEEP hypothesis received early criticism [31], further investigations have suggested a mechanism attributable to neuronal and glial cell swelling [32].

As noted, image distortion and susceptibility-induced signal losses are a greater problem for BOLD- than SEEP-weighted acquisitions. Strategies for minimizing these effects in BOLD-weighted EPI acquisitions include limiting voxel dimensions, reducing the echo-train length through the use of multi-shot acquisition, and parallel imaging techniques such as sensitivity encoding or generalized reconstruction from partially parallel acquisition [33–35]. The latter of these strategies are widely used in cerebral fMRI, and have been also adopted by various authors for spinal fMRI. The compromises arising from their use include longer acquisition times for the multi-shot approach, and enhanced noise in parallel acquisition images. Reducing the voxel dimensions, on the other hand, further decreases the already low SNR of spinal fMRI data and has not been adopted.

The slice orientation may also influence the degree of signal loss dependent on anatomical structure [36], but to date this has not been fully evaluated in the spine. Instead, the choice of image orientation has largely been based on the fact that sagittal images provide the advantage of covering a greater extent of the spinal cord, while axial images tend to offer better dorsal-ventral and left-right resolution, and allow greater slice thickness (and, consequently, better SNR) with less partial volume effect.

Backes et al. [37] used a multi-shot EPI approach to examine the relative sensitivity of sagittal and axial acquisitions and compare the responses recorded during a motor task (hand clenching) with those elicited by electrical stimulation of the median nerve. They found the frequencies of detecting BOLD signal changes with a hand clenching motor task to be 66% and 63% for axial and sagittal acquisitions respectively; similar to those observed by Stroman [25].

Regardless of acquisition method, the SNR, the number of images in the time-series and the extent of signal changes are important factors in determining the ability to detect a functional response. These factors must be taken into consideration when designing an experiment: indeed, inadequate statistical power can lead to either over- or underestimation of the magnitude of functional response, thus making a valid characterization difficult to attain [38]. The algorithm of Murphy et al. [39] for calculating the number of images necessary in order to detect a given functional response can be inverted to estimate the minimum signal change detectable with a given sequence, where SNR and number of sampled time-points are known. Reported SNR values (as stated by the authors, without description of the method used for measuring them) range from 20 for the FLASH method as applied by Stroman et al. [19], down to 5.0±0.6 for gradient-echo EPI, and 8.9±2.2 for TSE acquisitions in the study of Bouwman et al. [20]. For these SNR values and the number of time-points acquired in their respective studies (25 for FLASH and 35 for both gradient echo EPI and TSE), the minimum signal change likely to be detected with a p-value less than 0.05 would be roughly 4%, 13% and 7.5% respectively. It is notable that these minimum levels for detection are at least as large as the measured signal changes typically observed in brain fMRI studies. Further, as procedures such as the Bonferroni correction are not typically applied to spinal fMRI data, the presence of false positive activity must be assumed. In the study by Bouwman et al. the observed mean activity-related signal changes (10.5 and 5.2 % for gradient echo EPI and TSE respectively) [20] are less than the minimum signal changes that Murphy's algorithm suggests the experiments were designed to detect. The choice of statistical test and significance thresholds applied, being different from those considered in the derivation of Murphy's algorithm may account for this discrepency, but the scope for this is limited, highlighting the importance of a clearly stating the basis for the statistical power determination guiding a spinal fMRI study. Few papers in the human spinal fMRI literature (just two of the 33 cited herein) provide details of the static or

[1] CNR in fMRI time-series is defined as the ratio between the difference in signal between task conditions and the standard deviation of the noise calculated across the whole time-series. Thus, CNR reflects the detectability of the task-related signal change.

temporal SNR, and none present statistical power calculations; thus, it is difficult for the reader to judge the statistical soundness of the findings.

3. Developments in post-processing

Through independent component analysis (ICA) of high temporal resolution gradient-echo EPI data in resting subjects, Brooks et al. [40] have identified a number of signal components with frequency content close to cardiac or respiratory frequencies, or to cross-terms of these. In general, however, the sampling interval for spinal fMRI data collection is longer than the cardiac cycle, and sometimes longer than the respiratory cycle. One must therefore be concerned that aliasing of physiological noise may contribute to the observed signal with a periodicity close to those of the task, thus elevating the false-positive rate if left untreated, and the false negative rate if treated.

A coarse estimation of the false positive incidence can be obtained by repeating the data acquisition at rest without the experimental conditions (as, for example, in Ref. [41]). A substantive difference in the number of active voxels detected, or in the intensity of the response between the actual task and rest runs, would support claims of having detected a task-related response. Although strongly recommended, it must be remembered that this approach does not, take into consideration the possible role of task-related physiological noise in the run where the task is performed.

The impact of physiological noise can be reduced by performing image averaging during acquisition (a procedure that reduces the temporal resolution), or by using a band-pass rather than a high-pass filter when preprocessing the data for analysis (a procedure that presents the risk of introducing spurious signal components, if the cut-off frequencies are not chosen appropriately). The correlation of cardiac and respiratory cycles with signal changes in the spinal cord as well as with observed motion of the spinal cord has been invoked as the basis of a variety of noise reduction strategies. Records of the pulse and respiration cycles can be used as the basis for pre-whitening the time-series [40,42], applied directly as regressors in general linear model (GLM) analysis [43] or incorporated into a model for generation of such regressors [44,45]. The initial demonstrations of these physiological correction methods have shown them to modulate the number of active voxels and the degree of activation; however, they were based on block design experiments involving an active task [40,44,45] where the false-positive rates are not known, making their impact of these correction procedures difficult to judge. Using data acquired during a rest run, Harvey et al. [46] illustrated the reduction in voxel-wise signal variability in the brainstem achieved with combined respiratory and cardiac cycle based pre-whitening. Denoising prior to GLM, by subtracting ICA components whose spatial distribution does not include the spinal cord, and so are likely to represent physiological noise, has been proposed by Valsasina et al. [47] but not reported in practice.

Another issue is the adoption of spatial filtering procedures. Given the dimensions of the spinal cord, isotropic smoothing using a kernel width of several millimetres (typical for brain fMRI) produces extensively blurring of the CSF into the spinal cord. As the CSF tends to have a greater temporal variance and a stronger signal than the cord, this can cause severe contamination of the spinal cord signal. Whereas some early studies (e.g., Madi et al. [48]) used blurring kernels of several millimetres, more recent publications have tended to forego spatial smoothing or adopt anisotropic smoothing favouring the rostro-caudal axis of the cord. For sagittal images, Stroman et al. have introduced a process of shifting voxels along the dorso-ventral axis so that the midline, ventral edge of the spine is straight as a means to improve subsequent anisotropic smoothing [44].

4. Anatomical localization of the response

Three common expectations are seen in the interpretations of published spinal fMRI studies: (1) that the rostro-caudal distribution of activation will be dictated by the metameric organization of sensory input and motor output; (2) that a clear dorso-ventral difference will exist between sensory and motor-related activity; (3) that neuronal activity will be dominant on the side of the stimulation or motor task.

It is important to consider, however, the multiplicity of synaptic interconnections that characterize spinal neuronal circuits [49–52]. Because fMRI is able to reflect functional responses along polysynaptic pathways, even activation of a simple network may be associated with widespread responses within the spinal grey matter. For the same reason, the contribution from descending pathways to the recorded response may also be relevant [53]. In particular, laminar specificity should not be expected with spinal fMRI in humans (see Fig. 1).

Madi et al. [48] first attempted to demonstrate a spatial specificity of spinal activity related to movements of the finger, wrist and elbow. In a small subject population, they found a rostro-caudal ordering of the foci of activity consistent with the functional organization of sensory and motor circuits, albeit located slightly caudal to the expected spinal level.

A later report by Bouwman et al. [20] yielded inconsistent demonstrations of response localization. Gradient-echo EPI results showed a concentration of activity for a hand motion task in the expected vertebral levels (C5-T1), in accordance with the locus of activity found in both the Madi et al. and Yoshizawa et al. studies [18,48]. Using a TSE sequence, however, the number of activated voxels progressively decreased moving caudally along the spinal cord, a pattern that suggests a disconnection between physiological activity and fMRI responses.

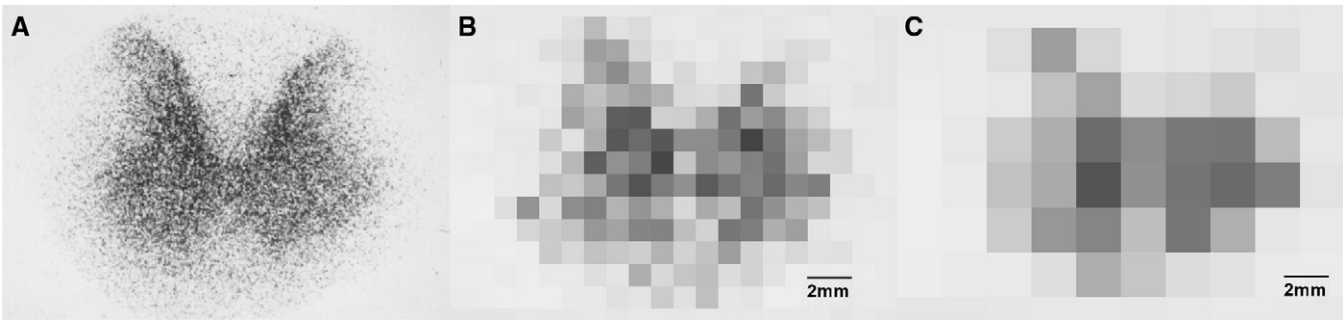

Fig. 1. (A) A 2-deoxyglucose autoradiogram derived from the cervical enlargement of the rat spinal cord, during tonic noxious stimulation of one forepaw. Despite the effective spatial resolution of about 100–200 μm, laminar distribution of activation is not apparent. Assuming the same distribution of activity at the scale of the human spinal cord (width 16 mm), panels (B) and (C) represent the same activity pattern sampled to resolutions of 1 and 2 mm, respectively, to illustrate the deterioration of localization that can be expected with high-resolution (e.g., 1 mm) and moderate-resolution (e.g., 2 mm) spinal fMRI studies.

Using SEEP-based contrast to explore the functional activity of the cervical spinal cord during a bilateral hand-gripping task, Ng et al. [28] found a maximum of activity at C6-C7 vertebral level. This study, performed at 0.2 T, may indicate the potential for SEEP to be used for fMRI at low field strengths, where BOLD contrast is weak. However, the long scan time (24 min) and the high number of motion-corrupted scans (30%) indicate that higher magnetic field strengths are preferable for spinal fMRI studies.

At 1.5 T, bilateral lumbar activation accompanying both passive and active pedalling has been demonstrated by Kornelsen and Stroman [29] in the dorsal horns of spinal cord segments S3 and S2, and in the ventral horns of the L4 through L1 segments. Compared to passive pedalling, active pedalling yielded a significantly stronger response in the dorsal horn between the L1 and L4 levels, and in the ventral horns at L5.

Stracke et al. [54], using skin indentation applied to individual fingers, reported that only stimulation of the thumb gave rise to consistent activation at the expected level in the majority of subjects. In addition, a focus of activity was found in the C3-C4 region in all subjects, independent of the stimulated digit. The authors attribute this rostral focus of activation to propriospinal neurons that have been demonstrated in the cat to integrate and project input from several descending pathways (corticospinal, rubrospinal, tectospinal and reticulospinal), possibly mediating the command for reaching movements [55]. A C3-C4 propriospinal neuron system has been demonstrated in macaque monkeys [56], and indirect evidence suggests that the system also exists in humans [57,58].

Using SEEP contrast, Stroman et al. [59,60] and Lawrence et al. [30] investigated the somatotopic distribution of somatosensory-induced activity along the spinal cord, as expressed by the number of active voxels at each spinal level. In a pair of studies, a thermal stimulus was applied to a series of dermatomes on the arm [59] and to the calf [60], while in the other [30], vibratory stimulation of Aβ fibres was applied to the hand palm and to the joints of the arm and of the leg. Thermal stimulation of the median aspect of the palm elicited a response in spinal cord segments C5 to C8 (peaking at C6), while thermal stimulation of the ulnar side of the palm elicited a response in spinal cord segments C7 and C8. Vibratory stimulation of the palms and wrist yielded apparent peaks of activation at the C7 level. Thermal stimulation of the forearm and vibratory stimulation of the biceps yielded activation over the C5-C7 and C6-C7 spinal levels, respectively. In the lumbar spinal cord, activation was observed throughout the T12-L5 range in response to thermal stimulation of the calf (L4 dermatome). Vibratory stimulation of both the knee and the Achilles tendon elicited a response centered at the T11 and T12 levels [30]. In contrast to the authors' expectations, a distinct ipsilateral dominance was not observed, and the activity was not clearly located in the dorsal horn. It is worth mentioning that the observed distribution of active voxels was neither compared to equivalent results in a rest scan, nor statistically compared between spinal levels.

In a recent study using BOLD contrast [61], we recorded the spinal cord responses to noxious and innocuous somatosensory stimuli (induced by laser heating and brush strokes, respectively) applied to a portion of the hand dorsum corresponding to the C6-C7 dermatomes. Significant responses were found to both noxious and innocuous stimuli in both the ipsi- and contralateral sides of the cord. Crucially, these responses were significantly larger than the noise levels measured in a corresponding scan at rest. In accordance with the results of autoradiographic studies [62,63], BOLD signal increases following noxious stimuli were significantly higher than those elicited by innocuous stimuli.

5. Time profile of the response

Giulietti et al. [64] determined the impulse response function (IRF) of the BOLD response in the cervical spinal cord to a 1-Hz ball-squeezing task performed for periods of 3, 6, 9, 15, 21, 27, and 42 s. They estimated a full width at half maximum of 9.14 s and a peak latency of 9.34 s, both values being longer than the corresponding ones in the brain.

This indicates that greater temporal damping of the hemodynamic response occurs in the spine. At the minimum task duration of 3 s, the response did not fit the modeled IRF, suggesting a non-linearity in the response at short durations.

6. Intensity dependence of the response

Madi et al. [48] provided the first evidence to support the hypothesis that the magnitude of the spinal fMRI response would correlate with the force applied in a voluntary isometric motor task. The magnitude of the signal change (20–40%) for the maximal force tested is, however, greatly in excess of those typically encountered in BOLD fMRI. They also observed a negative BOLD response, and proposed that this was related to sites of neural inhibition. A further observation can be made based on their figures, that voxels having a response directly proportional to the applied force exhibit a negative signal changes with respect to baseline at the lowest force level (and conversely for voxels with an inversely proportional response). These observations regarding a negative BOLD response are extremely difficult to explain with current physiological knowledge, and have not been confirmed in subsequent studies. It should be pointed out, in fact, that the resting state metabolic activity of the spinal cord is low in comparison with the brain [49], which probably reflects the low level of afferent excitatory somatosensory activity at rest, and the different organization of neuronal networks. Unlike the cerebral cortex, where most synaptic activity derives from local microcircuits [13,65], a strong decrease of neural activity in the spinal cord is therefore unlikely to occur or to be accompanied by large BOLD signal changes. A global increase in synaptic activity, either inhibitory or excitatory, would rather be accompanied by metabolic and haemodynamic increases (see the recent review by Mangia et al. [13]). Indeed, fMRI studies including appropriate control runs have not provided evidence for consistent negative stimulus-evoked signal changes at the spinal level in rats and humans [17,61].

Ng et al. [66] compared the BOLD responses elicited in the cervical spinal cord by unilateral finger tapping of different complexity. The intensity of BOLD signal changes in the whole cervical cord (encompassing C1 to C7 vertebral levels) was lower when performing a simple tapping sequence with the dominant hand; no between-hand difference was observed for the more complex motor sequence. The authors speculate that the task-related difference in spinal cord activity could be related to the more automated execution of the simple tapping sequence with the dominant hand.

Maieron et al. [41] performed a comparison of BOLD responses associated with finger tapping performed at two different frequencies (fastest vs. self-selected). The significantly greater activation at the faster finger tapping rate (Fig. 2), which mirrors similar demonstrations of frequency dependent responses in brain areas [67–69], provides perhaps the most convincing evidence of an intensity-dependent response in spinal fMRI.

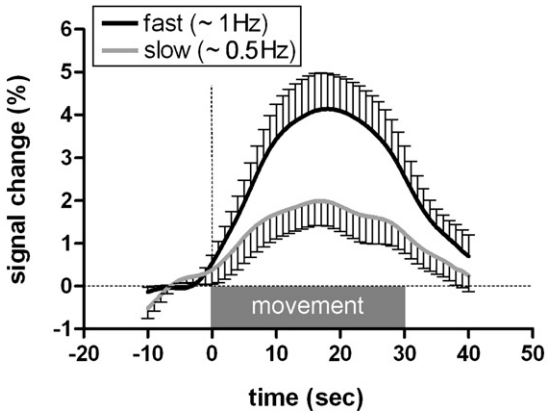

Fig. 2. Time courses of fMRI signals averaged around the movement (perimovement plots) in clusters related to movements of the right hand at low or high frequency. Note the higher signal changes during high-frequency movement. From Maieron et al. [41].

Stroman et al. [60] explored the effect of graded temperature reductions from 32°C to 10°C, delivered via a Peltier thermode to the inner calf in 15 healthy volunteers, using SEEP-sensitive acquisition. Averaged over all the volunteers, a clear increase in the intensity of the response was seen for temperatures below 15°C, corresponding with the transition from non-noxious to noxious sensation. A similar increase in activity on transition from non-noxious to noxious thermal stimulation has been reported for electrophysiological recordings from the spinothalamic tract [70]. The same group has subsequently reported a similar experiment in which non-noxious thermal stimuli were applied to the thenar eminence [53] and suggested that correlated signal time courses between anatomical regions of the midbrain and cervical spine could provide insights onto the functioning of intraspinal networks.

In a recent study, Wei et al. [71] used BOLD-sensitive EPI and ICA analysis, in an attempt to identify a resting state network within the spinal cord. The authors consider those ICA components predominantly located in the spinal cord and having the highest correlation between runs to depict the resting state of the spinal cord; however, they acknowledge that those components contain much of their power at frequencies corresponding to breathing and possibly heart rate and, so, are potentially artefactual.

7. Concluding remarks

fMRI of the human spinal cord offers a novel means of non-invasively studying the processing of information to and from the body. The studies of spinal somatosensory and motor systems performed to date provide reasonable evidence that task-related activity of physiological origin can be detected with spinal fMRI. Physiological issues of interest include, for example, refining our understanding of

human spinal somatotopy, and characterizing the spinal stimulus-response function and plasticity. The functional status of the spinal cord is also of clinical interest, in relation to traumatic injuries and disease processes such as multiple sclerosis or pain disorders.

The identification of subtle experimental modulations (e.g., by cognitive factors) and the investigation of pathophysiological changes within the spinal cord represent future challenges in spinal fMRI. These effects are likely to be much more difficult to detect than the differences between stimulation and rest conditions observed to date. Pioneering attempts to perform spinal fMRI in patients have not been entirely convincing in the comparison of function between the normal and diseased [72,73] or injured [60,74] spinal cord. Great care must be taken in such studies, if the risks of erroneously reporting the effects or lack thereof are to be avoided — particularly as the inconsistency of responses, even between normal volunteers remains to be fully addressed, before spinal fMRI can be used to characterize task-related activity in individual patients.

Obtaining good spatial and temporal resolution while achieving adequate SNR to detect task-related changes in spinal cord fMRI signal, remains a fundamental challenge. One avenue for advancement lays in the development of coils and sequences that are tailored to improve SNR in the spinal cord (e.g., Ref. [75]). Other avenues have already been established, such as adopting specific strategies for the motion correction of spinal cord fMRI images: these include limiting the region used for motion correction and, because the slice separation may be substantial (and the slice thickness large), using slice-based motion correction. Very recent reports have started looking at the effects of respiration on magnetic field homogeneity [8], which may lead to further refinements in physiological noise amelioration strategies.

There are also direct and immediate steps that researchers can take as the basis for good practice in spinal fMRI. Control experiments in the same subjects are an essential (and usually lacking) tool for interpreting the signal changes observed. Even with this measure, it must be remembered that the control data are only exemplar of the sequence performance in the resting condition. We would recommend that authors state the typical static and temporal SNR of spinal cord tissue for their specific sequence and scanner. The practice of a power estimation made prior to performing experiments should also be adopted universally to ensure that an adequate numbers of time-points is acquired, to support detection of a reasonable signal change in response to the task. Based on reports to date, targeting a signal change of between 2% and 4% for a robust sensory stimulation or motor task would appear acceptable whether using SEEP or BOLD contrast. We would encourage reviewers to require these basic elements be in evidence in any manuscript submitted for publication.

The case for adopting fMRI techniques for investigating brain function was greatly strengthened by the spatial correspondences found between the activation detected by fMRI, and those predicted on the basis of experimental studies using other techniques. At the resolutions likely to be achieved in spinal fMRI, however, fine-grain maps cannot be obtained. Thus, the onus is on the researchers carrying out spinal fMRI experiments, to take the steps necessary to ensure that their experiments and subsequent reports reflect good practice and fair interpretation of the results.

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References

[1] Iannetti GD, Wise RG. BOLD functional MRI in disease and pharmacological studies: room for improvement? Magn Reson Imaging 2007;25:978–88.
[2] Porro CA, Cavazzuti M, Baraldi P, Giuliani D, Panerai AE, Corazza R. CNS pattern of metabolic activity during tonic pain: evidence for modulation by beta-endorphin. Eur J Neurosci 1999;11:874–88.
[3] Stracke CP, Pettersson LG, Moller-Hartmann W, Krings T. Functional MRI of the spinal cord. Riv Neuroradiol 2004;17:292–9.
[4] Lai S, Glover GH, Haacke EM. Spatial selectivity of BOLD contrast: effects in and around draining veins. In: Moonen CTW, Bandettini PA, editors. Functional MRI. Berlin: Sringer-Verlag; 2000. p. 221–33.
[5] Lai S, Hopkins AL, Haacke EM, Li D, Wasserman BA, Buckley P, et al. Identification of vascular structures as a major source of signal contrast in high resolution 2D and 3D functional activation imaging of the motor cortex at 1.5T: preliminary results. Magn Reson Med 1993; 30:387–92.
[6] Birn RM, Smith MA, Jones TB, Bandettini PA. The respiration response function: the temporal dynamics of fMRI signal fluctuations related to changes in respiration. Neuroimage 2008;40:644–54.
[7] Chang C, Cunningham JP, Glover GH. Influence of heart rate on the BOLD signal: the cardiac response function. Neuroimage 2009;44: 857–69.
[8] Kim H, Zho SY, Kim D-H. Respiration-induced B0 fluctuation of spine. Proceedings of the 17th Scientific Meeting and Exhibition of the ISMRM, Honolulu, USA; 2009 (abstract 1301).
[9] Giove F, Garreffa G, Giulietti G, Mangia S, Colonnese C, Maraviglia B. Issues about the fMRI of the human spinal cord. Magn Reson Imaging 2004;22:1505–16.
[10] Stroman PW. Magnetic resonance imaging of neuronal function in the spinal cord: spinal FMRI. Clin Med Res 2005;3:146–56.
[11] Logothetis NK. The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. Philos Trans R Soc Lond B Biol Sci 2002;357:1003–37.
[12] Viswanathan A, Freeman RD. Neurometabolic coupling in cerebral cortex reflects synaptic more than spiking activity. Nat Neurosci 2007;10:1308–12.
[13] Mangia S, Giove F, Tkac I, Logothetis NK, Henry PG, Olman CA, et al. Metabolic and hemodynamic events after changes in neuronal activity: current hypotheses, theoretical predictions and in vivo NMR experimental findings. J Cereb Blood Flow Metab 2009;29:441–63.
[14] Coghill RC, Morrow TJ. Functional imaging of animal models of pain: high resolution insights into nociceptive processing. In: Casey

KL, Bushnell MC, editors. Pain imaging. Seattle: IASP Press; 2000.
[15] Maieron M, Bodurka J, Birn RM, Porro CA, Bandettini PA. Breath-hold induced MRI signal changes in the spinal cord imply BOLD contrast. 13th International Conference on Functional Mapping of the Human Brain, Chicago; 2007 (abstract Available on CD-Rom in NeuroImage 2007;36).
[16] Zhao F, Williams M, Meng X, Welsh DC, Coimbra A, Crown ED, et al. BOLD and blood volume-weighted fMRI of rat lumbar spinal cord during non-noxious and noxious electrical hindpaw stimulation. Neuroimage 2008;40:133–47.
[17] Zhao F, Williams M, Meng X, Welsh DC, Grachev ID, Hargreaves R, et al. Pain fMRI in rat cervical spinal cord: an echo planar imaging evaluation of sensitivity of BOLD and blood volume-weighted fMRI. Neuroimage 2009;44:349–62.
[18] Yoshizawa T, Nose T, Moore GJ, Sillerud LO. Functional magnetic resonance imaging of motor activation in the human cervical spinal cord. Neuroimage 1996;4:174–82.
[19] Stroman PW, Nance PW, Ryner LN. BOLD MRI of the human cervical spinal cord at 3 tesla. Magn Reson Med 1999;42:571–6.
[20] Bouwman CJ, Wilmink JT, Mess WH, Backes WH. Spinal cord functional MRI at 3 T: gradient echo echo-planar imaging versus turbo spin echo. Neuroimage 2008;43:288–96.
[21] Stroman PW, Krause V, Frankenstein UN, Malisza KL, Tomanek B. Spin-echo versus gradient-echo fMRI with short echo times. Magn Reson Imaging 2001;19:827–31.
[22] Bandettini PA, Wong EC, Jesmanowicz A, Hinks RS, Hyde JS. Spin-echo and gradient-echo EPI of human brain activation using BOLD contrast: a comparative study at 1.5 T. NMR Biomed 1994;7:12–20.
[23] Lowe MJ, Lurito JT, Mathews VP, Phillips MD, Hutchins GD. Quantitative comparison of functional contrast from BOLD-weighted spin-echo and gradient-echo echoplanar imaging at 1.5 Tesla and H2 15O PET in the whole brain. J Cereb Blood Flow Metab 2000;20: 1331–40.
[24] Poser BA, Norris DG. Fast spin echo sequences for BOLD functional MRI. MAGMA 2007;20:11–7.
[25] Stroman PW, Krause V, Malisza KL, Frankenstein UN, Tomanek B. Characterization of contrast changes in functional MRI of the human spinal cord at 1.5 T. Magn Reson Imaging 2001;19:833–8.
[26] Stroman PW, Krause V, Malisza KL, Frankenstein UN, Tomanek B. Extravascular proton-density changes as a non-BOLD component of contrast in fMRI of the human spinal cord. Magn Reson Med 2002;48: 122–7.
[27] Stroman PW, Kornelsen J, Lawrence J, Malisza KL. Functional magnetic resonance imaging based on SEEP contrast: response function and anatomical specificity. Magn Reson Imaging 2005;23: 843–50.
[28] Ng MC, Wong KK, Li G, Lai S, Yang ES, Hu Y, et al. Proton-density-weighted spinal fMRI with sensorimotor stimulation at 0.2 T. Neuroimage 2006;29:995–9.
[29] Kornelsen J, Stroman PW. fMRI of the lumbar spinal cord during a lower limb motor task. Magn Reson Med 2004;52:411–4.
[30] Lawrence JM, Stroman PW, Kollias SS. Functional magnetic resonance imaging of the human spinal cord during vibration stimulation of different dermatomes. Neuroradiology 2008;50:273–80.
[31] Jochimsen TH, Norris DG, Moller HE. Is there a change in water proton density associated with functional magnetic resonance imaging? Magn Reson Med 2005;53:470–3.
[32] Stroman PW, Lee AS, Pitchers KK, Andrew RD. Magnetic resonance imaging of neuronal and glial swelling as an indicator of function in cerebral tissue slices. Magn Reson Med 2008;59:700–6.
[33] Golay X, Pruessmann KP, Weiger M, Crelier GR, Folkers PJ, Kollias SS, et al. PRESTO-SENSE: an ultrafast whole-brain fMRI technique. Magn Reson Med 2000;43:779–86.
[34] Menon RS, Thomas CG, Gati JS. Investigation of BOLD contrast in fMRI using multi-shot EPI. NMR Biomed 1997;10:179–82.
[35] Schmidt CF, Degonda N, Luechinger R, Henke K, Boesiger P. Sensitivity-encoded (SENSE) echo planar fMRI at 3T in the medial temporal lobe. Neuroimage 2005;25:625–41.
[36] Chen NK, Dickey CC, Yoo SS, Guttmann CR, Panych LP. Selection of voxel size and slice orientation for fMRI in the presence of susceptibility field gradients: application to imaging of the amygdala. Neuroimage 2003;19:817–25.
[37] Backes WH, Mess WH, Wilmink JT. Functional MR imaging of the cervical spinal cord by use of median nerve stimulation and fist clenching. AJNR Am J Neuroradiol 2001;22:1854–9.
[38] Gelman A, Weakline D. Of Beauty, Sex and Power. American Scientist 2009;97:310–6.
[39] Murphy K, Bodurka J, Bandettini PA. How long to scan? The relationship between fMRI temporal signal to noise ratio and necessary scan duration. Neuroimage 2007;34:565–74.
[40] Brooks JC, Beckmann CF, Miller KL, Wise RG, Porro CA, Tracey I, et al. Physiological noise modelling for spinal functional magnetic resonance imaging studies. Neuroimage 2008;39:680–92.
[41] Maieron M, Iannetti GD, Bodurka J, Tracey I, Bandettini PA, Porro CA. Functional responses in the human spinal cord during willed motor actions: evidence for side- and rate-dependent activity. J Neurosci 2007;27:4182–90.
[42] Glover GH, Li TQ, Ress D. Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. Magn Reson Med 2000;44:162–7.
[43] Stroman PW. Discrimination of errors from neuronal activity in functional MRI of the human spinal cord by means of general linear model analysis. Magn Reson Med 2006;56:452–6.
[44] Stroman PW, Figley CR, Cahill CM. Spatial normalization, bulk motion correction and coregistration for functional magnetic resonance imaging of the human cervical spinal cord and brainstem. Magn Reson Imaging 2008;26:809–14.
[45] Figley CR, Stroman PW. Development and validation of retrospective spinal cord motion time-course estimates (RESPITE) for spin-echo spinal fMRI: Improved sensitivity and specificity by means of a motion-compensating general linear model analysis. Neuroimage 2009;44:421–7.
[46] Harvey AK, Pattinson KT, Brooks JC, Mayhew SD, Jenkinson M, Wise RG. Brainstem functional magnetic resonance imaging: disentangling signal from physiological noise. J Magn Reson Imaging 2008;28:1337–44.
[47] Valsasina P, Agosta F, Caputo D, Stroman PW, Filippi M. Spinal fMRI during proprioceptive and tactile tasks in healthy subjects: activity detected using cross-correlation, general linear model and independent component analysis. Neuroradiology 2008;50:895–902.
[48] Madi S, Flanders AE, Vinitski S, Herbison GJ, Nissanov J. Functional MR imaging of the human cervical spinal cord. AJNR Am J Neuroradiol 2001;22:1768–74.
[49] Porro CA, Cavazzuti M. Spatial and temporal aspects of spinal cord and brainstem activation in the formalin pain model. Prog Neurobiol 1993;41:565–607.
[50] Fetz EE, Perlmutter SI, Prut Y, Seki K, Votaw S. Roles of primate spinal interneurons in preparation and execution of voluntary hand movement. Brain Res Brain Res Rev 2002;40:53–65.
[51] Baldissera F, Borroni P, Cavallari P, Cerri G. Excitability changes in human corticospinal projections to forearm muscles during voluntary movement of ipsilateral foot. J Physiol 2002;539:903–11.
[52] Jankowska E. Interneuronal relay in spinal pathways from proprioceptors. Prog Neurobiol 1992;38:335–78.
[53] Stroman PW. Spinal fMRI investigation of human spinal cord function over a range of innocuous thermal sensory stimuli and study-related emotional influences. Magn Reson Imaging 2009;27:1333–46.
[54] Stracke CP, Pettersson LG, Schoth F, Moller-Hartmann W, Krings T. Interneuronal systems of the cervical spinal cord assessed with BOLD imaging at 1.5 T. Neuroradiology 2005;47:127–33.
[55] Pettersson LG. Forelimb movements in the cat; kinetic features and neuronal control. Acta Physiol Scand Suppl 1990;594:1–60.

[56] Alstermark B, Isa T, Ohki Y, Saito Y. Disynaptic pyramidal excitation in forelimb motoneurons mediated via C(3)-C(4) propriospinal neurons in the *Macaca fuscata*. J Neurophysiol 1999;82:3580–5.
[57] Nielsen J, Pierrot-Deseilligny E. Pattern of cutaneous inhibition of the propriospinal-like excitation to human upper limb motoneurones. J Physiol 1991;434:169–82.
[58] Pierrot-Deseilligny E. Propriospinal transmission of part of the corticospinal excitation in humans. Muscle Nerve 2002;26:155–72.
[59] Stroman PW, Krause V, Malisza KL, Frankenstein UN, Tomanek B. Functional magnetic resonance imaging of the human cervical spinal cord with stimulation of different sensory dermatomes. Magn Reson Imaging 2002;20:1–6.
[60] Stroman PW, Tomanek B, Krause V, Frankenstein UN, Malisza KL. Mapping of neuronal function in the healthy and injured human spinal cord with spinal BOLD fMRI. Neuroimage 2002;17:1854–60.
[61] Summers PE, Ferraro D, Duzzi D, Lui F, Iannetti G, Porro CA. A quantitative comparison of BOLD fMRI responses to noxious and innocuous stimuli in the human spinal cord. Neuroimage 2010;50: 1408–15.
[62] Porro CA, Cavazzuti M, Galetti A, Sassatelli L, Barbieri GC. Functional activity mapping of the rat spinal cord during formalin-induced noxious stimulation. Neuroscience 1991;41:655–65.
[63] Coghill RC, Mayer DJ, Price DD. The roles of spatial recruitment and discharge frequency in spinal cord coding of pain: a combined electrophysiological and imaging investigation. Pain 1993;53: 295–309.
[64] Giulietti G, Giove F, Garreffa G, Colonnese C, Mangia S, Maraviglia B. Characterization of the functional response in the human spinal cord: Impulse-response function and linearity. Neuroimage 2008;42:626–34.
[65] Gusnard DA, Raichle ME, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. Nat Rev Neurosci 2001;2:685–94.
[66] Ng MC, Wu EX, Lau HF, Hu Y, Lam EY, Luk KD. Cervical spinal cord BOLD fMRI study: modulation of functional activation by dexterity of dominant and non-dominant hands. Neuroimage 2008;39: 825–31.
[67] Jancke L, Peters M, Schlaug G, Posse S, Steinmetz H, Muller-Gartner H. Differential magnetic resonance signal change in human sensori-motor cortex to finger movements of different rate of the dominant and subdominant hand. Brain Res Cogn Brain Res 1998;6:279–84.
[68] Kim JA, Eliassen JC, Sanes JN. Movement quantity and frequency coding in human motor areas. J Neurophysiol 2005;94:2504–11.
[69] Turner RS, Grafton ST, Votaw JR, Delong MR, Hoffman JM. Motor subcircuits mediating the control of movement velocity: a PET study. J Neurophysiol 1998;80:2162–76.
[70] LaMotte RH, Thalhammer JG. Response properties of high-threshold cutaneous cold receptors in the primate. Brain Res 1982;244: 279–87.
[71] Wei P, Li J, Gao F, Ye D, Zhong Q, Liu S. Resting state networks in human cervical spinal cord observed with fMRI. Eur J Appl Physiol 2009.
[72] Agosta F, Valsasina P, Rocca MA, Caputo D, Sala S, Judica E, et al. Evidence for enhanced functional activity of cervical cord in relapsing multiple sclerosis. Magn Reson Med 2008;59:1035–42.
[73] Agosta F, Valsasina P, Caputo D, Stroman PW, Filippi M. Tactile-associated recruitment of the cervical cord is altered in patients with multiple sclerosis. Neuroimage 2008;39:1542–8.
[74] Kornelsen J, Stroman PW. Detection of the neuronal activity occurring caudal to the site of spinal cord injury that is elicited during lower limb movement tasks. Spinal Cord 2007;45:485–90.
[75] Bodurka J, Ledden P, Bandettini PA. SENSE optimized sixteen element receive array for cervical spinal cord imaging at 3T. Proceedings of the 16th Scientific Meeting and Exhibition of the ISMRM, Toronto, Canada; 2008 (abstract 1078).