Assessing spinal cord function in multiple sclerosis with functional neuroimaging: insights and limitations

Neuroinflammatory diseases such as multiple sclerosis (MS) and neuromyelitis optica (NMO) frequently affect the spinal cord. Spinal cord involvement is a key component for diagnosis of NMO, and the presence of cord lesions in clinically isolated syndrome is highly predictive of conversion to clinically definite MS. Furthermore, the degree of cord damage (e.g., reduction in cord cross-sectional area) and disability are related. Interestingly, spinal cord lesions are frequently associated with chronic pain and patients with pain have higher Expanded Disability Status Scale scores than those without pain. Whilst pathological changes occurring in the MS spinal cord are associated with altered sensorimotor function, it is not yet clear whether this is directly attributable to altered cord function, or disrupted transmission of nerve impulses to and from the brain due to white matter damage. To assess the integrity of cord tracts one could use techniques such as relaxometry, magnetisation transfer or diffusion weighted imaging; however, these approaches do not provide information about the functional integrity of spinal neurons. One way to assess functional responses from the spinal cord is by using functional magnetic resonance imaging (fMRI).

Spinal fMRI poses several technical challenges. The first relates to the small size of the cord, which makes the use of small voxel sizes (3–5 mm³) necessary – with the result that signal to noise is intrinsically low. The second challenge relates to the cord’s location close to potent sources of physiological noise, such as the heart and lungs. Physiological noise adds to the signal intensity recorded on functional images and, if not accounted for, can obscure responses due to applied stimuli. The third obstacle relates to the first two: cerebrospinal fluid (CSF) flow in the subarachnoid space and pulsation of spinal arteries will produce both cord displacement and large changes in signal intensity, the effects of which are exacerbated by the small dimensions of the cord.

The most widely published approach for fMRI of the spinal cord is based on a contrast mechanism known as SEEP (signal enhancement by extravascular protons). First reported in 2003, this technique relies on measuring changes in the proton density (or water content) in an area of activated neuronal tissue. The SEEP technique has been applied in groups of healthy controls to study spinal cord responses to a variety of different stimuli (e.g., vibrotactile, thermosensory, passive motor/proprioceptive, sensory), and patterns of activity observed in response to stimulation. However, the contribution of neuronal activity to data acquired using SEEP contrast is still under debate, and its reproducibility was found to be poorer than conventional BOLD (blood oxygenation level dependent) fMRI.

The interpretation of all fMRI data is critically dependent on the reported statistics for activation, but as a direct consequence of difficulties faced when recording data from the cord, spinal fMRI data are frequently published using ‘uncorrected statistics’, and thus do not meet the strict criteria normally applied to fMRI studies of the brain. When assessing false positive activation rates in spinal fMRI studies it is important to know not only the statistical threshold, but also the number of voxels tested and the number found to be active. Whilst one must be careful when interpreting voxel-wise patterns of activity, a region of interest (ROI) analysis based on a priori anatomical definition can minimise some of the problems of interpretation, and increase confidence in obtained results. Although information about the exact spatial location of activity is limited with an ROI approach, multiple comparisons can be accounted for by using an analysis of variance, as it is a single statistical test. By using ROIs the average parameter estimate or percentage signal change can be compared between groups, but the use of measures such average t or Z-score (passing a threshold) or total number of activated voxels is more problematic, as they are unlikely to be normally distributed and/or constitute a statistical test performed on a test statistic.

Spinal fMRI based on SEEP contrast has been applied in patients with MS with no known cord involvement, to measure cord activity in response to sensorimotor stimulation. Notably, Agosta and colleagues applied a proprioceptive stimulus (passive wrist flexion) and demonstrated that average cord signal was increased in patients with relapsing MS relative to controls. In the current edition of *Multiple Sclerosis Journal*, Rocca and colleagues have extended work from the earlier study by Agosta et al. to examine the relationship between spinal cord function and disability and fatigue in people with MS. Fatigued (F) and non-fatigued (NF) patients (both with no apparent cord pathology) and controls were studied with an identical paradigm to the earlier study, with the exception that the experiment used a punctate stimulus applied to the palm of the right hand i.e. a sensory task. Results were compared at different
significance levels ($p<0.05$, $p<0.01$ and $p<0.001$) and, broadly speaking, activation patterns (across the three groups) remained the same across the three levels. As before, increased cord activity was found in patients with MS compared with controls, with mean NF-MS cord activity higher than for F-MS. However, rather than using anatomical masks to define ROIs, percent signal change was calculated from only those voxels reaching significance, which may cause bias if there are systematic noise differences between the groups. In keeping with known anatomical pathways, controls demonstrated increased frequency/occurrence of activity in the hemicord ipsilateral to the stimulus, greatest in the dorsal portion. Intriguingly, this pattern was reversed in F-MS patients, who showed an increased frequency of activation, particularly in the left (contralateral) ventral quadrant relative to controls and NF-MS. This apparent contradiction, between increased percentage signal change in NF-MS compared with F-MS, and increased fMRI occurrence rate in F-MS compared with NF-MS, points to the difficulty in ‘scoring’ activation on the presence/absence of activity at different levels in the cord. Typically, increased percent signal change is associated with increased activation extent. Notwithstanding the difficulty in interpreting spinal fMRI data, the reported relationship between fatigue score and percentage fMRI occurrence is indicative of cord hyperactivity in response to a passive sensory task in patients without fatigue (NF-MS), and warrants further investigation.

Spinal fMRI is a relatively new technique, which is still undergoing development. Whilst data are beginning to emerge that do attempt to address the problem with multiple statistical comparisons and false positive detection rates, the examination of clinical populations with properly constructed ROI analyses is already beginning to produce promising results addressing questions about the nature and impact of spinal cord pathology in MS.

**References**


Jonathan CW Brooks
*Clinical Research and Imaging Centre,*
*University of Bristol, UK.*

**Corresponding author:**
Jonathan CW Brooks, *Clinical Research and Imaging Centre, University of Bristol, 60 St Michael’s Hill, Bristol, BS2 8DX, UK.*

**Email:** jon.brooks@bristol.ac.uk