Characterizing cortical responses to the stimulation of single mechanoreceptive afferents using fMRI at 7 T

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TARGET AUDIENCE: Neuroscientists and neuroimagers with an interest in ultra-high field MRI and/or somatosensory function.

PURPOSE: The technique of microneurography coupled with intraneural microstimulation (INMS) has been used to study the contribution of single, physiologically-characterized mechanoreceptive afferents (MRAs) to properties of somatosensory experience in awake human subjects (1). The combination of INMS with magnetic resonance imaging fMRI permits simultaneous measurement of the associated brain responses. INMS has been shown to produce robust BOLD activations responses in primary (SI) and secondary (SII) somatosensory areas at 3T (2). Here, we report its successful use at ultra-high field (7T) (Philips Achieva), for the first time. We compare the global patterns of brain activity generated by electrical microstimulation of single nerve MRAs, with those produced by mechanical stimulation of the skin.

METHODS: Four 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 INMS and fMRI; (iv) fMRI with 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 electrode was inserted percutaneously into the median nerve to stimulate and record from single MRAs. 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 the 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 of rest. Stimulation involved delivering a 0.5 s burst of stimulation (pulse frequency = 30 Hz; pulse width = 200 μs) once per second using an INMS current that generated a clear perception. Subsequently, vibrotactile stimulation was applied to each MRAs'unit's receptive field using identical paradigm timings to the INMS. A travelling wave paradigm was also performed so as to define each subjects' cortical somatotopic map (3). fMRI data 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. *Data Analysis:* fMRI data were analyzed using mrTools (http://www.cns.nyu.edu/heegerlab). For comparison of responses produced outside of SI by INMS and vibration, data were spatially smoothed (3mm FWHM) and statistical maps formed by thresholding (Z>3.08) after FDR correction and cluster-correction (p<0.01). The statistical maps depicting activity due to RA-unit stimulation at 30 Hz and application of vibration to the same units' receptive fields were projected into standard MNI space to allow computation of a map of common activation. INMS and vibration responses (unsmoothed) for each unit were also projected onto flattened representations of the contralateral central sulcus to compare the spatial localization with finger somatotopy in S1.

RESULTS: Data were obtained from 11 units (6 rapidly-adapting type I (RA), 3 slowly-adapting type I, 2 unclassified) across four subjects in the left hand. Figure 1 shows the locations of the units in the hand. Figure 2 compares 30 Hz RA INMS-induced fMRI responses (yellow) to vibration-induced responses (blue), with common responses also shown (green). BOLD responses to 30 Hz RA INMS were found in a number of sensory-related brain areas, including SI, SII, premotor cortex (supplementary motor area (SMA) and dorsal premotor cortex (PMC)), primary motor cortex (MI), insular cortex (anterior (AIC) and posterior (PIC) parts), prefrontal (PFC) and posterior parietal (PPC) cortex. Participants described the small, point-vibration applied to the unit site as feeling very similar in size and quality to the INMS. Common active areas include SI and SII, premotor and motor cortices and the contralateral PIC. Interestingly, INMS-only activated areas included AIC, PPC and the contralateral PFC. INMS activation patterns in the contralateral SI area were consistent with the expected spatial localization from digit somatotopy. Figure 3 shows an example of INMS-evoked BOLD responses for Unit 10, and the BOLD response from vibration at the location where Unit 10 was perceived, superimposed on a flattened representation of the central sulcus. Activations were well localized within the expected Digit 4 area (Fig 2C).

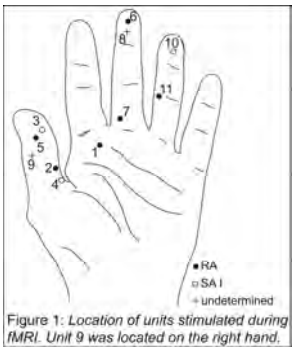

Figure 1: *Location of units stimulated during fMRI. Unit 9 was located on the right hand.*

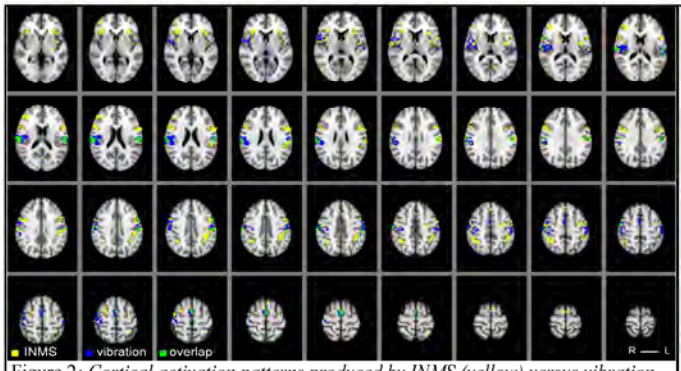

Figure 2: *Cortical activation patterns produced by INMS (yellow) versus vibration (blue) and overlap of both maps (green) in MNI space.*

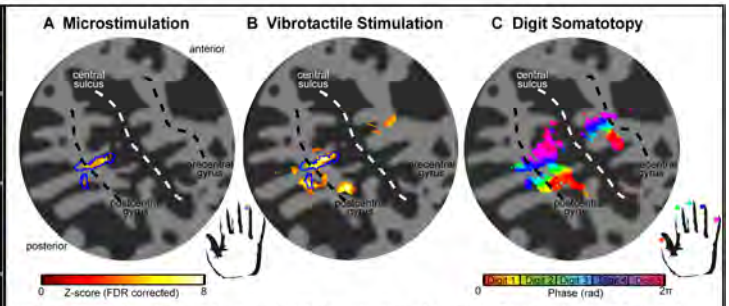

Figure 3: *(A) Spatial localization in S1 of activation due to INMS of Unit 10 (RA, tip of digit 4). (B) Vibrotactile stimulation applied to Unit's 10 receptive field (B). The blue line represents the border of Digit 4. (C) Left hand digit somatotopy. Digit 4 is indicated by the dark blue region.*

DISCUSSION: We successfully measured fMRI responses during INMS at 7T, showing that both INMS and vibrotactile stimulation engage sensory discriminatory areas such as SI, SII, and PIC, as well as areas involved in motor control, including SMA, PMC and M1. INMS was found to activate additional areas (AIC, PPC and the contralateral PFC), which have been shown to be part of a network identified as the cerebral signature for painful or unpleasant touch (4), even though the artificial touch sensation induced by INMS of single afferents was described as very similar to that of vibration. We show that INMS responses fell within the expected area of digit representation in contralateral SI. The combination of INMS and 7T fMRI provides a framework for the precise correlation of neural activity in the peripheral and central nervous systems. We now plan to study the effect of stimulation frequency using neurophysiologically recorded natural patterns of spike discharge activity to study the relationships between INMS patterns on perception and cortical activation.

REFERENCES: (1) Vallbo et al, *Brain* 107: 727-49, 1984. (2) Trulsson et al. *NeuroImage* 13: 613–622, 2001. (3) Sanchez-Panchuelo et al, *J Neurophysiol*, 103:2544-56, 2010. (4) Tracey. *Br J Anaesth* 101:32-9, 2008. **Acknowledgements:** This work was funded by the MRC, Royal Society and Pain Relief Foundation.