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Journal Article

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Abstract

Topographic maps of the receptive surface are a fundamental feature of neural organization in many sensory systems. While touch is finely mapped in the cerebral cortex, it remains controversial how precise any cortical nociceptive map may be. Given that nociceptive innervation density is relatively low on distal skin regions such as the digits, one might conclude that the nociceptive system lacks fine representation of these regions. Indeed, only gross spatial organization of nociceptive maps has been reported so far. However, here we reveal the existence of fine-grained somatotopy for nociceptive inputs to the digits in human primary somatosensory cortex (SI). Using painful nociceptive-selective laser stimuli to the hand, and phase-encoded fMRI analysis methods, we observed somatotopic maps of the digits in contralateral SI. These nociceptive maps were highly aligned with maps of non-painful tactile stimuli, suggesting comparable cortical representations for, and possible interactions between, mechanoreceptive and nociceptive signals. Our findings may also be valuable for future studies tracking the timecourse and the spatial pattern of plastic changes in cortical organization involved in chronic pain.

Introduction

Topographic maps are a fundamental feature of most sensory systems, and are amongst the best-known and wide-spread aspects of neural organization in the cerebral cortex (Thivierge and Marcus, 2007). While touch is mapped with exquisite precision in primary somatosensory cortex (SI) (Kaas et al., 1979; Maldjian et al., 1999), the spatial organization of the nociceptive system is controversial. In particular, it remains debated how precise a cortical nociceptive maps may be.

Fine-grained topographic neural organisation within SI is thought to allow precise spatial discrimination of tactile inputs (Kenshalo, 1968; Duncan and Boynton, 2007), and somatotopic maps of single digits have been repeatedly described (Kaas, 1983; Maldjian et al., 1999). Although there is both anatomical (Kenshalo et al., 1980; Gingold et al., 1991; Dum et al., 2009) and physiological evidence (Treede et al., 1999; Duerden and Albanese, 2011; Valentini et al., 2012) of nociceptive projections to SI, their spatial organization is less clear, and only broad somatotopies for hand, face and foot territories have been described in humans (Andersson et al., 1997; Bingel et al., 2004a) and monkeys (Kenshalo et al., 2000).

Interestingly, the distribution of mechanoreceptors across skin regions differs sharply from the distribution of nociceptors (McArthur et al., 1998; Johansson et al., 1999; Lauria, 1999; Lauria et al., 1999): nociceptive innervation density is poor in distal body territories as the digital papillae, where mechanoreceptor density is highest (Arthur and Shelley, 1959; Kelly et al., 2005). In contrast to the tactile system, the nociceptive system is often considered to lack a fovea at the fingertips. Therefore, the existence of finely-organised cortical maps of nociceptive input from single digits is unknown.

Previous investigations have been limited by technical and methodological difficulties. For example, traditional 3D group averaging analyses may fail to reveal small maps given variation in spatial organization of nociceptive responses between individuals (Bushnell et al., 1999; Baumgartner et al., 2010). We adapted a phase-encoded functional magnetic resonance imaging (fMRI) technique originally created to map the visual field (Sereno et al., 1995) to map the pain field.

Specifically, we studied the topographical organization of brain responses to radiant heat delivered to the fingers, using a Nd:YAP laser to provide a nociceptive-specific somatosensory input without coactivation of tactile afferents (Iannetti et al., 2006). Surface-based Fourier methods (Sereno and Huang, 2006) identify areas with differential responses at the stimulation frequency (e.g., Fig. 1a shows the raw BOLD signal elicited by the stimulation in a voxel across 12 cycles). These Fourier methods were used to compare somatotopic maps in SI elicited by nociceptive Aδ input eliciting painful pinprick sensations (Aδ maps) to those elicited by non-painful tactile input (Aβ maps).

The established organization of somatotopic maps of innocuous mechanical input to SI, together with the exquisite spatial precision in discriminating tactile inputs, provides a crucial point of comparison with the still debated spatial organization of nociceptive responses. We specifically test whether the response to Aδ stimulation of single digits is precisely represented in the cortical fields immediately adjacent to the central sulcus.

Materials and Methods

Participants. Right-handed participants (n = 7) took part in 2-3 fMRI imaging sessions each. Each gave informed consent according to procedures approved by UCL ethics committee.

Procedure. Participants lay with their right hand supine outside the scanner bore, and wore earplugs throughout the experiment. Repeated cycles of nociceptive or tactile stimulation (in separate sessions) were delivered successively to the volar surface of digits 2-5 (Fig. 1a). During each cycle, the four digits were stimulated sequentially one after each other. The stimulation of each digit consisted of somatosensory stimuli being delivered randomly to several locations on the volar surface of the digits (see details below). For nociceptive stimulation, 9 cycles of 56.9 sec trains of 4 ms-long laser pulses were delivered in each run, at a frequency of 0.42 Hz. For tactile stimulation, 12 cycles of 42.7 sec trains of XX ms-long air puffs were administered in each run, at a frequency of xx Hz.

Comment [FM1]: Marty, can you please fill these details?

To improve the signal-to-noise ratio, we averaged four functional runs for each subject (see Data acquisition and analysis).

In the same subjects, we compared nociceptive maps with tactile maps elicited by computer-controlled trains of air puff (Huang and Sereno, 2007) stimulation, delivered with similar procedures to the volar surface of the same digits (2-5).

Air puff stimulation. An air compressor in the scanner control room provided input to a 12-way solenoid manifold valve (Numatics) that was controlled by TTL pulses. Twelve plastic air tubes from the manifold valve passed through waveguides into the scanner room, where they connected to a block mounted beside the right hand, at the edge of the bore. The block served as rigid base for 12 flexible tubes with nozzles (Loc-Line), flexibly arranged to direct 500-ms air puffs (input air-pressure 2-3 bar) at 3 locations on the centre of each stimulated finger segment (d2-d5, Fig. 1a). Each air puff was perceived as a well-localised and light touch on a specific finger location.

Laser stimulation. Radiant-heat stimuli were generated by an infrared neodymium ytrium aluminum perovskite (Nd:YAP) laser with a wavelength of 1.34μm (Electronical Engineering, Italy). Laser pulses activate directly nociceptive terminals in the most superficial skin layers (Baumgartner et al., 2005; Iannetti et al., 2006). Laser pulses were directed at 12 possible locations on the glabrous skin of the fingers (d2-d5, 2 locations per finger-segment, aligned along the proximo-distal plane). A He-Ne laser pointed to the targeted location. The laser pulse (4-ms duration) was transmitted via optic fiber, passing through the control room to the scanner room. Beam diameter at the target site was approximately 7 mm. Pulse energy was adjusted for each subject (between 3 and 3.25 J) in order to elicit a clear pinprick painful sensation, related to the activation of Aδ fibers. The experimenter inside the MR scanner room checked, between successive MRI runs, that the stimuli were perceived as painful.

Data acquisition and analysis. Echoplanar images (3.2 x 3.2 mm^2 in-plane, 3.2 mm thick slices, 256 images per run, 24 axial slices, flip=90°, TE=39 ms, TR=2s, 64x64 matrix, bandwidth = 1474 Hz/pixel, data acquired with prospective motion correction) were collected during 4 runs (per modality) on a Siemens Avanto 1.5 T

MRI scanner with a 32-channel head coil. Functional series were aligned and motion-corrected using the AFNI program 3dvolreg. To improve the signal-to-noise ratio, we combined four functional runs for each subject. To correct for systematic regional variations in the shape of the hemodynamic response function, we interleaved index-to-little and little-to-index progressions (two runs each), and then combined opposite-direction data by vector addition of the complex-valued signal (the strength and phase of the response at the stimulus frequency), after reversing the phase in the opposite direction.

For each subject, we used FreeSurfer to reconstruct the cortical surface from 1-2 registered MPRAGE scans (1x1x1 mm, flip=7°, TR=2730msec, TI=1000ms, TE=3.57msec, matrix=256x224x160, 190 Hz/pixel). The last run of each functional session was a short alignment MPRAGE acquired in the plane of the functional runs (1x1x2 mm, flip=7, TE=4msec, TI=1000msec, TR=8.2msec, matrix=256x224x88, mSENSE accel.=2x, slab-selective excitation). The align scan was first registered to the high resolution scan. Using this as a starting point, functional-to-high resolution alignment was then refined using manual blink comparison. Four runs were combined to increase signal-to-noise (see above).

After removing the linear trend, functional data were analysed using a Fourier transform, computed for the time series at each voxel fraction (vertex). We computed an *F*-ratio by comparing the power of the complex-valued signal at the stimulus frequency to the power of the noise (other frequencies). Very low frequencies and harmonics were excluded. The *F*-ratio was then converted to an uncorrected *P*-value by considering the degrees of freedom of the signal and noise. The phase angle was displayed using a continuous color scale (red to blue to green), whose saturation was masked by the *p*-value (see colorbar insets in figures).

Surface-based cross-subject average map. Across-subjects map averages were performed with FreeSurfer by morphing individual brain surfaces into alignment with an average target brain, sampling the data onto a super-tessellated icosahedron. The complex signals were then combined by vector averaging, after reversing phase measures for sequences where stimuli were presented in little-index finger order. The vector sum strongly penalizes inconsistent phases across runs and corrects for stationary between-voxel differences in hemodynamic delay. Finally, an *F*-statistic

was calculated using the raw amplitude of the stimulus-frequency response (Hagler et al., 2007) and rendered back onto the cortical surface of one subject.

Map alignment measures. In order to quantify the alignment between nociceptive and air puffs-maps, we calculated alignment indices and circular correlation coefficients for each subject separately, as elsewhere (Sereno and Huang, 2006). Both measures were evaluated across a region of interest defined as a connected two-dimensional patch of surface vertices in SI that had a significant periodic response to both nociceptive and air puff stimuli. The alignment index of each pair of vertices was defined as

$$\text{Alignment index} = 1 - \frac{|\Delta\phi|}{\pi},$$

where is the difference between the phase angle in the two data sets in radians. The index ranges from 0 (π offset, i.e. when one phase angle is on the little finger and the other is on the index finger) to 1 (where the phase angle at a vertex is identical in the two data sets). A histogram of alignment indices that is sharply peaked near 1 indicates strong alignment between two maps. Conversely, an uncorrelated map would result in a shallow uniform distribution of alignment indices, in which every bin has low frequency ($2v/n$, where v is the number of vertices and n is the number of bins), illustrated by a red line in each alignment index histogram (Fig. 1b, 2-3).

For each comparison, we calculated the average of the alignment indices, the circular correlation of vertex-by-vertex phase angles (after controlling for angle wraparound) and its significance. The quantitative agreement between the two maps is constrained by cross-session alignment accuracy, which is itself constrained by the voxel size of the functional scans. During registration, we subsampled each session's functional data to 1x1x1mm and then did nearest neighbor smoothing in order to achieve sub-voxel alignment accuracy to the single 1x1x1 structural scan (approximately 1.5 mm).

Map location measures. We calculated the centroid of each map for Aδ and Aβ stimuli, for each subject separately, as the surface vertex coordinate closest to the average of the vertex coordinates in a region of interest defined as a connected two-

dimensional patch of surface vertices in SI that had a significant periodic response to the stimuli. To allow across-subject comparisons, we used morphed spherical coordinates, displayed on a 2D plane tangent to the spherical surface (Fig. 4), and also Talairach coordinates (Collins et al., 1994). In addition, a similar centroid calculation was made for the average map.

Results

(1) Fine-grained nociceptive maps of the digits in SI

For each subject, nociceptive stimulation of the fingers elicited a clear and strong somatotopic response within the hand area of the contralateral SI (BOLD response in two illustrative subjects, Fig. 1b and 2). These nociceptive maps were located on the convexity of the central sulcus, in a region overlapping that activated by air-puff stimulation (Fig. 1c).

We did not find any significant activation at the stimulus frequency in the ipsilateral hemisphere. Importantly, the Fourier-based methods employed only show areas with differential responses at the stimulation frequency (Fig. 1a), while regions that respond to every laser pulse are not visible.

Noteworthy is the variability in map size across individuals: in some subjects the nociceptive map was larger than the mechanical (Fig. 1), while in other subjects we observed the opposite pattern (Fig. 2).

(Fig 1 and 2 about here)

(2) High alignment of nociceptive and tactile maps

Within both Aδ and Aβ maps, the index finger was represented inferior to the little finger. Thus, nociceptive and tactile maps in contralateral SI have similar location and alignment (Fig. 1b and 2).

To quantitatively compare within-subject alignment between the two maps, we calculated an alignment index (Sereno and Huang, 2006) that ranged from 0 (π offset in response phase) to 1 (perfectly aligned) for each surface vertex in the hand area of the contralateral SI (dashed white line). In every subject the distribution of

such alignment indices was strongly skewed toward 1 (aligned), and the phase angles of the two maps were highly correlated (all $p < 10^{-10}$, Table I).

To average maps across subjects, we first inflated each participant's cortical surface to a sphere, and then non-linearly morphed it into alignment with an average spherical cortical surface using FreeSurfer (Fischl et al., 1999), which maximizes alignment between sulci (including the central sulcus) while minimizing metric distortions across the surface. Complex-valued mapping signals were then combined across subjects on a vertex-by-vertex basis by vector averaging (Sereno and Huang, 2006), and rendered back to the unfolded hemisphere of one subject (Fig. 3). Alignment histograms and correlations showed that the average fingers maps of tactile and nociceptive input were highly aligned, consistent with individual results (Fig. 3 and Table I).

(Fig. 3 and Table I about here)

(3) Location of the centroids of Aδ and Aβ maps in SI

To investigate the locations of the Aδ and Aβ maps, we calculated the centroid of the region that showed strong somatotopic response to each type of stimulus, on each morphed spherical surface in order to allow across-subjects comparisons. As shown in Fig. 4, the relative locations of the centroids of the two maps varied across individuals, with no consistent offset between the centroids of Aδ and Aβ maps. The locations of our maps appear consistent with previous studies mapping Aβ to the digits (e.g., Gelnar et al., 1998; Maldjian et al., 1999; McGlone et al., 2002; Overduin and Servos, 2004; Nelson and Chen, 2008), and Aδ input to the hand (Bingel et al., 2004b).

(Fig 4 about here)

Discussion

These results reveal that nociceptive input from each digit of the human hand is finely organized in SI, in a somatotopic fashion. Our nociceptive maps were highly

aligned with tactile maps obtained by innocuous somatosensory stimuli in every subject. Importantly, the two maps were essentially co-located, since there was no systematic offset in the centroid location of one map relative to the other. We also noted some inter-individual variability in map location. Traditional 3D group averaging analyses might therefore fail to reveal these relatively small Aδ maps, which may explain inconsistencies in previous reports of nociceptive spatial organization in SI. Phase-encoded methods have allowed us to develop a new approach to somatotopic mapping of nociceptive input, thus providing a new quantitative marker of the spatial coding of pain in the human brain.

Somatotopic organization of tactile and nociceptive RFs has been described in the dorsal horn (Swett and Woolf, 1985), the lateral thalamus (Albe-Fessard et al., 1985; Lenz et al., 1994), putamen (Bingel et al., 2004a), SI (Lamour et al., 1983b; Lamour et al., 1983a; Andersson et al., 1997; Kenshalo et al., 2000; Bingel et al., 2004b), and operculo-insular cortex (Brooks et al., 2005; Mazzola et al., 2009; Baumgartner et al., 2010). However, only gross somatotopy of the brain responses to nociceptive input has been observed in those studies. Reports of spatially-precise cortical maps in monkeys are based on stimuli that simultaneously activate Aδ and Aβ fibers (Chen et al., 2011). While many studies examined the brain responses in SI to nociceptive-specific stimulation of the hand (e.g., Andersson et al., 1997; Kanda et al., 2000; Ploner et al., 2000a; Timmermann et al., 2001; Bingel et al., 2004b; Liang et al., 2011; Zhang et al., 2012), no previous study, to our knowledge, has focused on the topographical organization of those responses within single hand digits. Our study reveals for the first time the existence of fine-grained nociceptive somatotopic maps in SI. Other studies focusing on different cortical regions might reveal somatotopic activations in other regions than SI.

The existence of fine-grained nociceptive maps of the *digits* in SI is remarkable, considering the available evidence of the anatomical distribution of nociceptive afferents in the periphery (McArthur et al., 1998; Johansson et al., 1999; Lauria, 1999; Lauria et al., 1999). Indeed, intra-epidermal nerve fiber density in the human skin appears to decrease from distal to proximal body parts (Holland et al., 1997; McArthur et al., 1998; Johansson et al., 1999; Lauria et al., 1999; Sumner et al., 2003), and particularly along the hand to the digital papillae (Arthur and Shelley, 1959; Kelly et al., 2005). Conversely, afferents that respond to mechanical innocuous touch show an opposite organization. The somatosensory homunculus (Rasmussen

and Penfield, 1947; Penfield and Rasmussen, 1950) shows enlarged representation of the digits relative to proximal skin regions. More recently, fMRI studies have confirmed enlarged cortical territories correlate with discrimination thresholds (Duncan and Boynton, 2007), confirming classical psychophysical measures of acuity (Boring, 1942).

Given the evidence of relatively poor nociceptive innervation density on the digits (Arthur and Shelley, 1959; Kelly et al., 2005) and the present finding of aligned Aδ and Aβ maps, we speculate that the fine nociceptive spatial resolution we have observed in SI might result from complex interactions between tactile and nociceptive central projections. The first candidate for such interactions may be the dorsal horn where, beside high-threshold nociceptive specific (NS), wide dynamic range (WDR) neurons respond to noxious stimulation and also to weak, mechanical stimuli as hair movement (Maixner et al., 1986). WDR projections might contribute to the striking alignment of laser/Aδ and airpuffs/Aβ maps we found. Noteworthy are also the vertical excitatory interneurons the allow connections between layers I-III, at least in rats' dorsal horn (Maxwell et al., 2007; Todd, 2010; Yasaka et al., 2010). The function of these vertical interactions is not fully understood, but it might favor communication between somatosensory submodalities. Other sites of possible interactions are the thalamus (Wepsic, 1966), and the post-central gyrus. Modular, columnar segregation in primate post-central areas has been reported only for mechanoreceptive afferents (Dykes et al., 1980; Sur et al., 1984; Friedman et al., 2004), but not for cortical neurons that respond to noxious stimuli (Mountcastle and Powell, 1959; Kenshalo and Isensee, 1983; Kenshalo et al., 2000). In particular, NS neurons in area 1 of SI seem to be vertically organized, and most prevalent in cortical layers III-IV (Kenshalo et al., 2000). Kenshalo et al (2000) reported the distributed presence of WDR neurons in SI, preferentially responding to noxious thermal stimulation, and with receptive fields overlapping those of NS neuron. Intermixed populations of mechanical and nociceptive neurons might be linked by local intrinsic connections within SI, thus allowing interactions between somatosensory submodalities. Accordingly, several neuroimaging studies report interactions between Aδ and Aβ stimuli in SI (Ploner et al., 2004; Inui et al., 2006).

Separate multiple somatotopic maps of mechano-receptive afferents are present in areas 3b, 1, and 2 of SI (Kaas et al., 1979; Krubitzer and Kaas, 1990; Friedman et al., 2004). Our neuroimaging method cannot readily separate the

responses from these different cortical fields. However, it is noteworthy that our Aδ and Aβ maps of the digits were highly aligned, without any consistent offset in their centroids across individuals (Fig. 4). Previous studies in humans directly comparing locations of SI responses to nociceptive and tactile stimuli to the hand reported that the nociceptive territory was located slightly medial to the tactile territory (Coghill et al., 1994; Iadarola et al., 1998; Ploner et al., 2000b).

Although the functional role of topographic maps in sensory systems is still debated (Kaas, 1997; Weinberg, 1997), a large body of evidence suggests that topographic mapping brings computational advantages and plays an important role in organization of sensory processing and cognition (for a review, see Thivierge and Marcus, 2007). Topographic connectivity within SI seems to underlie tactile spatial acuity (Kenshalo, 1968). Our results show a similar organization of Aδ and Aβ maps of the digits, and indeed possible interactions between those maps, and suggest a common neural substrate for spatial-discriminative aspects of tactile and pain perception. Accordingly, spatial precision for pain, assessed using one-point localization task, approaches, in the hairy skin, that of touch (Schlereth et al., 2001; Mancini et al., 2011). Psychophysical studies of tactile acuity for pain on the fingertips are lacking.

There has been extensive debate in the literature about whether pain is a purely interoceptive form of emotion (REF Craig) or an exteroceptive form of perception (Price et al., 2003).

~~Thus, although pain is considered to have not only an exteroceptive, but also an interoceptive aspect (Price $$$), our findings suggest that the exteroceptive aspect of pain has, at least for the~~ By showing that sensations elicited by Aδ input~~,~~ have an organization similar to that of unambiguously exteroceptive touch, our results provide important insight into the exteroceptive function of pain.

Comment [FM2]: Don't really know where to put it, and what to say…

MRL: I've had a bit of a go…

Finally, maladaptive reorganization of cortical topographic connectivity is often associated with~~to~~ chronic pain (Flor et al., 1995; Juottonen et al., 2002; Maihofner et al., 2003), highlighting the role of sensory maps in pain perception. In the context of clinical research, understanding and tracking the plastic changes in somatosensory maps has proven challenging because a precise measure of the spatial resolution of these maps was lacking. Here we demonstrated that precise somatotopic maps related to pain can be revealed using phase-encoded methods for fMRI,

providing novel, quantitative markers of the spatial coding of pain in the human brain. These markers could be a valuable measure of cortical organization in clinical pain syndromes, which is specifically targeted in treatments that use sensory discrimination training (Flor et al., 2001; Moseley et al., 2008) and non invasive brain stimulation techniques (Fregni et al., 2007).

Figure Captions

Figure 1. (a) *Phase-encoded protocol and raw BOLD response in one voxel.* The color coding scheme used for Aδ (laser) and Aβ (air puffs) maps in Figures 1-3 is shown in a. (b) *Aligned Aδ (laser) and Aβ (air puffs) maps for a single subject (subject 2, dorsolateral view).* Thick dashed white contours outline a region of interest defined as the connected surface patch of SI vertices with significant periodic response to both Aδ and Aβ stimulation. A similar alignment is evident for every color, representing stimulation to the digits (d2 to d5). The alignment index histogram shows the distribution of agreement in phase angle for each surface vertex within the dashed contour (1 = max alignment). The red line indicates the distribution of the alignment index that would be expected if the two maps were completely uncorrelated. (c) *Location of the two maps (red cross) in an illustrative single subject.*

Figure 2. *Aligned Aδ (laser) and Aβ (air puffs) maps for a single subject (subject 5).*

Figure 3. *Surface-based average Aδ (laser) and Aβ (air puffs) maps from seven subjects.* The complex-valued mapping data were averaged in a spherical surface coordinate system after morphing each subject's data into alignment with an average spherical sulcal pattern and were then rendered back onto the unfolded cortical surface of one subject.

Figure 4. *Map locations relative to the central sulcus.* For each subject, the central sulcus was identified and the location of the centroid of Aδ (laser) and Aβ (air puffs) maps was rendered onto a plane tangential to both the morphed spherical surface and in Talairach space (Collins et al., 1994).

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