Improved physiological noise modelling reveals expected pattern of pain-related spinal cord activation

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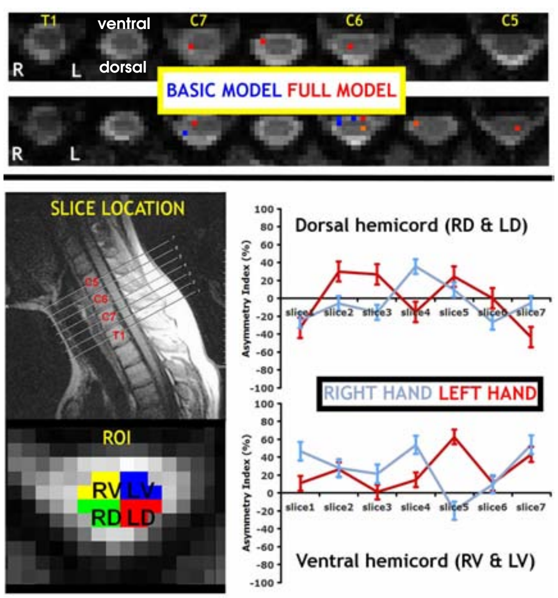
Introduction: The development of spinal functional magnetic resonance imaging (sfMRI) will provide a unique window on spinal cord function. To date, sfMRI has not been widely applied in humans, which may be due to concerns (1,2) over the proposed contrast mechanism (termed "SEEP"). However, the influence of physiological noise on spinal images has been largely overlooked. Previously, Friese et al (3) demonstrated the presence of cardiac and respiratory effects in spinal cord EPI. Crucially, they found that these 2 factors *interact*, and that low frequency signals (< 0.1Hz) may also be detected (4). The aims of this study were: (1) to compare activation maps (to painful thermal stimulation) obtained by modelling either with a "basic" block design or with a design that incorporated modifications to the standard RETROICOR (5) approach for physiological noise correction; and (2) examine the laterality of spinal activation following bilateral painful stimulation.

Methods: Ten healthy right handed subjects (4 female), aged 21 to 35 years, were imaged with a 1.5T Siemens Sonata whole body MR system. BOLD sensitive T2*-weighted images of the cervical spinal region (T1 to C5) were acquired with a gradient echo EPI pulse sequence (TE/TR/flip = 45/3000ms/90°), and resolution of 64^2, FOV=128mm and slice thickness 5mm. In two separate runs, alternating blocks (30s OFF/30s ON) of thermal heat pain were applied to the C8 dermatome (i.e. the lateral surface) of the right and left hand. Physiological data (pulse oximeter & respiratory bellows) and volume triggers were recorded during scanning. Following 2D motion correction, images were spatially smoothed (2mm FWHM) and high-pass filtered before being analysed using a general linear model (FEAT, part of FSL 3.3 software). Data were analysed in two ways: (1) <u>basic model</u> = single pain regressor; and (2) <u>full model</u> = pain regressor, standard RETROICOR plus 8 interaction terms (e.g. $sin(\theta_{cardiac}\pm\theta_{resp})$), and CSF regressor (mean time course of CSF signal surrounding the cord). Data were thresholded using cluster-based statistics and corrected $P<0.05$. Laterality of activation was assessed using regions of interest (ROI), based on pixels with positive BOLD signal parameter estimates (see Fig. 1).

Results: The mean±SD temperatures (and corresponding pain scores, out of 10) for the applied stimuli were 46.2±0.7°C (5.4±1.7) and 46.1±0.9°C (5.4±1.5) for the right and left hand, respectively. None of these was significantly different (paired t-test, $P>0.5$). Considering the cord as a whole, Z-scores were significantly higher (and fewer active pixels were observed in the CSF space surrounding the cord, see Fig.1 top panel) for the full model than for the basic model (paired t-test, right and left hand stimulation, $P<0.05$). Dorsal activation was observed ipsilateral to the stimulus at the expected nerve entry point to the spinal cord (slice 2/3), and was detected in more superior slices in the contralateral hemicord (see Fig. 1).



Discussion/Conclusions: By applying a modified RETROICOR model, to account for physiological noise, it was possible to detect pain-related spinal cord activation. The pattern of activation closely resembles that observed with autoradiography of the spinal cord during thermal stimulation in the rat (6), and matches the patterns of ipsilateral activity observed with sfMRI following hindpaw formalin injection (7) and electrical hindlimb stimulation in the rat (8). We conclude that with suitable correction for motion and physiological noise it is possible to demonstrate the expected pattern of pain-related activity in the spinal cord.

Figure 1: (<u>Top panel</u>) Model comparison: top row=right hand stimulation, bottom row= left hand stimulation. The basic model (blue pixels) has a larger number of active pixels in the CSF space when compared to the full model (red pixels). (<u>Bottom panel</u>) Graphs present activation asymmetry indices for dorsal and ventral hemicords separately (positive values = leftward asymmetry). E.g. dorsal: left hand thermal stimulation, slice 2 is more active ipsilaterally. Where, $AI(\%) = 100\cdot\left(\frac{left-right}{left+right}\right)$

References: (1) Stroman et al (1999) MRM **49**: 433-439; (2) Jochimsen et al (2005) MRM **53**: 470-473; (3) Friese et al (2004) Invest Radiol **39**:120-130; (4) Friese et al (2004) JCAT **28**: 255-262; (5) Glover et al (2000) MRM **44**:162-167; (6) Coghill et al (1991) J Neurophys **65**: 133-140; (7)Porszasz et al (1997) PNAS **94**:5034-5039; (8) Lilja et al (2006) J Neurosci 26: 6330-6336