

## Stimulus site and modality dependence of functional activity within the human spinal cord

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**Introduction:** Brain imaging has revealed a network of cortical regions active in response to nociceptive stimuli - the “pain matrix”. However, nociceptive input is initially processed within the spinal cord. The ability to record activity at the earliest stage of processing in the central nervous system (CNS) would aid our understanding of both clinical pain states, and the patterns of brain activity observed following noxious stimulation. In this study we explored the laterality and spatial distribution of spinal cord activation in response to painful thermal and punctate stimuli applied to the right and left lower arms using spinal fMRI and a physiological noise model (PNM).

**Methods:** 18 healthy subjects (11M:7F, age 28.4±4.6) were included in the study. Thermal and punctate stimuli were applied to the thenar eminence (base of thumb) and medial aspect of the lower forearm, respectively. Each 1 second long punctate stimulus was applied using a non-painful von Frey filament (60g, applied force = 588mN). Thermal stimuli (3s duration) were produced using an in-house built thermal resistor, with the temperature adjusted to produce a pain intensity rating of 5 out of 10. Twenty stimuli for each modality, thermal (T) or punctate (P), were applied to the right (R) and left (L) arms (giving 80 stimuli in total). After each stimulus subjects rated either pain intensity (thermal) or sharpness (punctate). Total scanning time was approximately 40 minutes.

Eight axial slices covering the expected locations for spinal activity from the C4 to C8 nerve root, were acquired on a 3T Siemens *Trio* scanner (12 channel head coil and 4 channel anterior/posterior neck insert) with gradient-echo echo-planar imaging and the following parameters: TE/TR=39/1000ms, FA=68°, GRAPPA (factor=2), phase encoding (P→A), resolution 1.33x1.33 mm in-plane (96x96), 4mm slice thickness with variable gap. Physiological monitoring used pulse oximeter and respiratory bellows. Each slice was motion corrected in 2D using FLIRT (part of FSL). Subsequently, data were spatially smoothed (3mm FWHM), high-pass temporal filtered (300s cut-off), and activity within each slice assessed independently using FEAT with the default HRF (3s stddev and 6s mean lag) and slice specific physiological noise regressors (Brooks et al, 2008). Group analysis was performed by co-registering hand drawn spinal cord masks for each subject to the “standard” cord template using an affine transformation (4 DOF: x,y translation and x,y scale). Activity was assessed using a mixed effects model with uncorrected  $p<0.01$ .

**Results:** Group average time-courses for the 4 main contrasts (punctate: RP & LP and thermal: RT & LT) are shown in (Fig 1A), note

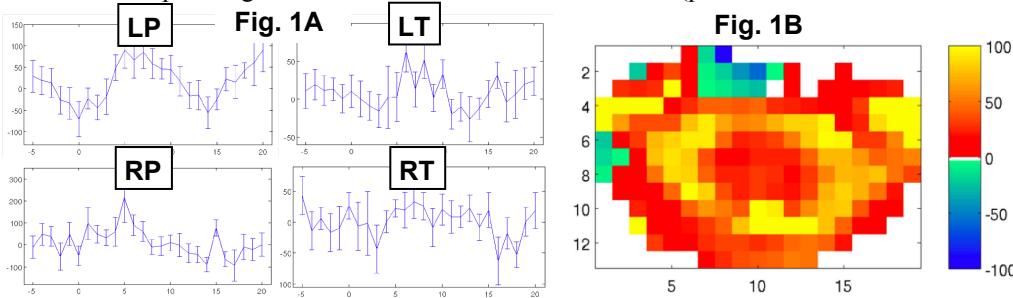
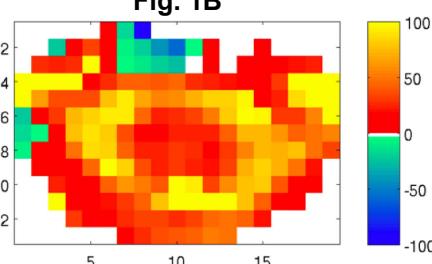
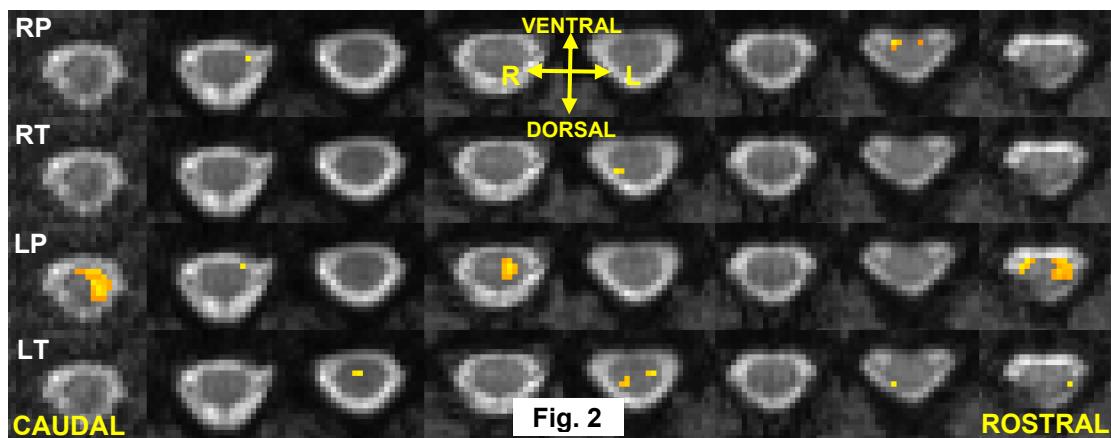


Fig. 1B



that a 6s haemodynamic delay seems appropriate for each modality (bars = standard error of mean). The improvement (percent change in t-score) obtained by including physiological noise regressors when modeling activity (in this case left hand punctate stimulation) may be seen in Fig 1B. Group maps for the 4 main contrasts is shown in Fig. 2.



Activity was observed across all slices from inferior (caudal) to superior (rostral). Lateralised activity was observed for right and left punctate stimulation, and was located more ventral than for thermal stimuli, which activated the superficial dorsal portion of the cord. Voxels were thresholded at  $p<0.01$  uncorrected, and of those only RP and LP remain at corrected  $p<0.05$  (FDR)

**Discussion:** Activity was primarily located ipsilateral to the side of stimulation, in agreement with the expected anatomical projection of nerve fibres entering the spinal cord. In response to punctate stimulation, active cord voxels were located ventral to those activated by thermal stimuli. This may reflect a difference in the neuronal populations targeted by these different modalities, with thermal heat stimulating C and A-delta fibres which project to both superficial (I) and deep (V) laminae, whilst punctate stimuli would preferentially activate neurons in deeper laminae. **Reference:** Brooks et al (2008). NeuroImage 39:680-692.