The Primary Somatosensory Cortex and the Insula Contribute Differently to the Processing of Transient and Sustained Nociceptive and Non-Nociceptive Somatosensory Inputs

Li Hu,[1]* Li Zhang,[2] Rui Chen,[1] Hongbo Yu,[2] Hong Li,[3] and André Mouraux[4]

[1]*Key Laboratory of Cognition and Personality (Ministry of Education) and Faculty of Psychology, Southwest University, Chongqing, China*
[2]*Center for Brain and Cognitive Sciences and Department of Psychology, Peking University, Beijing, China*
[3]*Research Center for Brain Function and Psychological Science, Shenzhen University, Shenzhen, China*
[4]*Institute of Neurosciences (IoNS), Université Catholique De Louvain, Brussels, Belgium*

Abstract: Transient nociceptive stimuli elicit consistent brain responses in the primary and secondary somatosensory cortices (S1, S2), the insula and the anterior and mid-cingulate cortex (ACC/MCC). However, the functional significance of these responses, especially their relationship with sustained pain perception, remains largely unknown. Here, using functional magnetic resonance imaging, we characterize the differential involvement of these brain regions in the processing of sustained nociceptive and non-nociceptive somatosensory input. By comparing the spatial patterns of activity elicited by transient (0.5 ms) and long-lasting (15 and 30 s) stimuli selectively activating nociceptive or non-nociceptive afferents, we found that the contralateral S1 responded more strongly to the onset of non-nociceptive stimulation as compared to the onset of nociceptive stimulation and the sustained phases of nociceptive and non-nociceptive stimulation. Similarly, the anterior insula responded more strongly to the onset of nociceptive stimulation as compared to the onset of non-nociceptive stimulation and the sustained phases of nociceptive and non-nociceptive stimulation. This suggests that S1 is specifically sensitive to changes in incoming non-nociceptive input, whereas the anterior insula is specifically sensitive to changes in incoming nociceptive input. Second, we found that the MCC responded more strongly to the onsets as compared to the sustained phases of both nociceptive and non-nociceptive stimulation, suggesting that it could be involved in the detection of change regardless of sensory modality. Finally, the posterior insula and S2 responded maximally during the sustained phase of

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*Correspondence to: Li Hu, Key Laboratory of Cognition and Personality (Ministry of Education), Faculty of Psychology, Southwest University, Chongqing, 400715, China. E-mail: huli@swu.edu.cn and Hong Li, Research Centre for Brain Function and Psychological Science, Shenzhen University, Shenzhen 518060, China. E-mail: lihongszu@szu.edu.cn

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non-nociceptive stimulation but not nociceptive stimulation, suggesting that these regions are preferentially involved in processing non-nociceptive somatosensory input. *Hum Brain Mapp 00:000–000, 2015.*
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INTRODUCTION

To investigate the cortical processes involved in the perception of pain in humans, a large number of studies have used non-invasive functional neuroimaging techniques, such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), to characterize the brain responses elicited by a short lasting nociceptive stimulus (e.g., a laser-generated pulse of radiant heat selectively activating heat-sensitive nociceptive free nerve endings of the epidermis) [Bromm and Treede, 1984; Treede et al., 2003]. Numerous studies have shown that such stimuli can elicit consistent brain responses in operculo-insular cortices (OIC) contralateral and ipsilateral to the stimulated hemibody, in the cingulate cortex, as well as in the contralateral primary somatosensory cortex (S1) [Apkarian et al., 2005; Garcia-Larrea et al., 2003; Hu et al., 2014; Valentini et al., 2012], and that brain responses in these regions can exhibit distinct stimulus-response and perception-response functions [Bornhovd et al., 2002; Buchel et al., 2002]. However, the functional significance of these brain responses, especially their dynamic relationship with the perception of *sustained* pain [Cecchi et al., 2012], remains largely unknown.

First, it has been shown that non-nociceptive somatosensory, auditory, and visual stimuli can also elicit a similar pattern of brain activation within operculo-insular and cingulate regions [Mouraux et al., 2011a], and that the magnitude of these brain responses is highly context-dependent and largely determined by the ability of the stimulus to capture attention [Downar et al., 2000; Mouraux and Iannetti, 2009; Mouraux et al., 2011a]. This has led several authors to suggest that the brain responses within the OIC and cingulate cortex are unspecific for nociception, and to postulate that they mainly reflect multimodal cognitive processes involved in the detection and reaction to salient sensory events [Downar et al., 2000; Mouraux and Iannetti, 2009; Mouraux et al., 2011a]. However, the observation that focal epileptic seizures engaging the insular cortex and direct electrical stimulation of the posterior insula can generate sensations qualified as painful [Isnard et al., 2011; Ostrowsky et al., 2002], as well as the fact that lesions of the OIC can be associated with hypoalgesia of the contralateral hemibody, has led some authors to conclude that the OIC (specifically, the posterior insula) may play a specific role in pain perception [Garcia-Larrea and Peyron, 2013; Greenspan et al., 1999].

Second, the involvement of S1 in the processing of nociceptive input remains a matter of strong debate [Bushnell et al., 1999]. Using conventional approaches to analyse EEG or fMRI data, the spatial distribution of the S1 response to nociceptive stimulation is indistinguishable from the spatial distribution of the S1 response to vibrotactile stimulation [Garcia-Larrea et al., 2003]. However, using methods with a higher spatial resolution, such as single-cell recordings performed in animals [Mountcastle et al., 1990], intracerebral recordings of local field potentials in humans [Frot et al., 2013] or multivariate pattern analysis of fMRI data [Liang et al., 2013], studies have suggested that nociceptive and non-nociceptive somatosensory stimuli can elicit spatially-distinct responses within S1. Such results have led some authors to conclude that, whereas non-nociceptive vibrotactile input is primarily processed in area 3b of S1, nociceptive input would be predominantly represented in area 3a and/or area 1 of S1 [Mountcastle et al., 1990; Whitsel et al., 2009]. Furthermore, neurons responding to nociceptive input in S1 appear to be involved in coding the location and intensity of nociceptive stimuli [Kenshalo and Isensee, 1983; Lee et al., 2009; Tarkka and Treede, 1993], whereas neurons responding to non-nociceptive input in S1 are involved in coding not only the location and intensity, but also other features, in particular, frequency and related texture information [Gardner and Kandel, 2000]. These differences suggest that the role of S1 in processing nociceptive and non-nociceptive somatosensory input could be different. Supporting this view, we recently showed that long-lasting monotonous trains of nociceptive stimuli delivered at a short and constant inter-stimulus interval elicited EEG responses having a symmetrical scalp topography compatible with little or no contribution from the contralateral S1, whereas non-nociceptive somatosensory stimuli displayed a clearly lateralized scalp topography compatible with a predominant contribution from the contralateral S1 [Mouraux et al., 2011b]. This dissociation suggests that, unlike the S1 response to non-nociceptive somatosensory stimulation, the S1 response to nociceptive stimulation is not obligatory to nociception.

Here, using fMRI, we compared directly the spatial patterns of the brain responses elicited by transient (0.5 ms) and sustained (15 and 30 s trains) stimuli selectively activating nociceptive (intraepidermal electrical stimulation) or non-nociceptive (transcutaneous electrical nerve

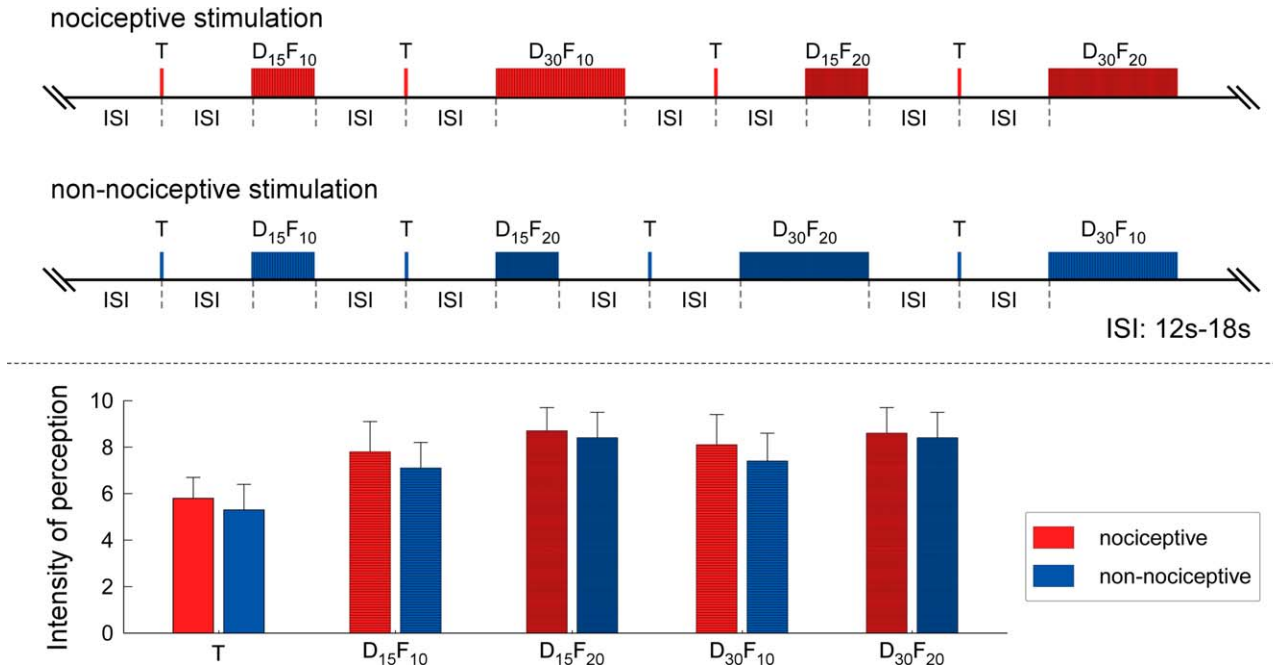


Figure 1.

Upper panel. Experimental design. Nociceptive and non-nociceptive somatosensory stimuli were delivered to the left hand as either as a transient pulse (*T*) or as a train of pulses of varying duration (*D*: 15 or 30 s) and frequency (*F*: 10 or 20 Hz). Nociceptive stimuli (intraepidermal electrical stimulation of the hand dorsum) and non-nociceptive stimuli (transcutaneous electrical stimulation using ring electrodes around the index finger) were delivered in separate runs. Each run (repeated twice) consisted of 20 transient stimuli and 20 trains of pulses (five trains for each type of stimulation train). Different types of stimuli were alternated within each run, such that two consecutive stimulation trains were always separated by a transient stimulus. The inter-stimulus interval (ISI) was 12, 15, or 18 s. Lower panel. Group-level average (±SD) subjective intensity of perception to all types of nociceptive and non-nociceptive somatosensory stimuli. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

stimulation) afferents, with the aim of characterizing how the OIC, cingulate cortex, and S1 respond to the onset and sustained phases of nociceptive and non-nociceptive inputs. We hypothesized that activity underlying processes related to detecting and responding to the occurrence of a sudden change in the sensory environment (i.e., processes involved in saliency detection) would primarily elicit activity at the onset of stimulation [Downar et al., 2000; Legrain et al., 2011; Mouraux and Iannetti, 2009; Mouraux et al., 2011a]. Conversely, activity obligatorily engaged by the sensory input and possibly underlying processes more directly related to the perception would be relatively preserved during the sustained phases of stimulation.

MATERIALS AND METHODS

Subjects

Thirty healthy right-handed subjects (15 males and 15 females) aged 19 to 28 years (mean ± SD, 22.3 ± 2.6), participated in the study. All subjects gave written informed consent. The local ethics committee of Southwest University approved the experimental procedures, which were in accordance with the standards of the Declaration of Helsinki.

Stimulation and Experimental Design

Nociceptive somatosensory stimuli (intraepidermal electrical stimuli, IES) were constant-current square-wave pulses (0.5 ms duration) delivered through three stainless steel concentric bipolar needle electrodes separated by an equal distance of 6 mm. Each electrode consisted of a needle cathode (length: 0.1 mm, Ø: 0.2 mm) surrounded by a cylindrical anode (Ø: 1.4 mm) [Inui et al., 2002, 2006]. The electrode was placed over the left hand dorsum, and the stimulus intensity was set to twice the individual absolute detection threshold (estimated using the method of limits). Because of its spatial configuration, the concentric needle electrode has been shown to selectively activate epidermal free nerve endings since they have a more superficial location as compared to encapsulated low-threshold mechanoreceptors, provided that low stimulation intensities are

used [e.g., twice the individual absolute detection threshold; Mouraux et al., 2010].

Non-nociceptive somatosensory stimuli (trans-cutaneous electrical stimuli, TES) were constant-current square-wave pulses (0.5 ms duration) delivered through a pair of ring electrodes placed around the left index finger, separated by a 1 cm interelectrode distance. As for IES, the stimulus intensity was set to twice the individual absolute detection threshold (estimated using the method of limits). These stimuli may be expected to predominantly activate non-nociceptive Aβ-fiber afferents [Garcia-Larrea et al., 1995; Hu et al., 2011], considering that small diameter fibers have a higher electrical activation threshold than large diameter fibers [Frahm et al., 2013]. Due to the different construction of the devices used to generate TES and IES, they could not be applied to the exact same skin site. However, it seems unlikely that the small difference in stimulus location (left hand dorsum vs. left index) would introduce region-level differences in the elicited BOLD responses.

Nociceptive (IES) and non-nociceptive (TES) stimuli were delivered either as a single transient pulse (T) or as a train of pulses of varying duration (D: 15 or 30 s) and frequency (F: 10 or 20 Hz): $D_{15}F_{10}$ (15 s and 10 Hz), $D_{15}F_{20}$ (15 s and 20 Hz), $D_{30}F_{10}$ (30 s and 10 Hz), and $D_{30}F_{20}$ (30 s and 20 Hz). The duration of the trains was chosen (1) to minimize the collinearity of the regressors modelling the onset and sustained phases of the stimulation trains, and (2) to ensure that the fMRI data acquisition session would last less than 1.5 h. After being familiarized with the stimuli, and prior to the MRI data acquisition, subjects were instructed to focus their attention on the stimuli and relax their muscles. They were then asked to rate the intensity of perception for each stimulus type (T, $D_{15}F_{10}$, $D_{15}F_{20}$, $D_{30}F_{10}$, and $D_{30}F_{20}$) and modality (nociceptive and non-nociceptive), using a visual analogue scale ranging from 0 (not perceived) to 10 (maximum intensity). Note that the scale can be considered as a subjective measure of perceived intensity, regardless of whether the percept was qualified as painful. For each sensory modality, the intensity of perception of the different types of stimulation trains were compared using a three-way repeated-measures analysis of variance (ANOVA), with train "duration" (two levels: 15 s and 30 s), "frequency" (two levels: 10 Hz and 20 Hz), and "modality" (two levels: nociceptive and non-nociceptive) as within-subject factors. When the interaction was significant, post hoc pairwise comparisons were performed.

During the functional MRI data acquisition, nociceptive and non-nociceptive somatosensory stimuli were delivered in separate runs. Each run was repeated twice, resulting in a total of four runs. The order of the runs was pseudo-randomized across subjects. Subjects were told in advance the modality of the stimuli before each run. Within each run, TES or IES was delivered either as a single transient pulse (T: 20 stimuli per run) or as a periodic train of pulses ($D_{15}F_{10}$, $D_{15}F_{20}$, $D_{30}F_{10}$, and $D_{30}F_{20}$: 20 stimuli per run; five stimuli for each type of train) (Fig. 1). Different types of stimuli were alternated within each run, such that two consecutive trains of stimuli were always separated by a transient stimulus (T). The interstimulus interval (ISI) was 12, 15 , or 18 s.

Data Acquisition

Functional MRI data was acquired using a Siemens 3.0 Tesla Trio scanner with a standard head coil at the Key Laboratory of Cognition and Personality (Ministry of Education) of the Southwest University (China). A gradient-echo, echo-planar-imaging sequence was used for functional scanning with a repetition time (TR) of 2200 ms (30 ms echo time, 36 contiguous 3.0 mm-thick slices to ensure the coverage of the whole cerebrum, 3 × 3 mm in-plane resolution, field of view 192 × 192 mm, matrix 64 × 64; flip angle = 90°). A high-resolution, T1-weighted structural image (1 mm^3 isotropic voxel MPRAGE) was acquired after functional imaging.

Data Processing

The functional MRI data was preprocessed and analyzed using Statistical Parametric Mapping software SPM8 (Wellcome Trust Center for Neuroimaging, London, UK). The first five volumes were discarded to allow for signal equilibration. Images were slice-time corrected, motion corrected, spatially-smoothed using a Gaussian kernel of 8 mm full width at half maximum (FWHM = 8 mm), temporally filtered using a high-pass filter with 1/128 Hz cut-off frequency, co-registered to the EPI template in SPM8, and normalized to the Montreal Neurological Institute (MNI) space by matching grey matter [Ashburner and Friston, 2005].

Whole Brain Voxel-by-Voxel General Linear Model Analysis

For each sensory modality, single-subject fMRI data were analyzed on a voxel-by-voxel basis, using a general linear model (GLM) approach [Frackowiak et al., 2004]. The fMRI time series were modelled as a series of events and blocks. The blood-oxygen-level dependent (BOLD) responses to the transient stimuli and to the onsets and offsets of the stimulation trains were modelled as a stick function. BOLD responses to the sustained phase of the stimulation trains were modelled as a boxcar function. Both functions were convolved with a canonical hemodynamic response function (HRF) [Downar et al., 2003]. Importantly, the temporal derivatives of the regressors were not included in the GLM model to avoid problems caused by multicollinearity of the regressors. For each sensory modality, contrasts were used to assess the BOLD responses associated with the transient stimuli, the onsets of the stimulation trains, the sustained phases of the stimulation trains, and the offsets of the stimulation trains

(the number of stimuli in each of these assessed conditions was identical; $n = 20$ for each subject). Group-level statistical analyses were carried out using a random effects analysis with the one-sample *t*-test as implemented in SPM8. The significance threshold was $P_{\text{uncorrected}} < 0.001$ at voxel level and $P_{\text{FWE}} < 0.05$ at cluster level in the whole-brain exploratory analyses [Bennett et al., 2009]. In addition, to identify small clusters in the hand representation area of S1 related to each type of stimulation, we adopted a small-volume correction to the anatomical S1 region [Worsley et al., 1996].

Conjunction Analysis

To identify brain regions that were activated both at the onsets of stimulation trains and during the sustained phase of stimulation trains, a conjunction analysis was performed on the group-level statistical volumes, using the activation to the onsets of stimulation trains as inclusive mask [Zahn et al., 2007]. The cortical regions that were commonly activated by the onsets and the sustained phases of stimulation trains were extracted by multiplying the inclusive mask with the activated maps to the sustained phase of stimulation trains.

Effect of Train "Duration" and "Frequency" on the BOLD Responses to the Sustained Phases of Stimulation Trains

Differential contrasts were used to assess the difference in BOLD responses to (1) the different train durations (15 s vs. 30 s) and (2) the different stimulation frequencies (10 Hz vs. 20 Hz) for each sensory modality. Group-level statistical analyses were carried out using a random effects analysis with the one-sample *t*-test as implemented in SPM8. The significance threshold was $P_{\text{uncorrected}} < 0.001$ at voxel level and $P_{\text{FWE}} < 0.05$ at cluster level in the whole-brain exploratory analyses [Bennett et al., 2009].

Region of Interest Analysis

For each type of stimulus (nociceptive and non-nociceptive) the mean BOLD signal amplitude to the onset and sustained phases of the stimulation trains was estimated by averaging the regression coefficients (GLM beta values) of the voxels located in the following anatomical regions of interest (ROI): thalamus (TH), secondary somatosensory cortex [S2, rolandic operculum; Garcia-Larrea et al., 2003], posterior and anterior insula [POST-INS, ANT-INS, defined by dividing the insula into anterior and posterior divisions around the central insular sulcus; Ture et al., 1999], and the anterior- and mid-cingulate cortex (ACC and MCC, defined by merging the left and right ACC and MCC regions), which were defined according to Anatomical Automatic Labeling model [Tzourio-Mazoyer et al., 2002] (Supporting Information Fig. 1). An additional ROI circumscribing the expected hand representation within S1 was defined as a 1 cm radius sphere centred at MNI coordinate $x = 37$ mm, $y = -33$ mm and $z = 60$ mm [Frot et al., 2013] (Supporting Information Fig. 1). A relatively large ROI was chosen for S1 because (1) the use of a small ROI could have led to differences in activation between TES and IES related to the fact that the two stimuli did not elicit sensations at strictly identical skin sites, and because (2) non-nociceptive and nociceptive somatosensory inputs may be expected to elicit activity within different subareas of S1 [Mountcastle et al., 1990; Whitsel et al., 2009].

The aim of the present study was to test whether the brain regions known to respond consistently to a transient nociceptive and non-nociceptive somatosensory stimulus [Colon et al., 2012; Mouraux et al., 2011b] respond differently to the onset and sustained phases of nociceptive and non-nociceptive somatosensory stimulation (the number of stimuli in each of these assessed conditions was identical; $n = 5$ for each subject). Importantly, a direct comparison of the magnitude of the responses elicited by nociceptive and non-nociceptive stimulation within the different ROIs would be difficult to interpret because the observed differences could reflect simply a difference in the strength of the peripheral afferent inputs (IES generates a very focal electric current and is thus expected to activate a much smaller number of afferents than TES). Similarly, direct comparison of the magnitude of the responses to the onset and sustained phases of stimulation would be difficult to interpret because the observed differences could result from habituation or fatigue induced by stimulus repetition leading to an overall reduction of the elicited neural activity, or to a nonlinear relationship between the magnitude of sustained neural activity and the magnitude of the resulting haemodynamic response. Therefore, for each modality (nociceptive and non-nociceptive) and for each response type (onset and sustained), the magnitudes obtained in each ROI (contralateral TH, S1, S2, POST-INS, ANT-INS, ACC, and MCC) were converted to *z*-scores by subtracting the mean and dividing the standard deviation of the response magnitudes obtained across all ROIs (averaged across the different stimulation frequencies and durations). This procedure was chosen to assess *relative* differences in the magnitude of the responses elicited in the different ROIs, by cancelling out differences across conditions affecting similarly the signals measured across all ROIs.

The standardized estimates of response magnitude were then compared using a three-way repeated-measures ANOVA with "ROI" (seven levels: TH, S1, S2, POST-INS, ANT-INS, ACC, and MCC), "modality" (two levels: nociceptive and non-nociceptive) and "response type" (two levels: onset and sustained) as within-subject factors. Post hoc tests were performed using two-way repeated-measures ANOVAs assessing the effect of "modality" and "response type" within each ROI. When significant, post hoc pairwise comparisons were used to compare the onset and sustained responses to nociceptive and non-

nociceptive stimulation. Because, for each ROI, the magnitude of the response obtained in each condition was expressed relative to the mean and standard deviation of the magnitudes obtained across all ROIs, these post hoc tests allowed us to assess whether each brain structure responds differently during the onset vs. sustained phase and/or responds differently to nociceptive vs. non-nociceptive stimulation.

Finally, we assessed and compared the asymmetry of the responses in the contralateral and ipsilateral TH, S1, S2, ANT-INS, and POST-INS. For this purpose, a three-way repeated-measures ANOVA was conducted on the average standardized beta values using "hemisphere" (two levels: contralateral and ipsilateral to the stimulated hand), "modality" (two levels: nociceptive and non-nociceptive), and "response type" (two levels: onset and sustained) as within-subject factors. When a significant effect of "hemisphere" was found, post hoc pairwise comparisons of the responses obtained in the two hemispheres were performed.

RESULTS

Intensity of Perception

The average ratings (mean ± SD) of the intensity of perception to all types of nociceptive and non-nociceptive somatosensory stimuli (T, $D_{15}F_{10}$, $D_{15}F_{20}$, $D_{30}F_{10}$, and $D_{30}F_{20}$) are summarized in Figure 1 (bottom panel) and Supporting Information Table 1. Trains of nociceptive stimuli elicited a clear, slightly painful pinprick sensation, regardless of stimulation frequency. Trains of non-nociceptive stimuli elicited a clear vibrotactile sensation, which was not perceived as painful. The three-way repeated-measures ANOVA conducted using train "duration," "frequency," and "modality" as within-subject factors showed a significant main effect of "frequency" ($F = 92.5$, $P < 0.001$), as well as a significant interaction between the factors "frequency" and "modality" ($F = 12.0$, $P = 0.002$), and between the factors "frequency" and "duration" ($F = 8.1$, $P = .008$; Table I). Post hoc pairwise comparisons showed that nociceptive stimulation elicited a stronger percept than non-nociceptive stimulation at 10 Hz ($P = 0.015$), but not at 20 Hz ($P = 0.315$). In addition, 20 Hz stimulation elicited a stronger percept than 10 Hz stimulation for both nociceptive and non-nociceptive modalities, as well as for 15 s and 30 s train durations ($P < 0.001$ for all comparisons).

TABLE I. Three-way repeated-measures ANOVA to assess the effects of train "duration" (15 and 30 s), "frequency" (10 and 20 Hz), and "modality" (nociceptive and non-nociceptive) on the subjective intensity of perception

Three-way ANOVA	F value	P
Duration	0.5	0.473
Frequency	92.5	0.000***
Modality	3.5	0.07
Duration × frequency	8.1	0.008**
Duration × modality	0.5	0.490
Frequency × modality	12.0	0.002**
Duration × frequency × modality	0.003	0.954
Post hoc pairwise comparisons of duration × frequency		
10 Hz (15 s vs. 30 s)		0.112
20 Hz (15 s vs. 30 s)		0.718
15 s (10 Hz vs. 20 Hz)		0.000***
30 s (10 Hz vs. 20 Hz)		0.000***
Post hoc pairwise comparisons of frequency × modality		
10 Hz (nociceptive vs. non-nociceptive)		0.015*
20 Hz (nociceptive vs. non-nociceptive)		0.315
Nociceptive (10 Hz vs. 20 Hz)		0.000***
Non-nociceptive (10 Hz vs. 20 Hz)		0.000***

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

BOLD Responses to Transient and Sustained Nociceptive and Non-Nociceptive Stimulation

Figure 2 shows the cortical regions significantly activated by the different types of nociceptive and non-nociceptive somatosensory stimuli. Transient nociceptive and non-nociceptive stimuli as well as the onsets of nociceptive and non-nociceptive stimulation trains elicited consistent activity within the same network of brain regions, including the bilateral TH, contralateral S1 (small-volume correction; significant for the onsets of nociceptive and non-nociceptive stimuli and for transient non-nociceptive stimuli, but not for transient nociceptive stimuli), bilateral S2, bilateral INS, ACC, and MCC (voxel level: $P_{\text{uncorrected}} < 0.001$, cluster level: $P_{\text{FWE}} < 0.05$). MNI coordinates and statistical t values of significant BOLD responses to nociceptive and non-nociceptive somatosensory stimulation are summarized in Supporting Information Table 2.

Overall, the responses to the sustained phase of nociceptive and non-nociceptive stimulation were markedly reduced as compared to the responses to the stimulation onsets. During the sustained phase of nociceptive stimulation, significant activation was found in a small portion of the contralateral S1 (small-volume correction), contralateral S2, and bilateral INS (Fig. 2). During the sustained phase of non-nociceptive stimulation, significant activation was found in the contralateral S1, bilateral S2, and bilateral INS. In addition, nociceptive and non-nociceptive stimulation induced significant decreases of BOLD signal, predominantly in regions within the default mode network during the sustained phase of periodic stimulation.

The offset of nociceptive stimulation trains did not elicit any significant activation (Fig. 2). In contrast, the offsets of non-nociceptive stimulation trains elicited significant activity in the bilateral TH, contralateral S1, bilateral S2, and bilateral INS (Fig. 2). The reduction of brain activation from onsets to offsets of prolonged stimulation might be caused by fatigue or habituation of peripheral afferents by stimulus repetition. In addition, it might be explained by a differential

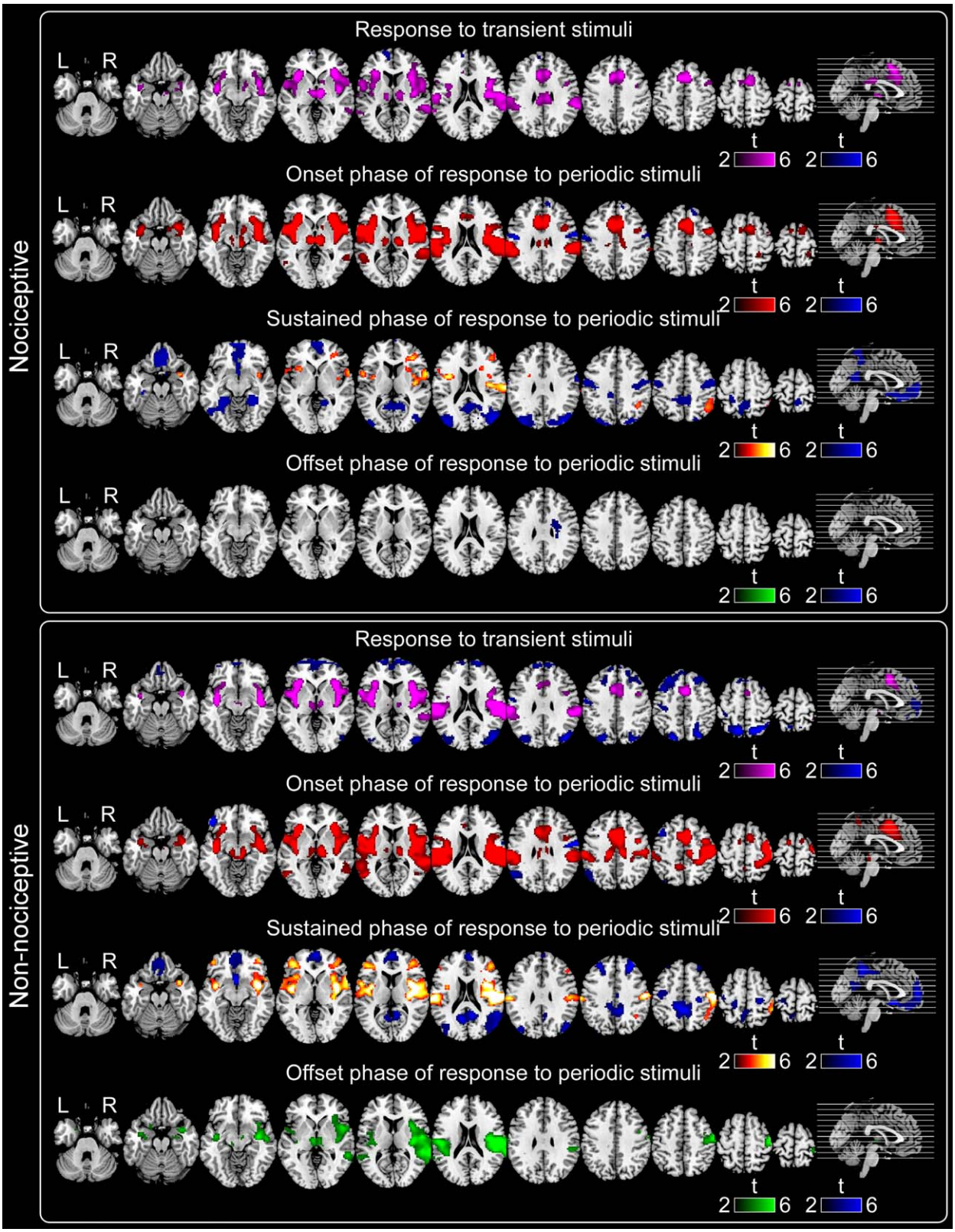


Figure 2.

BOLD responses to nociceptive and non-nociceptive somatosensory stimulation of the left hand. Significant increases in BOLD signal to transient stimuli, to the onsets of stimulation trains, the sustained phases of stimulation trains and the offsets of stimulation trains are shown in purple, red, orange, and green, respectively. Significant decreases in BOLD signal to any type of stimuli are shown in blue. L: left, R: right. Only areas that survived at voxel level: $P_{uncorrected} < 0.001$ and cluster level: $P_{FWE} < 0.05$ are shown. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

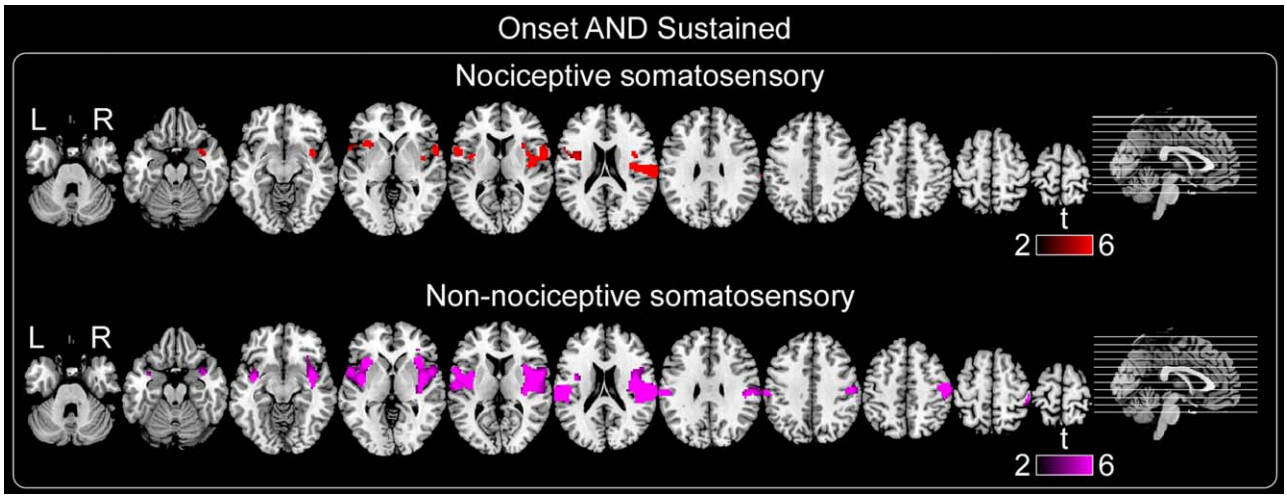


Figure 3.

Brain regions activated by both the onsets and the sustained phases of stimulation trains (voxel level: $P_{uncorrected} < 0.001$, cluster level: $P_{FWE} < 0.05$). During nociceptive stimulation, the contralateral S2 and bilateral insula were activated by both the onsets and the sustained phases of stimulation trains (red). During non-nociceptive stimulation, the contralateral S1, bilateral S2, and bilateral insula were activated by both the onsets and the sustained phases of stimulation trains (purple). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

contribution of rapidly- and slowly-adapting neurons [Kyriazi et al., 1994]. Indeed, only rapidly-adapting neurons may be expected to elicit a marked response at stimulation offset [Jones et al., 2004].

The brain regions that were activated both at the onset and the sustained phases of nociceptive and non-nociceptive stimulation trains are shown in Figure 3. Contralateral S2 and bilateral INS responded to the onset and the sustained phase of nociceptive stimulation trains, while contralateral S1, bilateral S2, and bilateral INS responded to the onset and the sustained phase of non-nociceptive stimulation trains.

The BOLD responses to the sustained phase of nociceptive stimulation were not significantly different between the two stimulation frequencies (10 Hz vs. 20 Hz) and train durations (15 s vs. 30 s), except within a small portion of the contralateral frontal cortex, which showed stronger activation to short (15 s) as compared to long (30 s) trains (Supporting Information Fig. 2, top panel). BOLD responses to the sustained phase of non-nociceptive stimulation were not significantly different between two train durations (15 s vs. 30 s). However, the BOLD responses to 10 Hz trains were significantly greater than the BOLD responses to 20 Hz trains in somatomotor areas (Supporting Information Fig. 2, bottom panel).

ROI Analysis of Transient and Sustained Responses to Nociceptive and Non-Nociceptive Stimulation

The relative amplitude of the responses in each ROI (contralateral TH, S1, S2, POST-INS, ANT-INS, ACC, and MCC) to the onset and sustained phases of nociceptive and non-nociceptive stimulation trains are shown in Figure 4.

Comparison of these responses using a three-way repeated-measures ANOVA with the factors "ROI" (contralateral TH, S1, S2, POST-INS, ANT-INS, ACC, and MCC), "response type" (onset and sustained), and "modality" (nociceptive and non-nociceptive) showed a significant interaction between the three factors ($F = 3.4$, $P = 0.003$) (Table II). This indicates that the relative amplitude of the responses obtained in the different ROIs differed according to both the type of response (onset vs. sustained) and the modality of stimulation (nociceptive vs. non-nociceptive; Fig. 4).

To assess the effect of "response type" and "modality" within each ROI, a two-way repeated-measures ANOVA with these two factors was then performed separately for each ROI (Table II).

In the contralateral TH and ACC there was no significant effect of the two factors suggesting that the TH and ACC responded similarly to the onset and sustained phases of nociceptive and non-nociceptive stimulation.

In contrast, the contralateral S1 showed a strong main effect of "modality" ($F = 15.0$, $P < 0.001$) and a marginally significant interaction between the factors "modality" and "response type" ($F = 4.1$, $P = 0.05$). Post hoc pairwise comparisons showed that the onset response to non-nociceptive trains was significantly greater than the sustained responses to non-nociceptive ($P = 0.016$) and nociceptive ($P < 0.001$) trains, as well as the onset response to nociceptive trains ($P < 0.001$). This indicates that S1 responded preferentially to the onset of non-nociceptive stimulation trains.

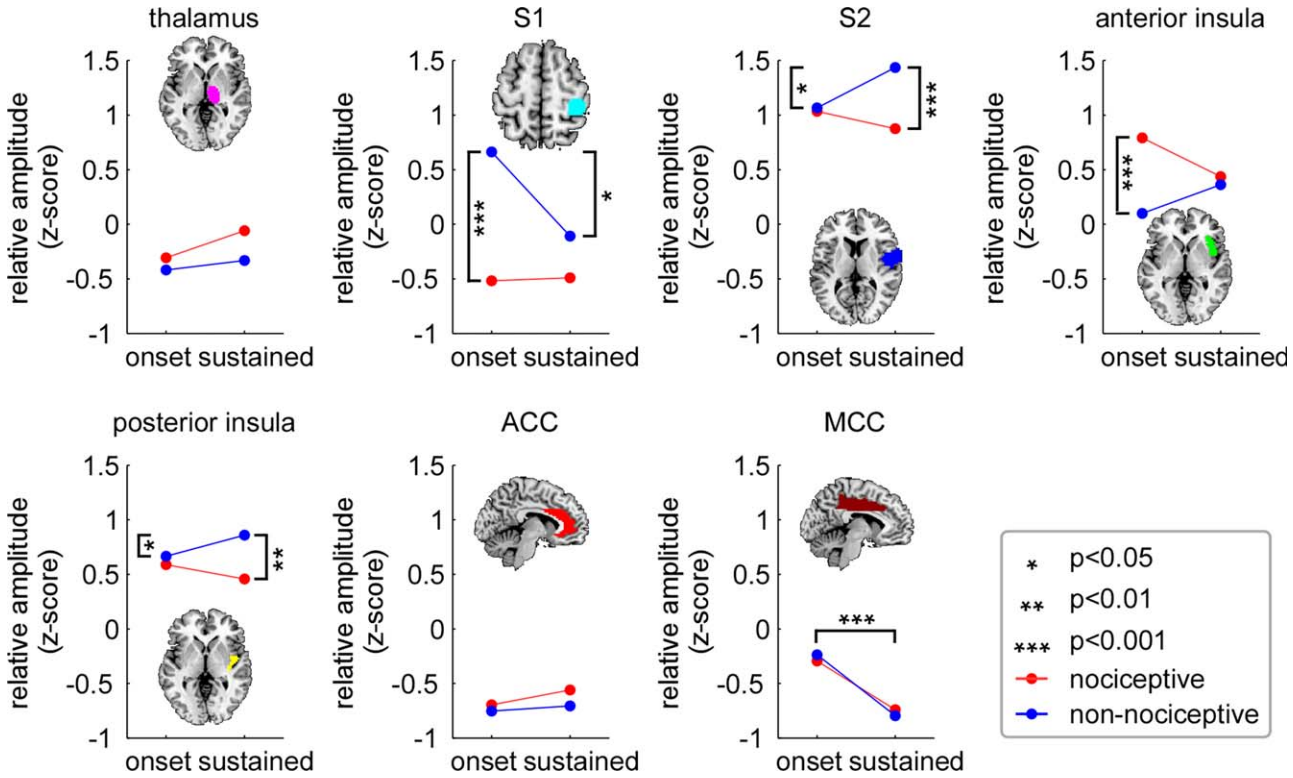


Figure 4.

Relative amplitude of the BOLD responses elicited by the onset and sustained phases of nociceptive (red) and non-nociceptive (blue) trains of stimulation in the contralateral TH, contralateral S1, contralateral ANT-INS, contralateral POST-INS, contralateral S2, ACC, and MCC. The contralateral TH and ACC responded similarly to the onset and sustained phases of nociceptive and non-nociceptive stimulation. In contrast, contralateral S1 responded preferentially to the onset of non-nociceptive stimulation, whereas the contralateral ANT-INS responded preferentially to the onset of nociceptive stimulation. Both the contralateral POST-INS and contralateral S2 responded predominantly during the sustained phase of non-nociceptive stimulation but not nociceptive stimulation. The MCC responded preferentially to the onsets of both nociceptive and non-nociceptive stimulation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The contralateral S2 as well as the contralateral POST-INS showed a significant effect of "modality" (S2: $F = 11.9$, $P = 0.002$; POST-INS: $F = 10.8$, $P = 0.003$) and a significant interaction between the factors "modality" and "response type" (S2: $F = 9.7$, $P = 0.004$; POST-INS: $F = 4.1$, $P = 0.05$). Post hoc pairwise comparisons showed that the sustained response to non-nociceptive trains was significantly greater than the onset response to non-nociceptive trains (S2: $P = 0.026$; POST-INS: $P = 0.041$) as well as the sustained response to nociceptive trains (S2: $P < 0.001$; POST-INS: $P = 0.002$). This indicates that relative amplitude of the BOLD signal in S2 and POST-INS predominated during the sustained phase of non-nociceptive stimulation but not nociceptive stimulation.

The contralateral ANT-INS showed a significant effect of "modality" ($F = 10.9$, $P = 0.003$) and an interaction between the factors "modality" and "response type" ($F = 13.5$, $P = 0.001$). Post hoc pairwise comparisons showed that the onset response to nociceptive stimulation was significantly greater than the onset response to non-nociceptive stimulation ($P < 0.001$). In contrast, there was no significant difference between the sustained responses to nociceptive and non-nociceptive stimulation ($P = 0.624$).

The MCC showed a significant main effect of "response type" ($F = 22.2$, $P < 0.001$). Both for nociceptive and non-nociceptive stimulation, the onset responses were greater than the sustained responses.

ROI Analysis of BOLD Response Hemispheric Lateralization

In all bilateral ROIs (TH, S1, S2, POST-INS, ANT-INS; Fig. 5), the three-way repeated-measures ANOVA conducted using "hemisphere," "modality," and "response type" as within-subject factors showed a significant main effect of "hemisphere" (TH: $F = 19.4$, $P < 0.001$; S1:

TABLE II. Three-way repeated-measures ANOVA to assess the effect of "ROI" (contralateral TH, S1, ANT-INS, POST-INS, S2, ACC, and MCC), "response type" (onset and sustained), and "modality" (nociceptive and non-nociceptive) on the relative amplitude of the BOLD response

Three-way ANOVA		*F* value	*P*
	ROI	88.4	0.000***
	Response type	12	0.002**
	Modality	13	0.001***
	ROI × response type	2.9	0.011*
	ROI × modality	9.09	0.000***
	response type × modality	0.5	0.484
	ROI × response type × modality	3.4	0.003**
Post hoc two-way ANOVA within each ROI			
Contralateral TH	Response type	2.3	0.143
	Modality	3.1	0.087
	Response type × modality	0.3	0.58
Contralateral S1	Response type	2.5	0.125
	Modality	15	0.001***
	Response type × modality	4.1	0.05*
Contralateral ANT-INS	Response type	0.1	0.752
	Modality	10.9	0.003**
	Response type × modality	13.5	0.001***
Contralateral POST-INS	Response type	0.3	0.611
	Modality	10.8	.003**
	Response type × modality	4.1	.05*
Contralateral S2	Response type	0.6	0.452
	Modality	11.9	0.002**
	Response type × modality	9.7	0.004**
ACC	Response type	0.4	0.512
	Modality	0.6	0.461
	Response type × modality	0.1	0.774
MCC	Response type	22.2	0.000***
	Modality	0	0.995
	Response type × modality	0.3	0.568

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

$F = 5.8$, $P = 0.022$; S2: $F = 61.8$, $P < 0.001$; POST-INS: $F = 22.5$, $P < 0.001$; ANT-INS: $F = 6.7$, $P = 0.015$) (Supporting Information Table 3). Furthermore, there was a significant interaction between the factors "hemisphere" and "response type" in all ROIs (TH: $F = 9.5$, $P = 0.004$; S2: $F = 25.3$, $P < 0.001$; POST-INS: $F = 12.6$, $P = 0.001$; ANT-INS: $F = 5.2$, $P = 0.03$) but S1 ($F = 2.6$, $P = 0.117$). There was no significant interaction between the factors "hemisphere" and "modality" in all ROIs, but there was a significant triple interaction in S2 ($F = 5.1$, $P = 0.031$) and ANT-INT ($F = 8.2$, $P = 0.008$). Post hoc pairwise comparisons are reported in Supporting Information Table 4.

DISCUSSION

Here, we show that the spatial patterns of onset and sustained brain responses to nociceptive and non-nociceptive somatosensory stimulation differ significantly, indicating that stimulus-evoked activities in the different brain regions responding to nociceptive and non-nociceptive stimulation reflect functionally distinct cortical processes. These differences can be summarized as follows.

First, we found that the contralateral S1 responds more strongly to the onset of non-nociceptive somatosensory stimulation as compared to the onset of nociceptive stimulation and the sustained phases of nociceptive and non-nociceptive stimulation. Conversely, the anterior insula responds more strongly to the onset of nociceptive stimulation as compared to the onset of non-nociceptive stimulation and the sustained phases of nociceptive and non-nociceptive stimulation. Contrasting with the specificity of S1 and the anterior insula, we found that the MCC responds more strongly to the onsets as compared to the sustained phases of both nociceptive and non-nociceptive stimulation. Finally, we found that posterior operculo-insular areas (S2 and the posterior insula) respond maximally during the sustained phase of non-nociceptive stimulation but not nociceptive stimulation.

The finding that the relative amplitude of the S1 response to non-nociceptive somatosensory stimulation is significantly greater than the relative amplitude of the S1

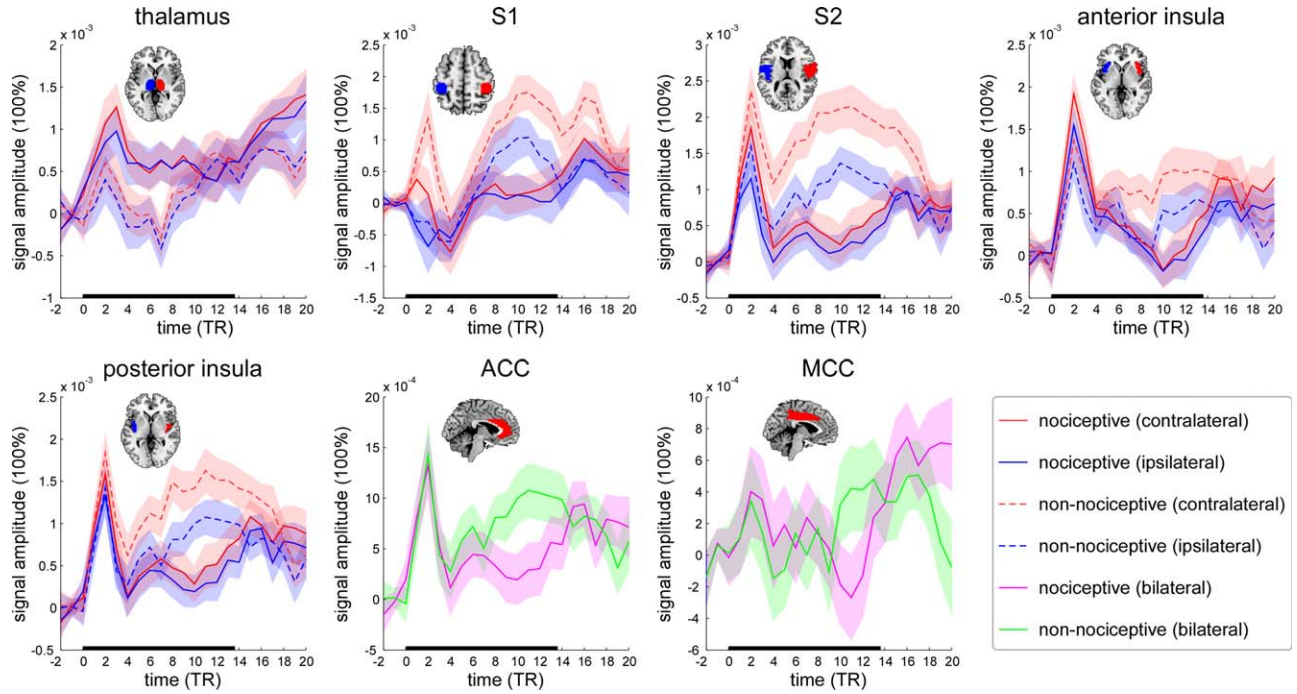


Figure 5.

Average BOLD signal time courses in the TH, S1, anterior insula, posterior insula, S2, ACC, and MCC during the application of 30 s nociceptive and non-nociceptive trains of stimulation. Note the clear hemispheric lateralization (contralateral > ipsilateral) of the responses in the TH, S1, insula, and S2 for both onset and sustained phases of nociceptive and non-nociceptive stimulation. Also note that, in the contralateral S1, the response to the onset of non-nociceptive stimulation is stronger than the response to the onset of nociceptive stimulation. In contrast, in the anterior insula, the response to the onset of nociceptive stimulation is greater than the response to the onset of non-nociceptive stimulation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

response to nociceptive stimulation indicates that nociceptive and non-nociceptive somatosensory inputs are represented differently in S1. This is compatible with the results of single unit recordings in animals showing that neurons responding to nociceptive input are sparse in S1 [Apkarian, 1995; Shi et al., 1993], and that nociceptive and non-nociceptive somatosensory inputs may predominantly project to different subregions of S1 [Mountcastle et al., 1990; Whitsel et al., 2009]. Whereas neurons responding to nociceptive input in S1 appear to be involved in coding the location and intensity of nociceptive stimuli [Kenshalo and Isensee, 1983; Lee et al., 2009; Tarkka and Treede, 1993], neurons responding to non-nociceptive input in S1 are involved in coding not only the location and intensity, but also other features, in particular, frequency and related texture information [Gardner and Kandel, 2000]. Whereas non-nociceptive input mainly projects to area 3b, nociceptive input has been suggested to predominantly project to areas 1 and/or 3a [Baumgartner et al., 2011; Garcia-Larrea et al., 2003]. This is also compatible with the fact that functional neuroimaging techniques reliably detect increased activity in S1 following non-nociceptive somatosensory stimulation [Friebel et al., 2011], whereas activation of S1 following nociceptive stimulation is less consistent and more debated (only about 76% of functional neuroimaging studies report significant S1 activation following nociceptive stimulation) [Apkarian et al., 2005; Peyron et al., 2000]. Our observation that S1 does not respond strongly to nociceptive stimulation would also explain the fact that steady-state evoked potentials (SS-EPs) elicited by sustained periodic nociceptive stimulation (periodic intra-epidermal electrical stimulation as well as thermal laser stimulation) do not show any lateralized activity compatible with a source originating from the contralateral S1, while SS-EPs elicited by sustained non-nociceptive stimulation (transcutaneous electrical stimulation and mechanical vibrotactile stimulation) predominate over the parietal region contralateral to the stimulated side, indicating a predominant contribution of the contralateral S1 [Colon et al., 2012; Mouraux et al., 2011b]. Importantly, because our observation is based on a comparison of S1 amplitudes expressed *relative* to the amplitude of the responses in other activated brain regions, it is unlikely that the reduced S1 response to nociceptive stimulation could be explained by the fact that intra-epidermal stimulation activates only a small number of afferents.

Interestingly, the relative amplitude of the onset response to non-nociceptive somatosensory stimulation was significantly greater than the sustained response to non-nociceptive somatosensory stimulation in S1. It is unlikely that this relative reduction of the sustained response in S1 resulted from fatigue or habituation of peripheral afferents. Indeed, a reduction in peripheral input during sustained stimulation would be expected to translate in a reduction of the sustained response in all activated brain regions, and such a reduction was not observed in some regions of interest such as S2 and the posterior insula. In the auditory modality, it has been shown that the primary auditory cortex is sensitive to the occurrence of an infrequent change in a repetitive sequence of sounds, as evidenced by the "mismatch negativity" elicited by deviant auditory stimuli embedded in a monotonous stream of standard stimuli [Naatanen et al., 1992, 2007]. Some recent studies have suggested that deviant somatosensory stimuli can also elicit a mismatch response originating in part from the contralateral S1 [Akatsuka et al., 2007]. Therefore, the reduced response to sustained non-nociceptive somatosensory stimulation suggests that S1 could be specifically sensitive to the occurrence of a change in the incoming flow of non-nociceptive somatosensory input. Although Downar et al. [2000] failed to demonstrate S1 activity triggered by the occurrence of a change in the somatosensory modality (tapping vs. brushing of the skin), other studies have shown habituation within S1 [e.g., Klingner et al.,2011].

Whereas S1 was specifically responsive to the onset of non-nociceptive somatosensory stimulation, the anterior insula was specifically responsive to the onset of nociceptive somatosensory stimulation. This leads to an interesting possibility: that S1 could be specifically involved in the detection of changes in non-nociceptive somatosensory input, whereas the anterior insula could be specifically involved in the detection of changes in nociceptive somatosensory input. This difference in the cortical processing of nociceptive and non-nociceptive sensory inputs could be related to the results of previous studies suggesting that ascending non-nociceptive somatosensory thalamocortical input projects primarily to the contralateral S1 [Gardner and Kandel, 2000; Hu et al., 2012; Iwamura, 1998], whereas ascending nociceptive somatosensory thalamocortical input predominantly projects to other brain structures such as insular and cingulate cortices [Frot et al., 2008; Inui et al., 2004; Ploner et al., 2009]. Importantly, our observation does not rule out other possible functions of the anterior insula in nociceptive processing [e.g., representation of prediction error; Seymour et al., 2005]. Possibly, a better understanding of these functions could be obtained by exploring the temporal dynamics of the elicited responses (e.g., assessing the difference of response latencies in these regions), for example, by optimizing the temporal sampling frequency of BOLD signals [Pomares et al., 2013], by studying the spatial distribution of the elicited responses in a more fine-grained fashion [Kurth et al., 2010], for example, by increasing the spatial resolution of the data using limited spatial smoothing, or by using other methods to sample neural activity with a high temporal and spatial resolution such as the recording of local field potential data obtained from electrodes implanted for the presurgical evaluation of patients with refractory seizures [Almashaikhi et al., 2014].

Contrasting with S1 and the anterior insula, the midcingulate cortex responded strongly to both the onset of nociceptive stimulation and the onset of non-nociceptive stimulation. This observation is compatible with the notion that the cingulate cortex is involved in the processing of salient sensory input regardless of the sensory modality through which it is conveyed [Downar et al., 2000; Mouraux et al., 2011a]. For example, Downar et al. [2000] showed that this brain region is indifferently activated by the occurrence of a change in somatosensory, visual, or auditory streams of sensory input, and concluded that this brain region is part of a multimodal network involved in the bottom-up capture of attention by salient sensory events. In addition, the cingulate cortex has numerous projections to motor systems, and may play an important role in triggering motor responses to nociceptive and non-nociceptive stimuli [Devinsky et al., 1995; Vogt, 2005].

Previous studies have suggested that posterior operculoinsular regions are specifically involved in the processing of nociceptive input and the perception of pain [Apkarian et al., 2005; Frot and Mauguiere, 2003; Garcia-Larrea, 2012; Garcia-Larrea et al., 2003]. Lesions of the posterior insula can, in some cases, lead to a reduction in the ability to perceive painful and non-painful thermonociceptive stimuli [Greenspan et al., 1999]. Electrical stimulation or epileptic activity in this region has been reported to induce pain-related experiences [Isnard et al., 2011; Ostrowsky et al., 2002]. Although these observations are commonly interpreted as evidence that the posterior insula is specifically involved in pain perception, it is important to take into considerations the reports of patients with extensive insular lesions and no or little deficit in pain perception [Greenspan et al., 1999]. Furthermore, direct electrical stimulation of the posterior insula [Ostrowsky et al., 2002] elicited painful sensations in only 17 out of 93 stimulation sites and in only 14 patients out of 43 (nonpainful somesthetic sensations were elicited in 21 out of 93 stimulation sites and in 16 patients out of 43). Most importantly, there was an important overlap between the electrode contacts at which stimuli elicited painful somesthetic sensations and those at which stimuli elicited non painful somesthetic sensations, leading the authors to conclude that painful and nonpainful somesthetic representations overlap in the posterior insula. In the present study, we found that S2 and the posterior insula responded similarly to the onsets of nociceptive and non-nociceptive stimulation. Furthermore, we found that non-nociceptive stimulation—but not nociceptive stimulation—elicited a prominent response

during sustained stimulation. Although nociceptive-specific neurons may exist in posterior operculo-insular areas, our results indicate that these areas *as a whole* respond more strongly to sustained non-nociceptive somatosensory input and, hence, that their function cannot be summarized as a "nociceptive cortical matrix" specifically devoted to first-order obligatory stages of nociceptive processing [Garcia-Larrea and Peyron, 2013].

The interpretation of fMRI data should take into consideration the fact that BOLD signals are an indirect measure of neural activity, and that the relationship between the magnitude of neural activity and the magnitude of the related hemodynamic response may not be linear [Arthurs and Boniface, 2002]. On this account, it should be emphasized that several studies have suggested that haemodynamic responses can be considered as "roughly" additive even when the eliciting stimuli are repeated at a short interval (i.e., that the BOLD response elicited by repeated stimuli "roughly" corresponds to the sum of the BOLD responses that would be elicited by each stimulus presented in isolation) [Burock et al., 1998; Inan et al., 2004]. Importantly, our approach to analyze the *relative* differences in BOLD signals across ROIs did not rely on the assumption that the BOLD response to sustained constant neural activity necessarily remains constant over time, but on the assumption that the temporal dynamics of the relationship between BOLD signal and neural activity would be similar across brain regions.

CONCLUSION

Our study demonstrates that stimulus-evoked activities in the different brain regions responding to transient and sustained nociceptive and non-nociceptive stimulation reflect functionally distinct cortical processes. First, S1 is specifically sensitive to changes in incoming non-nociceptive input, whereas the anterior insula is specifically sensitive to changes in incoming nociceptive input. Second, MCC could be involved in the detection of change regardless of sensory modality. Third, the posterior insula and S2 are preferentially involved in processing non-nociceptive somatosensory input. These findings provide novel insights into the functional significance of the brain processing underlying the brain responses to transient and sustained nociceptive and non-nociceptive somatosensory stimuli.

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