Combined intraneural microstimulation and high resolution fMRI at 7T

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Introduction:
Intraneural microstimulation (INMS) via percutaneously inserted microelectrodes can be used to study the cutaneous projections and associated perceptions of single sensory units in the human median nerve (1). Previously, INMS and fMRI have been combined at 3T to allow simultaneous measurement of the haemodynamic responses to microstimulation of single units (2). Here, fMRI scanning at 7T was carried out during INMS applied in median nerve so as to resolve the central projections of individually characterised single afferents. Specific aims were: (a) to validate the novel combination of single unit electrical stimulation and ultra-high field (7T) fMRI, (b) to resolve (spatially & temporally) the haemodynamic responses to stimulation of individual sub-classes of peripheral afferents and (c) to assess the effect of increasing INMS current, which typically results in the recruitment of sensations from more units.

Methods: Two subjects participated in each scan session of ~4 hours' duration, involving: (i) characterization of a single tactile unit, (ii) assessment of the effect of microstimulating the unit, (iii) concurrent microstimulation and fMRI and (iv) fMRI during mechanical vibration applied to the unit's receptive field. For steps (i) and (ii), subjects lay on the scanner bed outside the bore of the magnet. A tungsten needle microelectrode was inserted percutaneously into the median nerve to stimulate and record from single afferent units. Once a single unit was identified, its characteristics were examined and it was then stimulated with short bursts of 30 Hz electrical pulses delivered using a constant current stimulator (ADI, Castle Hill, Australia) with amplitude increasing until the subject reported a sensation. If the perceived location of rhe electrically elicited sensation matched the location where mechanical stimulation of the skin generated a response, the protocol continued. *fMRI paradigm:* The subject was carefully moved into the bore of the magnet. The INMS protocol consisted of 8 cycles of 8 s stimulation followed by 23 s rest. Stimulation involved delivering a 0.5 s burst of stimulation (pulse frequency = 30 Hz ; pulse width = 200 μs) once per second. The protocol was repeated multiple times with increasing microstimulation current. Subsequently, vibrotactile stimulation was applied to each units' receptive field using identical paradigm timings to the microstimulation, and a travelling wave paradigm was also performed so as to define each subjects' cortical somatotopic map (3). fMRI data (7T Philips Achieva) were collected using a GE-EPI acquisition (TR=2 s, TE=25 ms, 32 axial slices, 1.5 mm in-plane resolution, 2.5 mm slice thickness). High resolution structural data were also acquired. fMRI data were analysed using FEAT (FMRIB) and statistical maps threshold ($Z>3.08$) and cluster-corrected ($p<0.05$) to define significant ROIs. To assess the effect of microstimulation current on the haemodynamic response, the beta values (fitted haemodynamic response amplitude) in defined ROIs (active clusters in primary sensorimotor cortex (S1), supplementary motor area (SMA), insula and secondary somatosensory (S2) cortex based on overlapping responses across microstimulation runs) were assessed.

Results: For Subject 1, a single rapidly adapting (RA, Meissner) afferent with a 'flutter' percept on the right thumb was isolated at 4.4 μA in the first fMRI run. Increasing the current to 6 μA recruited a second RA unit in the same finger in the second fMRI run. For Subject 2, five INMS fMRI runs were completed, the first three runs isolated a single RA unit on the left palm, during the 1st run, at 5.5 μA, the sensation was just below the perceptual threshold, for the 2nd and 3rd runs, at 7 μA, a buzzing sensation was felt distinctly. On increasing the current to 9 μA, an additional RA unit was recruited on the left middle finger (for the 4th run a clear sensation was felt for both units, during the 5th run the percept for the unit on the middle finger was weak). For both subjects, robust activation patterns were found for all microstimulation runs, except for run 1 of Subject 2, in which the stimulus intensity was below the sensation threshold. Figure 1 shows the effect of increasing the current on the haemodynamic response for Subject 2; below sensation threshold (5.5 μA) the response is within the noise, but increases dramatically when a single afferent was perceived (7 μA), further increasing when an additional topographically-distinct sensation was reported (9 μA), but reducing in S1in the 5th run, reflecting the loss of the additional unit on the middle finger. fMRI responses to vibrotactile stimulation were localized to the same regions as the INMS responses for both subjects. Figure 2A shows an example of an activation map to microstimulation and vibrotactile stimulation for Subject 2 for different fMRI runs; responses to the unit/location in the palm alone are mapped in blue, whilst responses to the simultaneous stimulation to the palm and middle finger units/locations are mapped in yellow, overlapping areas are shown in green. The arrows indicate where the middle finger cluster (yellow) extends medial to the palm location in contralateral S1. Figure 2B plots the mean beta values in the palm and middle finger ROIs in S1 for the INMS and vibrotactile stimulation runs, illustrating the lower response in the middle finger ROI for the runs where percept was on the palm alone, compared with the higher current runs when the middle finger response was also recruited.

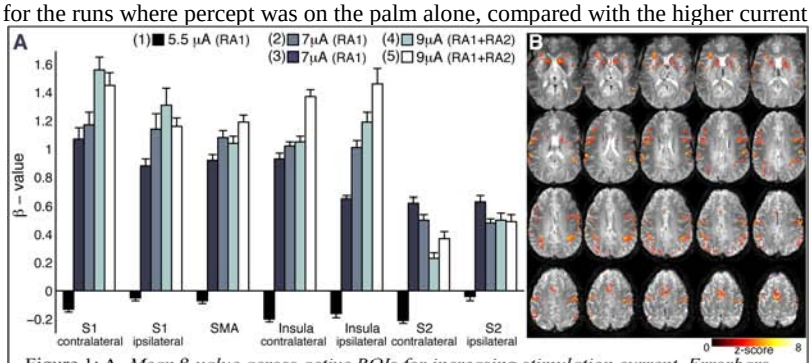

Figure 1: A. *Mean β value across active ROIs for increasing stimulation current. Errorbars indicate standard error. B. Activation map due to microstimulation (7 μm) of the palm unit (RA1) overlaid onto a subset of EPI slices.*

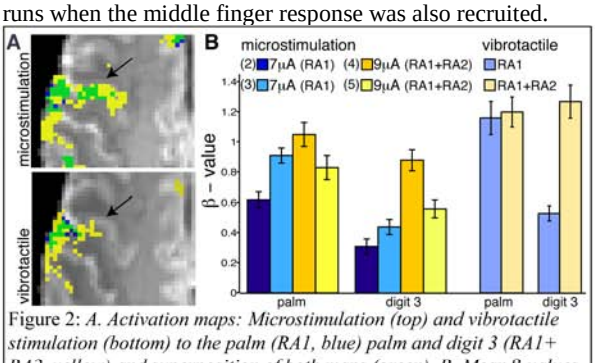

Figure 2: *A. Activation maps: Microstimulation (top) and vibrotactile stimulation (bottom) to the palm (RA1, blue) palm and digit 3 (RA1+ RA2, yellow) and superposition of both maps (green). B. Mean β values for ROI in S1 for palm and digit 3 (blue and yellow clusters respectively, shown by arrow) across fMRI runs 2-5. Errorbars: standard error.*

Discussion: We successfully measured fMRI responses during INMS at 7T. For all perceived microstimulated units, robust responses were found, which were consistent with the activation pattern seen using vibrotactile stimulation applied to the receptive field of the units. However, activation was not found for microstimulation at sub-sensation thresholds confirming reports that somatosensory perception requires activation of S1. We showed that high-resolution fMRI allows discrimination of different INMS sites on the hand (Figure 2). This demonstration opens the way for further studies using high resolution fMRI acquisitions focused on S1 to resolve responses to INMS of different unit types, coupled with exploration of the perception and cortical activation associated with neutrally-derived INMS stimulus patterns.

References: (1) Vallbo & Hagbarth, *Exp. Neurol*,21: 270–289, 1968. (2) Trulsson et al. *NeuroImage* 13: 613–622, 2001. (3) Sanchez-Panchuelo et al, *J Neurophysiol*, 103:2544-56, 2010. **Acknowledgements:** This work was funded by the MRC and pain relief foundation.