Within-finger maps of tactile and nociceptive input in the human parietal cortex

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Supplemental data

<u>*Mechanical stimulation of Aβ fibers.*</u> Aβ fibers in the glabrous skin of the digits were stimulated with a plastic probe with a flat tip. At the end of each run, we asked participants whether the stimulation was always clearly detectable, what was its average perceived intensity on a scale from 0 ('no touch') to 10 ('extremely intense touch'), whether the sensation was experienced as unpleasant or painful at any point during the run and to estimate how frequently it happened. In all participants, the mechanical stimulation was clearly detectable (mean 'touch' intensity rating: 4.18; SD across participants: 1.03; mean rating variability across runs: 0.04) and was never perceived as unpleasant or painful.

<u>*Radiant heat stimulation of Aδ/C fibers.*</u> Nociceptive-selective stimuli were radiant heat pulses generated by an infrared neo-dymium:yttrium-aluminum-perovskite laser (wavelength: 1.34μm; pulse duration: 5ms; beam diameter on skin: 7mm; Electronical Engineering). At this wavelength, laser pulses excite Aδ and C nociceptive free nerve endings in the epidermis directly and selectively (Mancini et al. 2014). Pulse energy was adjusted for each subject (range 0.45-0.65 J/mm^2) in order to elicit a clearly-detectable pinprick painful sensation. To avoid receptor fatigue or sensitization, the laser beam was manually displaced after each pulse by ~7mm within the target area. At the end of each run, we asked participants whether the stimulation was always clearly detectable and pinprick, what was its average perceived intensity on a scale from 0 ('no pinprick pain') to 10 ('extremely intense pinprick pain'), and whether the sensation did not feel as a pinprick pain at any point during the run. The laser stimulation was clearly detectable in all participants (mean 'pinprick pain' intensity rating: 6.24; SD across participants: 1.48; mean rating variability across runs: 0.38). Participants estimated to have experienced a more diffuse burning hot sensation, instead of a well-localised pinprick sensation, for 1.6± 2.54% of the stimulation time. There was no consistent pattern in the location of these reported sensations.

<u>*Generalized Linear Model analyses.*</u> fMRI data were registered to high-resolution structural and standard space images using a full search with 12 degrees of freedom in FLIRT and FNIRT. fMRI data were subject to motion correction using MCFLIRT, non-brain removal using BET, 3mm spatial smoothing, grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor, and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma 50s). Time-series statistical analysis was carried out using FILM prewhitening with local autocorrelation correction and double-gamma hemodynamic response function convolution.

<u>*Phase-encoded analyses (preprocessing).*</u> Preprocessing of functional images was re-performed for surface-based phase-encoded analyses following a well-established approach that performs smoothing only after the statistics is computed (Mancini et al. 2012; Mancini et al. 2018). First, we discarded the measurements during the rest period at the beginning and at the end of each functional scan. Functional series were aligned and motion-corrected with

AFNI program '3dvolreg'. Using this as a starting point, functional-to-high resolution alignment was then refined using manual blink comparison and field distortions were manually corrected using FreeSurfer's TkRegister. After removing the linear trend, aligned data from the 3 runs per modality were raw-averaged, by combining opposite-direction data by vector addition of the complex-valued signal after reversing the phase in the opposite direction (before averaging, time-reversed scans were time-shifted of one TR to compensate for hemodynamic delay). The vector sum strongly penalizes inconsistent phases across runs and corrects for stationary between-voxel differences in hemodynamic delay.

In each subject, the raw-averaged responses were analysed using a fast Fourier transform, computed for the time series at each voxel fraction (vertex): this resulted in complex-valued signals with the phase angle and magnitude of the BOLD response at each voxel (Chen et al. 2017). The phase angle of the BOLD response at each voxel indicates the neural selectivity to the spatial frequency of stimulation. Both Fourier and statistical analysis were performed using CSURF (http://www.cogsci.ucsd.edu/~sereno/.tmp/dist/csurf). No spatial smoothing was performed before statistical analyses. Very low frequencies and harmonics (<0.005Hz) were excluded, because these frequencies are dominated by movement artefacts: therefore, this procedure is virtually identical to regressing out signals correlated with low frequency movements. High frequencies up to the Nyquist limit were allowed (i.e. half the sampling rate): this corresponds to no use of low pass filter. For display, a vector was generated whose amplitude is the square root of the F-ratio calculated by comparing the signal amplitude at the stimulus frequency to the signal at other noise frequencies and whose angle was the stimulus phase. The Fourier-transformed data were then sampled onto the individual surface. To minimize the effect of superficial veins on BOLD signal change, superficial points along the surface normal to each vertex (top 20% of the cortical thickness) were disregarded. Clusters were defined as significant when they survived a surface-based correction for multiple comparisons of $p<0.05$ and a cluster-level, FDR correction of $p<0.05$. Correction was based on the cluster size exclusion method as implemented by surfclust and randsurfclust within the csurf FreeSurfer framework (Hagler et al. 2006). These significance thresholds were used to identify significant digit maps at the individual level.

To average maps across subjects who undertook the within-finger mapping task, 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's tool mri_surf2surf. This procedure maximizes alignment between sulci (including the central sulcus), while minimizing metric distortions across the surface. Five steps of nearest-neighbour smoothing (~1.5mm FWHM in 2D) were applied to the data after resampling on the isocohedral surface. Complex-valued mapping signals were then combined across subjects on a vertex-by-vertex basis by vector averaging (Sereno and Huang 2006). The amplitude was normalized to 1, which prevented overrepresenting subjects with strong amplitudes. Finally, a scalar cross-subject F-ratio was calculated from the complex data and rendered back onto 'fsaverage' (uncorrected, $p<0.01$). To correct for multiple-comparisons, we calculated the FDR-correction for p-values at level 0.05, in two a-priori defined regions of interest, one encompassing S1 and another encompassing the cortex surrounding the IPS.

Supplemental Table I. Cluster statistics for tactile-induced activity.

Columns present the cluster index, the value of the maximum 'intensity' within the cluster (Z-score), the location of the maximum intensity voxel given as X/Y/Z values in MNI coordinates.

Cluster Index	Z-score	x	y	z
4	13	-50	-32	60
4	9.59	-44	-34	64
4	9.42	-52	-40	58
4	9.21	-46	-14	58
4	8.35	-28	-16	70
4	8.07	-42	-38	68
3	6.29	36	-36	56
3	6.2	62	-20	48
3	6	34	-48	62
3	5.9	32	-42	64
3	5.88	38	-44	60
3	5.87	56	-22	46
2	5.04	32	-4	68
2	4.8	38	-4	62
2	4.66	36	-10	56
2	4.63	28	-12	70
2	4.52	26	-4	62
2	4.44	48	-4	58
1	6.43	-6	-8	58
1	5.7	2	0	62
1	4.4	-4	-10	62
1	4.34	-2	-4	74
1	4.2	-4	-12	50
1	4.15	-6	-6	76

Supplemental Table II. Cluster statistics for noxious-induced activity.

Columns report the cluster index, the value of the maximum 'intensity' within the cluster (Z-score), the location of the maximum intensity voxel given as X/Y/Z values in MNI coordinates.

Cluster Index	Z-score	x	y	z
1	4.05	-58	-26	44
1	4.03	-36	-46	46
1	3.91	-42	-34	48
1	3.84	-40	-48	46
1	3.8	-34	-40	50
1	3.6	-38	-32	38