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# Differences in Cortical Coding of Heat Evoked Pain Beyond the Perceived Intensity: An fMRI and EEG Study

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**Abstract:** Imaging studies have identified a wide network of brain areas activated by nociceptive stimuli and revealed differences in somatotopic representation of highly distinct stimulation sites (foot vs. hand) in the primary (S1) and secondary (S2) somatosensory cortices. Somatotopic organization between adjacent dermatomes and differences in cortical coding of similarly perceived nociceptive stimulation are less well studied. Here, cortical processing following contact heat nociceptive stimulation of cervical (C4, C6, and C8) and trunk (T10) dermatomes were recorded in 20 healthy subjects using functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). Stimulation of T10 compared with the C6 and C8 revealed significant higher response intensity in the left S1 (contralateral) and the right S2 (ipsilateral) even when the perceived pain was equal between stimulation sites. Accordingly, contact heat evoked potentials following stimulation of T10 showed significantly higher N2P2 amplitudes compared to C6 and C8. Adjacent dermatomes did not reveal a distinct somatotopical representation. Within the assessed cervical and trunk dermatomes, nociceptive cortical processing to heat differs significantly in magnitude even when controlling for pain perception. This study provides evidence that controlling for pain perception is not sufficient to compare directly the magnitude of cortical processing [blood oxygen level dependence (BOLD) response and amplitude of evoked potentials] between body sites. *Hum Brain Mapp 35:1379–1389, 2014.* © 2013 Wiley Periodicals, Inc.

**Key words:** contact heat evoked potentials; laser evoked potentials; nociception; dermatomes; trunk

## INTRODUCTION

Brain imaging studies have disclosed a network of cortical areas involved in nociceptive processing [Apkarian et al., 2005; Peyron et al., 2000], as well as demonstrated somatotopic organization of nociception in a number of these areas (e.g., primary and secondary somatosensory cortices, S1 and S2, respectively) [Baumgärtner et al., 2010; Bingel et al., 2004; Brooks et al., 2005; DaSilva et al., 2002; Xu et al., 1997].

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There is less information available regarding how stimulation site directly affects cortical processing, beyond the perceived stimulation intensity and somatotopic organization. So far, laser and contact heat evoked potential (laser evoked potential (LEP) and contact heat evoked potential (CHEP), respectively) studies have revealed site dependent effects that are unrelated to differences in subjective rating of intensity. For example, LEPs and CHEPs are larger following stimulation of the face and trunk compared with the hands and feet, a finding which holds true regardless of whether rating of intensity is matched between sites [Haefeli et al., 2012; Treede et al., 2003]. Since an objective measure of pain should be more closely correlated with stimulus perception than location per se, site dependent effects extending beyond differences in rating of perceived intensity represent a limitation of LEPs and CHEPs. Whether blood oxygen level dependence (BOLD) in response to contact heat or laser stimulation follows a similar pattern, or better reflects the subjective rating of pain is unknown.

Additionally, brain imaging studies applying nonpainful stimuli to the foot and hand have shown a large representation in S1 and distinct cortical somatotopy within S1 and S2 [Kurth et al., 1998; Ruben et al., 2001]. In comparison, tactile stimulation of trunk dermatomes revealed a rather small cortical representation and overlapping somatotopy [Itomi et al., 2000] while the nociceptive processing of thoracic areas has rarely been studied [Strigo et al., 2003].

The aim of this study was to examine whether the magnitude of the cortical response elicited by a nociceptive stimulus can be used as an objective measure of pain perception. We therefore assessed if nociceptive stimulation of a trunk dermatome resulted in significantly higher BOLD responses compared to hand stimulation, independent of the perceived intensity. Further, we intended to examine if nociceptive stimulation of adjacent dermatomes activates cortical distinct areas using functional magnetic resonance imaging (fMRI). To address these issues, combined fMRI, electroencephalography (EEG) and quantitative sensory testing was applied in healthy subjects in predefined cervical and trunk dermatomes using standard (fixed temperature at 52°C) and adjusted stimulation intensities (adjusted temperature to the individual pain threshold). Two temperatures were applied to distinguish response pattern dependent on absolute and subjective stimulation intensities.

## METHODS

### Subjects

Twenty male, right-handed healthy volunteers without any neurological disorders and MRI contraindications participated in this study (age range: 20–40 years). The study was approved by the Ethics committee of the University of Zurich according to the guidelines of the Declaration of Helsinki. Prior to the onset of the study, the experimental procedure was explained and informed written consent was obtained from each subject.

### Contact Heat Stimulation

Heat stimuli were delivered with a contact-heat stimulator (Pathway Pain and Sensory evaluation System, Medoc, Ramat Yishai, Israel) using a MRI compatible thermode (thermode area: 572.5 $mm^2$; diameter: 27 mm). The device is able to generate a rapid heat pulse with a heating rate up to 70°C/s, and the Peltier device allows a cooling rate of 40°C/s.

### Experimental Procedure

The experiment was conducted within two sessions separate in time (mean time between sessions 26 ± 24 days). In the first session, the pain threshold (PTh) examination and fMRI scanning during contact heat stimulation was performed, in the second session the PTh was tested again and contact heat evoked potentials (CHEP) were recorded with EEG.

### PTh Measurement

The PTh was tested at four different dermatomes (C4, C6, C8, and T10) in a randomized order according to the International Standards for the Neurological Classification of SCI (ISNCSCI) map of key sensory points [Kirshblum et al., 2011]. Briefly, C4 was stimulated in an area over the acromioclavicular joint, C6 and C8 were stimulated on the lateral and medial aspect of the dorsum of the hand, and T10 was stimulated in an area 5 cm lateral to the umbilicus. The PTh was determined on each dermatome by increasing the temperature from 35°C in 1°C increments with an interstimulus interval of 4–6 s until the subjects verbally rated the stimulus as a strong pinprick (corresponding to a 7–8 rating on a visual analog scale). The PTh was examined twice and set as the mean between the two reported temperatures, respectively.

### Contact Heat Stimulation for the fMRI

During fMRI acquisition dermatomes (C6, C8, and T10) were stimulated in a randomized order, with an "in-scanner" pause of ~1 min to change the position of the thermode. The dermatome C4 could not be assessed in the MR scanner due to interference of the magnetic field.

For each dermatome, a total number of 40 stimuli with two different temperatures were applied in a randomized order: 20 stimuli were given with a standard temperature of 52°C; the other 20 stimuli were adjusted to the individual PTh (PTh + 3°C). Heat stimuli were applied from a 35°C baseline temperature with a heating rate of 70°C/s and a

cooling rate of 40°C/s. The duration of the heat stimuli depended on the peak temperature applied (52°C, PTh + 3°C). The inter-stimulus interval between consecutive heat pulses varied randomly between 12 and 20 s. The thermode was repositioned after each stimulus within the borders of the targeted dermatome. Subjects rated the perceived intensity of the stimulus by a button press with the fingers of the left hand (not perceived, low, middle, and high rating).

### fMRI Acquisition

MRI data was collected on a Philips 1.5T Achieva system (Philips Medical Systems, Best, the Netherlands) using an eight-channel Philips Sense head coil. Functional time series were acquired with a sensitivity-encoded (reduction factor 2), single-shot echo-planar sequence (SENSE-sshEPI) [Schmidt et al., 2005], with a measured resolution of 2.75 × 2.75 × 4 mm. The 29 axial slices without interslice gaps covered the entire cerebrum. Other scan parameters were as follows: echo time = 50 ms; flip angle = 90°; repetition time = 2500 ms; field of view = 220 mm; and a reconstruction matrix of 128 × 128. The first three scans were acquired to reach steady-state magnetization and then discarded. In total, 840 volumes were acquired (280 per dermatome/session).

A 3D T1-weighted anatomical reference scan was also acquired using a spoiled gradient echo sequence with the following imaging parameters: 160 sagittal slices, a turbo factor of 150 with an isotropic resolution of 1 × 1 × 1 $mm^3$. Further parameters were as follows: echo time = 3.7 ms; flip angle = 8°; repetition time = 8.1 ms; a shot duration of 3000 ms; SENSE reduction factor of 1.5 in phase encoding direction and scan duration of 7:30 min.

### fMRI Data Analysis

FMRI data were analyzed in Matlab R2010b using the statistical parametric mapping software SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Images were realigned to the first scan, unwarped to control for movement- and susceptibility-induced image distortions [Andersson et al., 2001], spatially coregistered to the individual T1-weighted image, and normalized to the Montreal Neurologic Institute (MNI) anatomical standard space. Finally, the functional data was smoothed spatially with an isotropic Gaussian kernel of 8 mm full-width-at-half-maximum.

A first-level analysis using the general linear model [Friston et al., 1995] was performed for each subject. Stimulus-related changes in fMRI signal were estimated at each voxel by convolving the onsets of the stimuli with a canonical hemodynamic response function. Parameter estimates reflecting activations with two temperatures (52°C and PTh + 3°C) in three dermatomes (C6, C8, and T10) were computed and constituted six statistical parametric maps per individual. Motor responses due to pain rating were incorporated into to the design matrix as parameter of confound. The time series were high-pass filtered with a cut-off at 128 s. Six movement parameters ($x$, $y$, $z$, pitch, roll, and yaw) resulting from the image realignment were modeled as additional repressor to control for movement artifacts. The first level produced contrast images representing the subject-specific activation after heat stimulation in C6, C8, and T10 dermatomes. These contrast images then entered two separate (standard and individual temperature) second-level factorial design with within-subject factor dermatome (three levels: C6, C8, and T10). Voxels exceeding a corrected threshold of $P < 0.05$ (family wise error corrected) are reported as significant.

As our main aim was to investigate nociceptive processing at different stimulation locations the main effect of stimulation site was assessed in the bilateral S1, bilateral operculum (OP) 1–4, bilateral insula, bilateral anterior cingulate cortex, and bilateral somatosensory thalamus. The areas OP 1–4 are an anatomical correlate to the functionally defined human S2 region [Eickhoff et al., 2006a]. The region of interest (bilateral S1, bilateral OP 1–4, bilateral insula and bilateral somatosensory thalamus) were defined in the MNI space using the spm8 compatible toolbox Anatomy [Eickhoff et al., 2005] and the anterior cingulate cortex using the wfu pickatlas [Maldjian et al., 2003]. Their localization was checked on the normalized anatomical image of the individual subject.

### Calculation of Somatotopy

To determine the somatotopic organization of the three stimulation sites (C6, C8, and T10) in the bilateral S1 and the bilateral OP 1–4, the differences in the coordinates in the $x$, $y$, and $z$ plane were compared. Further, the measurement of the Euclidean distance was applied described by Wrigley et al. [2009]. To adjust for high inter-subject anatomical variability, we referenced each maximally activated voxel during dermatome stimulation (e.g., C6, C8, and T10) to an individual anatomical landmark (i.e., where the central sulcus meets the midline). The ED was then calculated as the distance between the maximally activated voxel during dermatome stimulation in S1 and OP 1–4 and the individual anatomical landmark.

### EEG Acquisition

Equal to the MRI session for the CHEP acquisition subjects were lying in a supine position and the dermatomes (C4, C6, C8, and T10) were stimulated with two different intensities in randomized order (52°C and PTh + 3°C). Each dermatome was stimulated with 20 heat pulses of the respective temperatures with an interstimulus interval of 8–10 s. The perceived pain sensation of each stimulus had to be rated upon an acoustic signal on a visual analog scale ranging from 0 to 10.

EEG was recorded from 62 scalp electrodes and two additional electrodes bellow the outer canthus of each eye using a QuickAmp amplifier system (Brainproducts, Munich, Germany). Data was recorded with a sampling frequency of 500 Hz with the average reference as recording reference. Subject ground was at the AFz position and impedances were kept bellow 20 kΩ [Ferree et al., 2001].

### EEG Data Analysis

EEG data were processed off-line using Brainvision Analyzer software (Brainproducts, Munich, Germany) and band pass filtered from 1.5 to 30 Hz (Butterworth). Ocular artifacts were corrected by applying an independent component analysis [Jung et al., 2000] algorithm. Segmentation was conducted relative to marker position from −100 to 1000 ms and averaged for every subject relative to electrode position. N2 and P2 event related potentials were visually detected at the Cz electrode. N1 waveforms were displayed using the central- frontal montage (C3− Fz) proposed recently [Hu et al., 2010]. Single subjects' averages were than averaged over the group to obtain grand-average waveforms. Average scalp topographies were calculated by averaging scalp topographies obtained at individual-level peak latencies and computed by spherical splines interpolation. N2 scalp topographies were plotted at the most negative and P2 topographies at the most positive deflection after stimulus onset of the Cz electrode in the grand averaged waveform for each stimulation site. The topographies for the N1 were plotted at the negative deflection preceding the N2 event-related potential.

### Statistics

To determine statistically, the somatotopic organization of nociceptive stimulation, a linear mixed model was used to compare ED, the *x*, *y*, and *z*-coordinates with the stimulation site as a fixed effect. The PTh and pain rating, N2P2 and N1 amplitudes were examined by a repeated measure analysis of variance (ANOVA). The main effect of stimulation site (C4, C6, C8, and T10) and stimulation temperature and the interaction between stimulation site * stimulation temperature was examined. In the event of significant effects, a post hoc pairwise comparison was used. All multiple comparisons were Bonferroni corrected. The statistical analysis was done in IBM SPSS Statistics 19.

Finally, we assessed which brain areas encode the relationship between EEG parameters and BOLD response, with a specific interest of pain intensity processing. A voxel-wise linear regression analysis within S1 and OP 1–4 was used testing the EEG measurement parameters (N2P2 and N1 amplitude after stimulation at 52°C and PTh + 3°C), the PTh and the BOLD contrast of all the measured dermatomes. Statistical parametric maps were computed displaying where a linear increase in activation could be explained by the parameter investigated.

## RESULTS

### Subjects

In the fMRI session, four subjects had to be excluded from further analysis because of technical problems (two subjects) and head movement associated with the stimulus (two subjects). The remaining 16 subjects had a mean age of 27.6 ± 4.0 years. For the EEG 15 of the 16 subjects (27.5 ± 4.1) with viable fMRI were included (one subject was not available for the EEG measurement).

### PTh and Pain Rating of the fMRI Session

There was significant effect of stimulation site on PTh in the experimental session preceding fMRI ($F(2, 30) = 9.239$; $P = 0.002$). PTh was significantly higher in C8 (49.8 ± 4.8) compared with C6 (46.9 ± 4.3) and T10 (46.3 ± 4.8) (C8–C6: $P = 0.001$; C8–T10: $P = 0.014$). There was a significant interaction effect between stimulation site and pain rating in response to 52°C contact heat stimulation ($F(4,60) = 5.588$, $P = 0.001$). Comparatively, when stimulated with a temperature adapted to the individual PTh there was no interaction between stimulation site and pain rating category ($F(4,60) = 0.451$, $P = 0.771$). This contrast suggests that subjects perceived stimuli differently depending on the stimulation site when a fixed temperature was applied across all dermatomes, but rated dermatomes equally when the temperature was adjusted.

### fMRI Response

The whole-brain analysis for both stimulation temperatures (52°C and PTh + 3°C), revealed that contact heat stimulation at C6, C8, and T10 elicited consistent activity in a wide network of brain regions known to be involved in nociceptive processing (Fig. 1). The analysis of the main effect of location within the predefined region of interest [S1, OP 1–4, insula, anterior cingulate cortex and somatosensory thalamus (Fig. 2)] for the fixed stimulation temperature (52°C) showed increased BOLD signal in the contralateral S1 (Table I). The effect of location of the temperature adapted to the individual PTh (PTh + 3°C) induced increased BOLD response in the contralateral S1 and the ipsilateral OP 1–4 (Fig. 3 and Table I), whereby T10 stimulation elicited a higher percentage BOLD signal intensity change in S1 and OP 1–4 compared with C6 and C8.

### Calculation of Somatotopy

The comparison of the different stimulation sites did not reveal any significant differences in the *x*, *y*, and *z* coordinates in the left S1 (*x*: $F = 2.179$, $P = 0.148$; *y*: $F = 1.892$, $P = 0.185$; *z*: $F = 3.335$, $P = 0.063$), in the left OP 1–4 (*x*: $F = 1.827$, $P = 0.195$; *y*: $F = 0.237$, $P = 0.792$; *z*: $F = 0.066$, $P = 0.937$) and in the right OP 1–4 (*x*: $F = 0.194$, $P = 0.825$; *y*: $F = 1.288$, $P = 0.305$; *z*: $F = 1.140$, $P = 0.346$).

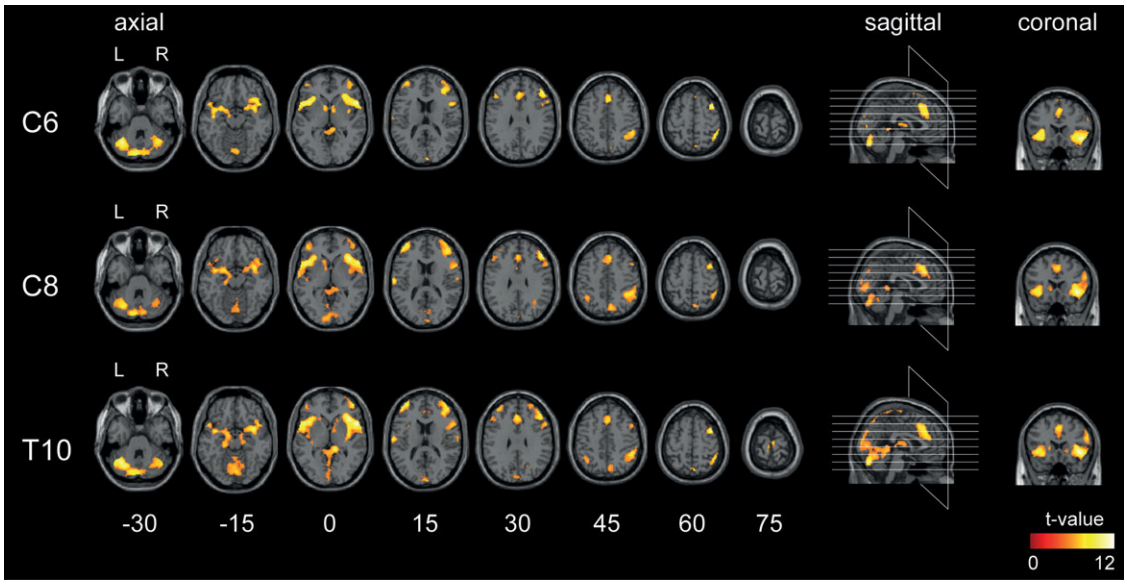


**Figure 1.**

Statistical parametric maps showing the BOLD response to heat stimulation of both stimulation temperatures (52°C and PTh + 3°C) at the dermatomes C6, C8, and T10 over the whole brain family wise error corrected for multiple comparisons ($P < 0.05$). For the axial slices, the location is indicated by the MNI z-coordinate below the images and the slices are further illustrated in the sagittal view by horizontal lines. The location of the coronal slice is also indicated in the sagittal view by a transversal plain. BOLD responses are overlaid onto a standardized anatomical brain provided by SPM. The color bar represents the *t*-value. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Accordingly, the comparison of the Euclidean distance did not reveal any significant differences between stimulation sites in the left S1 ($F = 3.064$, $P = 0.077$), left OP 1–4 ($F = 0.049$, $P = 0.953$) and right OP 1–4 ($F = 0.579$, $P = 0.573$).

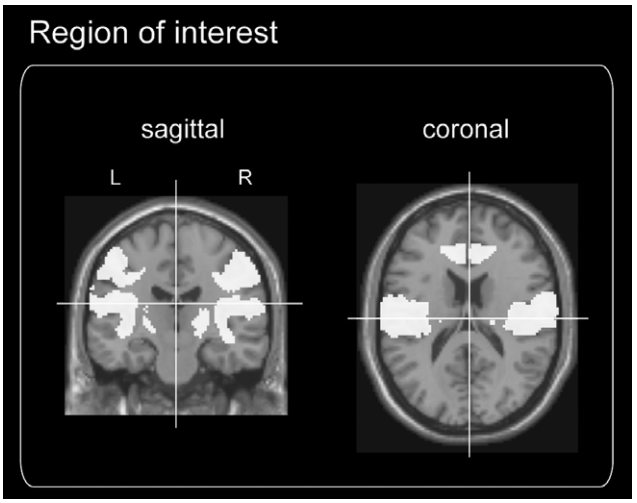


**Figure 2.**

Region of interest are marked in white including the S1, OP 1–4, anterior cingulate cortex, insula, and somatosensory thalamus.

## PTh and Pain Rating of the EEG Session

PTh did not differ significantly between the different stimulation sites ($F(1.682,42) = 1.582$; $P = 0.227$). The stimulation site had a significant effect on the pain rating ($F(1.636,42) = 6.341$; $P = 0.009$) with C4, C6, and T10 having a higher rating compared with C8 (C4–C8: $P = 0.013$; C6–C8: $P = 0.002$; T10–C8: $P = 0.004$). Further, the stimulation temperature had a significant effect on the pain rating ($F(1,14) = 16.082$; $P = 0.001$) with a higher rating after stimulation with a fixed temperature (52°C) compared

**TABLE I. Summary of the main effect of stimulation site in the left S1 and bilateral OP 1–4**

| Stimulation temperature | Region label | Side | *P*-value (FWE-corrected) | *F*-Score | Coordinates (mm) | | |
|---|---|---|---|---|---|---|---|
| | | | | | *x* | *y* | *z* |
| 52°C | S1 | L | 0.021 | 19.12 | −42 | −20 | 52 |
| | | L | 0.040 | 18.76 | −58 | −16 | 46 |
| PTh + 3°C | S1 | L | 0.013 | 11.12 | −32 | −30 | 60 |
| | | L | 0.023 | 10.20 | −40 | −30 | 58 |
| | S2 | R | 0.030 | 9.83 | 46 | −8 | 18 |

FWE, family wise error; OP, operculum; S1, primary somatosensory cortex.

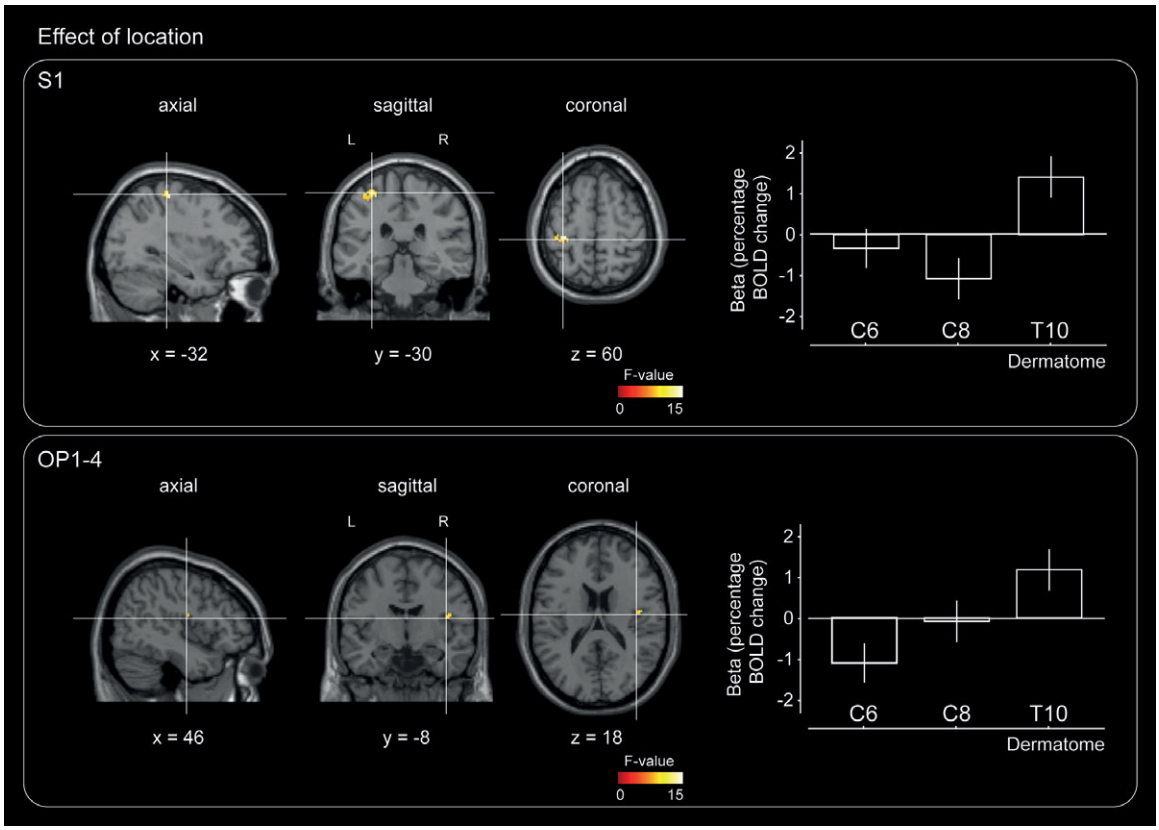


**Figure 3.**

Statistical parametric maps (threshold at $P < 0.001$, uncorrected for display purposes only) showing the significant activation during heat stimulation of the dermatomes in S1 (upper panel) and OP 1–4 (lower panel) adapted to the individual PTh (PTh + 3°C). The peak percentage BOLD change (beta) within the same cluster in S1 ($x = -32$, $y = -30$, $z = 60$) and OP 1–4 ($x = 46$, $y = -8$, and $z = 18$) shows that heat stimulation of dermatome T10 evokes the highest percent BOLD signal changes followed by dermatome C8 and C6. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

with the individual stimulation temperature (PTh + 3°C; 52°C-PTh + 3°C: $P = 0.001$).

## Evoked Potentials

All parameters of the CHEPs are listed in Table II and displayed in Figure 4. Excluding one subject, contact heat stimulation to 52°C and adjusted PTh (PTh + 3°C) evoked clear N2P2 potentials (in one subject N2P2 could not be confirmed after stimulation of the C8 dermatome with the adjusted stimulation temperature (PTh + 3°C). Figure 4 shows the grand average waveform at the Cz electrode of all stimulation sites with scalp topographies at the maximal deflections for both the N2 and P2 waveform. There was a

**TABLE II. Summary of PTh, N1, amplitude, N2P2 amplitude and rating**

| Stimulation temperature | | Stimulation site | | | | | | | | Significant pair-wise comparisons ($P < 0.05$) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | C4 | | C6 | | C8 | | T10 | | |
| | | Mean | ±SD | Mean | ±SD | Mean | ±SD | Mean | ±SD | |
| 52°C | N1 Amplitude (μV) | −7.44 | 3.67 | −7.72 | 3.46 | −5.45 | 2.57 | −8.00 | 5.26 | ns |
| PTh + 3°C | | −7.47 | 4.39 | −7.43 | 3.46 | −5.67 | 2.40 | −7.53 | 4.37 | ns |
| 52°C | N2P2 Amplitude (μV) | 12.66 | 4.82 | 10.91 | 4.66 | 9.57 | 4.39 | 14.21 | 6.21 | C6-T10, C8-T10 |
| PTh + 3°C | | 13.51 | 5.32 | 10.19 | 5.14 | 8.34 | 4.30 | 15.40 | 6.58 | |
| 52°C | Pain Rating | 6.83 | 1.56 | 6.21 | 1.13 | 5.01 | 1.18 | 5.82 | 1.96 | C4-C8, C6-C8, C8-T10 |
| PTh + 3°C | | 5.87 | 1.29 | 5.05 | 1.85 | 4.07 | 1.24 | 5.64 | 1.31 | |

ns, nonsignificant; PTh, pain threshold; SD, standard deviation.

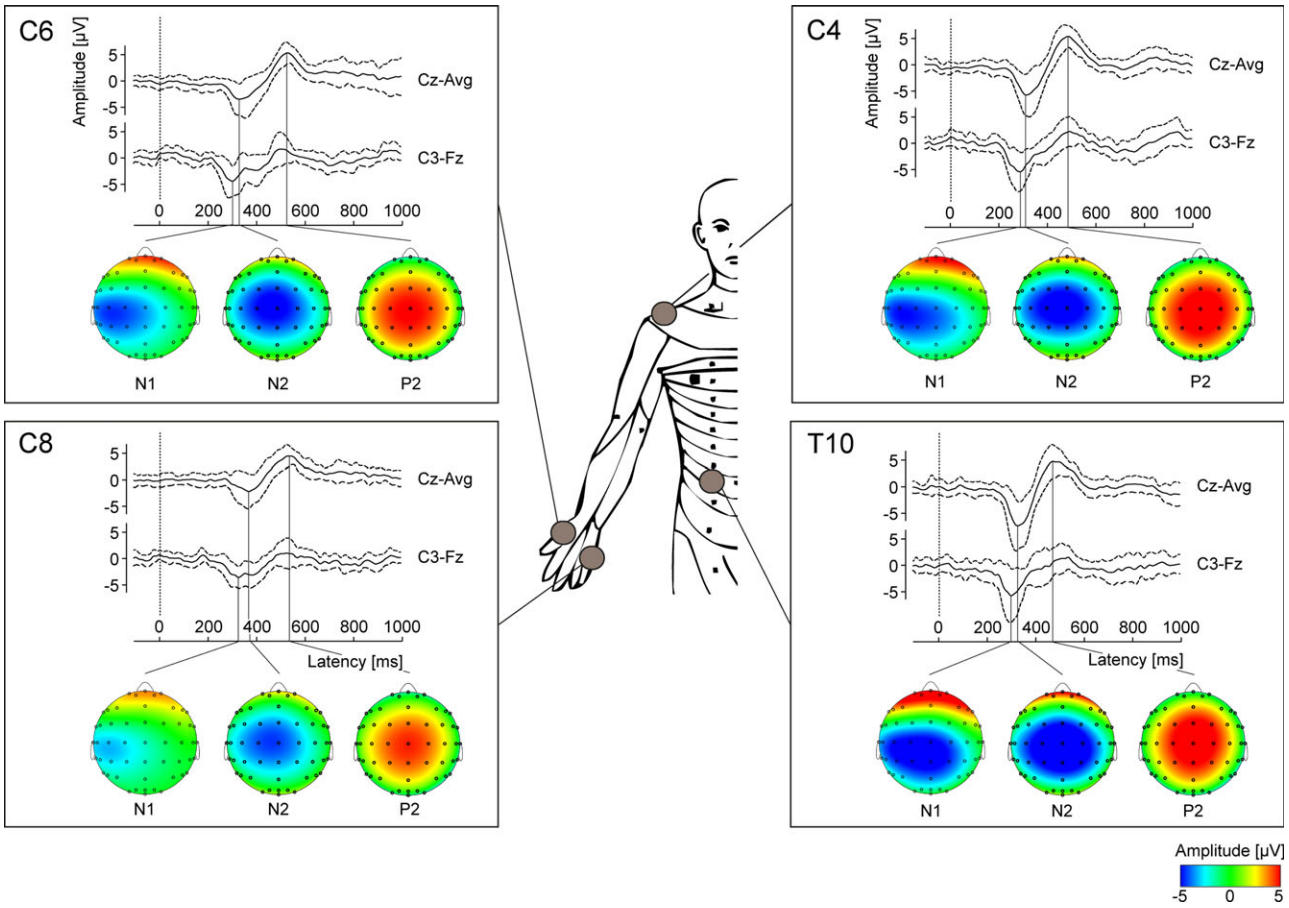


**Figure 4.**

Grand average waveforms of the Cz-Avg montage for the N2P2 waveform and the C3-Fz montage for the N1 waveform at PTh + 3°C stimulation temperature elicited by the stimulation of C4, C6, C8, and T10 are displayed. The straight line represents the average waveform and the standard deviation is shown as a dotted line. Average of scalp topographies obtained at individual-level peak latencies for the N1, N2, and P2 peak are shown for each stimulation site. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

significant main effect of dermatome on N2P2 amplitude ($F(1.773,42) = 6.706$; $P = 0.006$). Comparably to the fMRI results, T10 showed a higher activation (N2P2 amplitude) than C6 and C8 (T10–C6: $P = 0.003$; T10–C8: $P = 0.002$). The N2P2 amplitude were not different between the two stimulation temperatures ($F(1,14) = 0.003$; $P = 0.955$) and there was no interaction between stimulation site*stimulation temperature ($F(3,42) = 1.913$; $P = 0.142$).

N1 could be measured in 113 of the 120 measured evoked potentials (4 dermatomes × 2 temperatures × 15 subjects). There was no main effect of stimulation site ($F(3,24) = 2.806$; $P = 0.061$) or temperature ($F(1,8) = 0.306$; $P = 0.798$), and the interaction effect of temperature on stimulation site was not significant for N1 amplitude ($F(3,24 = 0.135$; $P = 0.938$).

### Regression of fMRI and EEG Findings

The results of the linear regression analysis are summarized in Table III. Briefly, linear regression analysis revealed a positive relationship between the N2P2 amplitude and the BOLD contrast in the T10 dermatome within the bilateral OP 1–4 at the fixed stimulation temperature (52°C). Furthermore, there was a negative relationship of the PTh and the BOLD contrast within the bilateral OP 1–4 after stimulating T10 with fixed temperature (52°C) (Fig. 5). Additionally, the N1 amplitude showed a positive relationship at 52°C stimulation of the T10 in the bilateral OP 1–4. Further significant regressions were found in the contralateral OP 1–4 in the C6 dermatome at a fixed stimulation temperature and in the ipsilateral OP 1–4 in the C8 dermatome at PTh + 3°C stimulation.

## DISCUSSION

This study addressed differences in the cortical representation and processing of painful contact heat stimulation delivered to cervical and trunk dermatomes. Contact

**TABLE III. Summary of the regression of stimulation site in the bilateral OP 1–4**

| Parameter | Stimulation site | Stimulation temperature | Side | *P*-value (FWE-corrected) | Z-value | Coordinates (mm) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | *x* | *y* | *z* |
| N2P2 amplitude | T10 | 52°C | Left | 0.016 | 4.16 | −62 | −2 | 10 |
| | | | Left | 0.045 | 3.83 | −50 | −12 | 10 |
| | | | Right | 0.000 | 5.05 | 64 | −16 | 16 |
| | | | Right | 0.006 | 4.38 | 62 | −8 | 14 |
| | | | Right | 0.036 | 3.84 | 54 | −12 | 10 |
| N1 amplitude | T10 | 52°C | Left | 0.026 | 5.30 | −62 | −4 | 16 |
| | T10 | 52°C | Right | 0.037 | 5.39 | 64 | −6 | 16 |
| | C6 | 52°C | Left | 0.020 | 4.10 | −52 | −10 | 20 |
| | C8 | PTh + 3°C | Right | 0.034 | 5.60 | 50 | −26 | 12 |
| PTh | T10 | 52°C | Left | 0.005 | 4.49 | −62 | 0 | 10 |
| | | | Right | 0.011 | 4.18 | 62 | −14 | 8 |

FWE, family wise error; OP, operculum; PTh, pain threshold.

heat stimulation activated cortical structures consistent with the processing of nociceptive stimuli (e.g., OP 1–4, insula, and anterior cingulate cortex). fMRI and EEG revealed similar patterns of activation, most notably that stimulation of trunk resulted in increased responses (BOLD response in S1 and OP 1–4, and N2P2 amplitude of CHEPs) compared with distal cervical dermatomes (C6 and C8). The increase in activation following trunk stimulation was observed regardless of whether the peak temperature was matched to individual PTh or set at fixed stimulation intensity (i.e., 52°C). That is, the same perceived intensity of pain resulted in markedly increased cortical activation following trunk compared with distal arm stimulation. These findings suggest that BOLD response to stimulus-evoked pain is not only dependent on the subjective rating of perceived pain, but also on the area stimulated. A cortical somatotopic organization between adjacent cervical and trunk dermatomes was not disclosed.

### Cortical processing of nociceptive stimuli between cervical and trunk dermatomes

As expected, stimulation of a trunk dermatome with the same peak temperature as delivered to the hand resulted in significantly greater cortical activation according to both fMRI and EEG measures. This corresponds to the well-established relationship between perceived measures of pain and stimulation intensity (i.e., trunk stimulation was rated as more painful) [Bromm and Lorenz, 1998; Coghill et al., 2003].

Interestingly, higher cortical activation (i.e., BOLD) in S1 and OP 1–4 was also observed after stimulation of T10 compared with C6 and C8 when the peak temperature was adjusted to the individual PTh. This novel finding suggests that the BOLD response in S1 and OP 1–4 encodes afferent information beyond the perceived intensity of pain. This may include effects of spatial and temporal summation of afferent inputs, which in the case of trunk stimulation may be increased due to shorter peripheral conduction distance and shorter stimulus durations required to achieve a lower peak stimulation temperature [Haefeli et al., 2012; Iannetti et al., 2004]. Further, differences in nerve fiber density between stimulation areas could induce higher cortical responses after trunk in comparison to hand stimulation, as proximal areas have a known higher nerve fiber densities than distal areas [Lauria et al., 1999; McArthur et al., 1998]. An alternative explanation for the higher cortical activation after trunk stimulation could be that trunk stimuli are processed as being more threatening than stimuli delivered to the hand. Indeed, a recent study demonstrated that the same intensity stimuli resulted in changes in blink reflexes depending on the proximity of the stimuli in peri-personal space (i.e., closer to the face, larger blink response) [Sambo et al., 2012]. Regardless of the underlying mechanisms, our findings reveal that controlling for the rating of perceived pain is of limited value to assume comparable levels of BOLD activation between different stimulation sites.

In a recent study, OP 4, a subregion of S2, was found to be activated during pain but not tactile stimulation, and was ascribed to play a major role in coding pain intensity [Mazzola et al., 2012]. In this study, corroborating findings with a significant relation between PTh, EEG parameters (N2P2 and N1 amplitude), and BOLD responses, with most significant relationship within the OP 4 subregion (Fig. 5), substantiates OP 4 as an area important for coding pain intensity.

### The somatotopic organization of painful dermatomal stimulation

The majority of brain-imaging studies have confirmed that S1 and S2 are involved in processing of painful afferent stimuli [Apkarian et al., 2005; Peyron et al., 2000]. A number of studies have also addressed the question as to

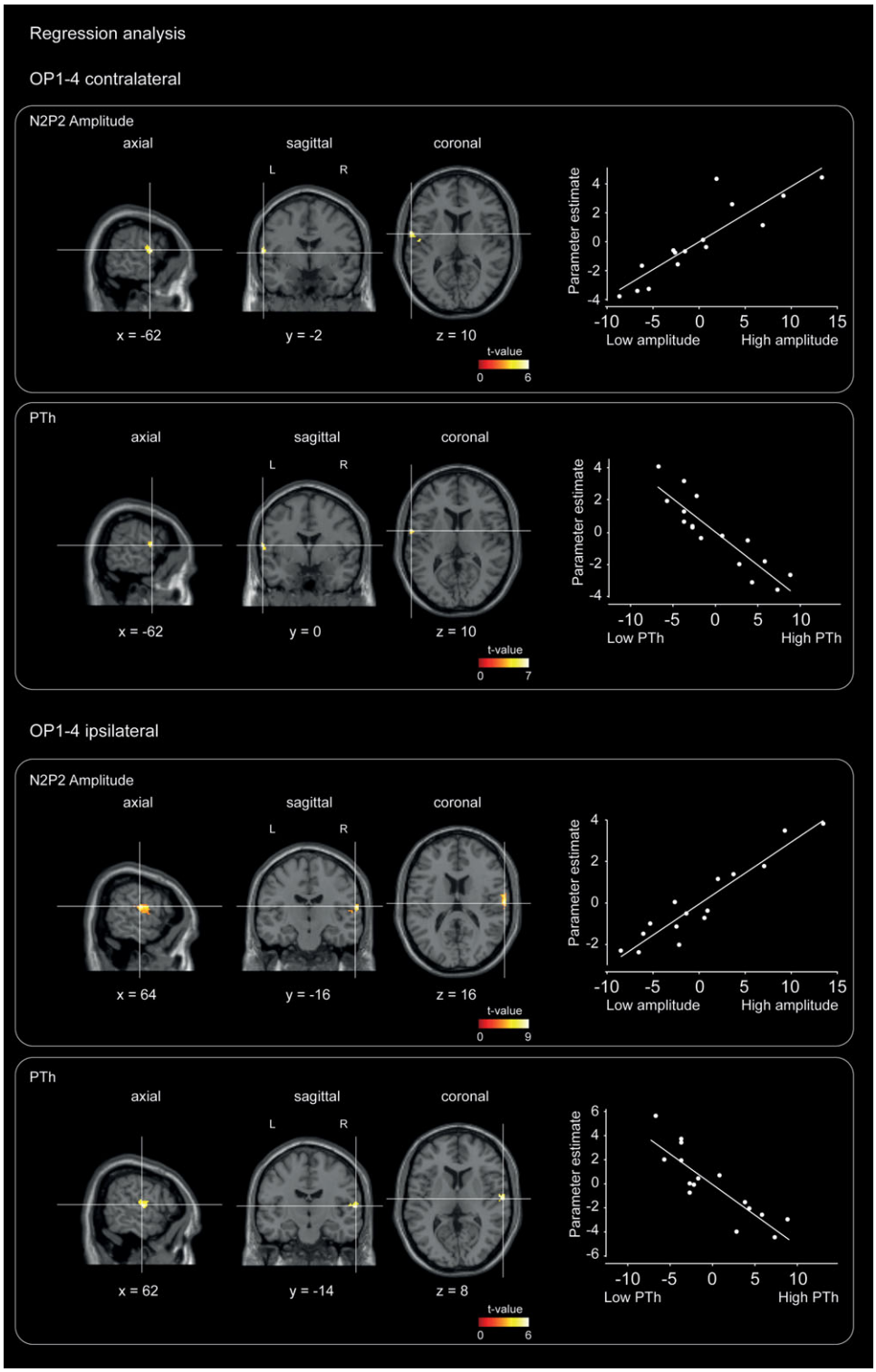


**Figure 5.**

Statistical parametric maps (threshold at $P < 0.001$, uncorrected for display purposes only) showing the relation between contact heat related brain activity and the contact heat evoked potential amplitude and the pain threshold (PTh) within the bilateral OP 1–4. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

whether nociceptive processing in cortical areas is somatotopically organized [Andersson et al., 1997; Baumgärtner et al., 2010; Bingel et al., 2004; Brooks et al., 2005; DaSilva et al., 2002; Ferretti et al., 2004; Ogino et al., 2005; Valentini et al., 2012; Xu et al., 1997].

While these studies support that nociceptive stimuli are somatotopically organized in S1 (i.e., hand activation contralateral to the stimulation and foot activation close to the midline [Valentini et al., 2012]), evidence of somatotopic organization in S2 is less clear. One factor which may account for discrepancies regarding somatotopy in S2 is that a variety of region of interests have been applied across different studies [Bingel et al., 2004; Brooks et al., 2005; Ferretti et al., 2004; Ogino et al., 2005; Xu et al., 1997]. Eickhoff et al. [2006a,b] defined the functional area of S2 by identifying four structurally independent cytoarchitectonic areas called OP 1–4. Our analysis of S2 included OP 1–4 as a single region of interest and demonstrated no distinct organization of nociceptive stimuli into hand and trunk areas, with the average most activated voxels independent of stimulation site within OP 4 (ipsilateral and contralateral). However, Baumgärtner et al. [2010] provided evidence of somatotopy within OP 1 in response to nociceptive stimuli of the hand and foot. Therefore, we cannot exclude that there may be multiple somatotopic representations within the other single opercula (OP 1, 2, and 3). Factors potentially explaining that we did not find a distinct somatotopy of cervical versus a trunk dermatome within S1 include that there was, in general, a low activation in S1 following stimulation with contact heat regardless of the area and intensity of stimulation. This might be attributable to characteristics of the stimulus (i.e., temporal and spatial summation) [Peyron et al., 2000] and event-related potential fMRI design [Birn et al., 2002]. Additionally, the representation of the trunk may be comparably small to the hand and feet [Itomi et al., 2000].

### Limitations

While we implemented a random, intermingled stimulation design to reduce total scan time and the influence of stimulation order, the difference in perceived pain between fixed and adjusted peak temperatures may have influenced our findings. In the case of T10, where the difference in rating between the two stimuli was greatest, stimulation saliency may have inadvertently increased. In turn, increased stimulation saliency may have yielded larger cortical responses to nociceptive stimuli [Iannetti et al., 2008]. Comparatively in C6 and C8, stimulation saliency may have been reduced by intermingled intensities that were perceived similarly, which would have the opposite effect of reducing the overall magnitude of the cortical response. However, in an earlier study, we assessed different stimulation locations (C4, C5, C6, C8, and T4) using fixed and adjusted stimulation temperatures in separate block designs. Similar to this study, evoked potentials were increased in proximal areas compared with distal areas even if the pain perception was equal between the examined areas [Haefeli et al., 2012]. Therefore, we suggest that the stronger cortical responses at thoracic area compared with the hand cannot be entirely explained by differences in saliency of the stimuli.

## CONCLUSION

The study provides information on the differences between stimulation sites (cervical and trunk) that are unrelated to the perceived rating of intensity. Therefore, effects of stimulation sites beyond the perceived sensation have to be accounted for when cortical responses (BOLD and EEG) are compared between stimulation sites.

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