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Diffuse Optical Tomography of Pain and Tactile Stimulation: Activation in Cortical Sensory and Emotional Systems

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Abstract

Using Diffuse Optical Tomography (DOT) we detected activation in the somatosensory cortex and frontal brain areas following tactile (brush) and noxious heat stimulation. Healthy volunteers received stimulation to the dorsum of the right hand. In the somatosensory cortex area, tactile stimulation produced a robust, contralateral to the stimulus, hemodynamic response with a weaker activation on the ipsilateral side. For the same region, noxious thermal stimuli produced bilateral activation of similar intensity that had a prolonged activation with a two-peak similar to results have been reported with functional MRI. Bilateral activation was observed in the frontal areas, oxyhemoglobin changes were positive for brush stimulation while they were initially negative (contralateral) for heat stimulation. These results suggest that based on the temporal and spatial characteristics of the response in the sensory cortex, it is possible to discern painful from mechanical stimulation using DOT. Such ability might have potential applications in a clinical setting in which pain needs to be assessed objectively (e.g. analgesic efficacy, pain responses during surgery).

Keywords

pain; somatosensory cortex; human; oxyhemoglobin; deoxyhemoglobin; bilateral activation; near infrared spectroscopy (NIRS)

INTRODUCTION

Central nervous system processing of pain in humans has been studied extensively with neuroimaging techniques (for reviews see (Peyron et al. 2000; Apkarian et al. 2005). The first studies were carried out utilizing positron emission tomography (PET) (Jones et al. 1991; Talbot et al. 1991) and later with functional MRI (fMRI) (Davis et al. 1995; Apkarian et al. 1999; Becerra et al. 1999). Several studies have reported robust activation in the primary somatosensory cortex (S1) in experimental models of pain (Apkarian et al. 2005) and in clinical pain conditions (Becerra et al. 2006; Maihofner et al. 2006). However, a significant number of studies do not consistently observe activation in S1 (Bushnell et al. 1999; for reviews, see

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Peyron et al., 2000; Apkarian et al., 2005). Some of the reasons for the lack of consistent activation in S1 have been attributed to cognitive modulation, inhibitory processes, and methodological differences (Bushnell et al. 1999).

Nevertheless, neuroimaging results indicate that it is possible to identify signature characteristics in cortical activation that differentiates noxious from innocuous stimuli. Coghill and colleagues demonstrated with PET that pain is a distributed bilateral process, while for non-noxious heat stimulation, only contralateral activation is observed (Coghill et al. 1999). In addition, other investigators have found temporal differences for noxious and non-noxious cortical responses (Becerra et al. 2001; Chen et al. 2006). These studies seem to indicate that the temporal response to noxious stimuli in S1 is distinct from innocuous stimuli; pain seems to produce a prolonged or biphasic response usually extending beyond the duration of the stimulus whereas innocuous stimuli produce a response similar to other evoked hemodynamic responses.

The involvement of frontal structures in pain processing in humans has been studied by several groups. A putative role for these cortical regions has been linked to mapping external space and surrounding, short term memory, planning response to external stimuli (Maihofner et al., 2004); cognitive and emotional responses (Lorentz et al., 2002); and the placebo response (Wager et al., 2004). In disease (chronic pain) frontal regions have altered activation responses (Witting et al. 2006) as well as morphological changes (Apkarian et al. 2004).

In this study, we sought to detect the hemodynamic response in somatosensory cortex as well as in frontal brain areas to innocuous mechanical and noxious thermal stimulation utilizing Diffuse Optical Tomography (DOT) in healthy volunteers. We wished to determine whether robust signals could be measured using this approach and whether or not signals in somatosensory regions could be differentiated based on their duration or pattern. For example we have previously reported a biphasic BOLD response to noxious heat with fMRI that is not observed to mechanical or non-noxious thermal stimuli (Becerra et al., 1999, 2001). In addition, given the ability of DOT to measure changes in multiple cortical regions, we also wished to determine if we could measure changes in frontal regions that might provide additional information on emotional processing of pain in a similar manner to that reported for fMRI,

METHODS

Subjects

9 healthy volunteers were recruited through local advertisements, all were right-handed males of 18–40 years in age. Subjects with a history of neurological trauma, neurological or psychiatric disorders, or diabetes were excluded. Subjects were also excluded if they were taking any psychoactive medications or were unable to keep their head still for a period of 360 consecutive seconds. Written informed consent was obtained from all subjects according to the guidelines established by the Massachusetts General Hospital Institutional Review Board who reviewed and approved this study.

Equipment

The equipment has been described in detail elsewhere (Franceschini et al. 2006). Briefly, a multichannel continuous wave optical imager (CW5, TechEn Inc., Milford, MA) was used to emit the two wavelengths of light, 690nm and 830nm. These two wavelengths are used to measure changes in cortical deoxyhemoglobin (HbR) and oxyhemoglobin (HbO) concentration via differential absorption characteristics of the two wavelengths of light by these two molecules. The head probe used in this study consisted of 26 sources and 26 detectors (Figure 1A). Source fibers emitting the 690nm wavelength were paired off with those emitting

the 830nm wavelength to form an "optode." The main probe was arranged with one central, anterior-posterior row of 6 optodes per hemisphere. Each row of optodes was flanked on either side by a row of 6 detectors strategically placed 3 cm away from the sources in order to measure activation at cortical depth. Additionally, 2 optodes were placed on the forehead in order obtain prefrontal cortex activation. These two source optodes were similarly flanked on either side by single detectors.

During the experiment, subjects were connected to a physiological monitor for continuous monitoring of heart rate (pulse oximeter, Norin Medical Inc, Plymouth, MN), respiratory rate (strain gauge belt, Sleepmate/Newlife Technologies, Resp-EZ, Midlothian, VA) and blood pressure (in-house, custom-made device). Subjects remained sitting in a reclined position for the duration of the experiment. Lights were turned off in the room during data acquisition to minimize signal contamination from ambient light sources.

Paradigm

Tactile (brush) stimuli were delivered manually to each subject's hand using a soft toothbrush. Prior to the experiment a 3×3 cm^2 area of the dorsum of the right hand was marked for stimulus (brush or heat) delivery. Care was taken to consistently deliver the stimulus to the same location on the hand and to apply the same amount of pressure each time. The same investigator applied the stimuli to all subjects. A 3×3 cm^2 thermode (TSA-2001, Medoc Inc., Haifa, Israel) was used to deliver the painful 46 °C thermal stimuli. This equipment has been utilized in other fMRI pain experiments (Becerra et al. 2001). The thermal probe was lowered down onto the hand of the subject upon prompting and removed at the end of each stimulus. The probe was always applied with a similar force (pressure) predetermined at the beginning of the experiment with a scale to be around 2 pounds. For both brush and heat the paradigm consisted of 26 stimuli of 5 second duration over 6 minutes with a jittered inter-stimulus interval (ISI) of 6–13 seconds and average ISI of 8.5 seconds (Figure 1B). The paradigm was applied twice for each stimulus type. Prompts to apply stimuli were presented audibly via headphones to the investigator.

Subjects were asked at the end of the thermal scan to rate the pain intensity of the stimuli in a Lickerts 11point-scale (0 no pain, 10 maximum pain).

Data Analysis—Analysis was carried out using the open source software Homer (available at http://www.nmr.mgh.harvard.edu/homer) which is implemented in Matlab (Mathworks, Natick, MA). The analysis has been described in detail elsewhere (Franceschini et al. 2006). Here, data was corrected for motion artifacts using principal component analysis in a similar manner to the procedure previously outlined in Wilcox et al and Zhang et al., 2005 (Wilcox et al., 2005;Zhang et al., 2005). Single trial averages (STA's) were calculated for each detector for the oxy- (HbO) and deoxyhemoglobin (Hb) changes detected

The resulting data was displayed spatially for each detector and the signal corresponding to the somatosensory cortex was identified on the contralateral hemisphere to the stimulated side (detectors around source 4, see Figure 1). The farthest posterior response used was the Source 5- Detector 5 pairing, and the farthest anterior response taken was the Source 3- Detector 3 pairing. For simplicity, this activation is referred in the manuscript as S1 activation. The signal corresponding to ipsilateral S1 was identified as the mirroring ipsilateral source-detector pairings corresponding to those considered to be S1 on the contralateral side.

Hemodynamic Model Decomposition and Group Statistical Analysis—Average HbO STA for brush and heat in S1 depicted potentially monophasic (brush) and biphasic (heat) responses, respectively (Figure 3). Individual responses to brush and heat were fitted non-linearly using a one or two gamma response model, respectively. Gamma functions included a delay factor (tau) as presented in the equation (1) below:

$$H(t-tau)=(t-tau)^{a}*exp(-(t-tau)*b) \quad (1)$$

The non-linear fit was carried out using Matlab. The fit parameters were used to calculate Time to peak (TTP) for brush and heat responses:

$$TTP=tau+a/b \quad (2)$$

Group statistics were obtained by the following approach: For brush, individual HbO changes to the 26 stimuli were fitted linearly with an explanatory variable (EV) constructed from the temporal profile of the stimuli convoluted with a standard hemodynamic response (gamma function with delay of 6 s and standard deviation of 3s, see Becerra et al., 2001). For heat, following our previous fMRI study, two EV's were used (one delayed 10 seconds from the other, see Becerra et al., 2001).

Parameter estimates (PE) and residual variances for each EV were carried on to perform group level analysis.

Group results were obtained using a fixed effects approach as described in Beckmann et al. (Beckmann et al., 2003); briefly, to calculate the group average each individual parameter estimate is weighted by the inverse of the residual variance (hence, subjects with large variances might have their contribution attenuated even if they have large PEs). For group activation comparisons (i.e., contralateral vs. ipsilatearal), a pair-wise approach was used.

A corrected p value (0.05/26 detectors= 0.002) was used as threshold for statistical significance.

RESULTS

Subjects

Nine subjects were recruited to the study. All nine data sets for the brush stimuli were kept, while one data set for the thermal stimuli was eliminated due to an excessive number of motion artifacts. Subjects with data included in the results were 29 ± 6 years of age.

Pain Scores

None of the subjects perceived brush stimulation as painful (average rating 1.6±1.0). Subjects rated the painful stimuli as 5.0±2.1 that is considered moderately painful. None of the subjects prematurely terminated the experiment because of excessive pain.

Brush Stimulation

The single trial average responses after applying PCA filtering to the data are displayed in Figure 2A for one subject. Clear activation is detected in the contralateral S1 (left hemisphere) to the stimulus side. Ipsilateral activation was also observed but not to the same extent then the contralateral response (**Figure 2As**). In all subjects, frontal activation had significant larger artifacts.

Figure 3A depicts average S1 group activation to brush as detected in the HbO signal contralateral (red) and ipsilateral (orange) to the stimulus. In addition, the HbR signal is depicted in the same figure (contralateral-blue, ipsilateral-green). Average group activation in frontal areas is displayed in Figure 3C. The group activation was statistically significant ($p<0.002$) for both contralateral and ipsilateral activation in S1 and frontal areas. Comparing the contralateral response vs. the ipsilateral one, the difference was significant for S1 ($P<0.002$)

but not for frontal areas (p=0.06). For both frontal and S1 areas, brush stimulation elucidated a single hemodynamic response.

Heat Stimulation

Noxious stimulus elicited moderately painful sensations. The single trial average responses after PCA filtering for all detectors are shown in Figure 2B for one subject. S1 activation was observed bilaterally to the same level of activation, a similar result obtained with other neuroimaging techniques (Hansson and Brismar 1999; Tracey et al. 2000; Sutherland and Tang 2006). It is important to note that systemic effects were ruled out for each subject through the use of a head probe that maps a large area of the cortex. Responses used for averaging were localized to their respective ROIs and did not occur ubiquitously across all of the detectors.

Activations in S1 (Figure 3B) as detected in the HbO signal contralateral (red) and ipsilateral (orange) are very similar in size and temporal profile. Both responses seem to display two waves or phases (early and late). A pattern observed previously with fMRI (Becerra et al. 2001; Chen et al. 2006). Frontal activation was different in its temporal profile (Figure 3D) with an initial contralateral negative change in HbO. Group results indicated significant contralateral and ipsilateral activation ($p<0.002$) in S1 and only late phase in the frontal areas (ipsilateral: $p<0.002$). Comparing contralateral vs. ipsilateral activation, the difference was found not significant in S1 and frontal areas (p=0.16).

Time to Peak

Non-linear fit results for one response for brush and two responses for heat are displayed in Figure 4. The TTP for brush and the first (early) heat response were 6.42±0.50 and 5.49 ± 0.68 s, respectively, and were not significantly different from each other. The second (late) response to heat had a TTP of 12.60±0.83 and it was significantly different from brush or the early heat response. These timings agree well with previously observed activation in S1 (Becerra et al., 2001; Cheng et al., 2002).

DISCUSSION

Our results indicate a robust signal in somatosensory cortex to mechanical and painful stimuli can be measured. However, the temporal and spatial characteristics of the hemodynamic responses to these two stimuli are markedly different from each other and in alignment with previous fMRI results (Becerra et al., 2001; Chen et al., 2002). Furthermore, a positive change in frontal areas to brush stimuli but an early negative change to heat stimuli was also observed. Collectively, these results might indicate that it is possible to discern differences in the pattern of activation between painful and non-painful stimuli based on the spatial and temporal characteristics utilizing DOT.

Activation in the Somatosensory Region

Studies of sensorimotor cortical activation following innocuous stimulation have reported both unilateral (Hoshiyama et al. 1997; Suzuki et al. 2004) as well as bilateral SI activation (Jantsch et al. 2005; Nihashi et al. 2005; Sutherland and Tang 2006). Furthermore, some studies indicate bilateral activation with a prominent component contralateral to the stimulus (Hansson and Brismar 1999; Franceschini et al. 2003) while others have found inhibition of ipsilateral activation (Hlushchuk and Hari, 2006). Taken together, these results seem to indicate that contralateral activation is routinely detected while concomitant ipsilateral is not sought, is activated at a lower level, or even suppressed. Several of these were carried out with electrical stimulation of a main nerve (Hoshiyama et al. 1997; Suzuki et al. 2004; Nihashi et al. 2005; Sutherland and Tang 2006). As a result, multiple fiber subtypes (innocuous and noxious

specific subtypes) are stimulated and the observed responses may include nociceptive-related activation.

Our results, however, point to a robust activation to a pure dynamic mechanical stimulation with no noxious component on both hemispheres with a larger response contralateral to the stimulated side. These results seem to validate studies employing electrical stimulation as non-painful sensory with a significant contralateral activation and a weaker ipsilateral response.

Activation in primary somatosensory cortex to pain has not been consistently observed with fMRI (Bushnell et al. 1999). Potential reasons are cognitive modulation, inhibitory processes, and experimental differences (Bushnell et al. 1999). In studies reporting activation in the somatosensory cortex, pain produces activation mainly contralateral to the stimulated side as detected by several imaging modalities (for a review, see (Apkarian et al. 2005)). Other pain studies using fMRI have also reported bilateral activation following unilateral stimulation (Tracey et al. 2000; Derbyshire et al. 2004; Wager et al. 2004). In addition, a clinical fMRI study found bilateral representation in the somatosensory cortex (Fabri et al. 2006) and contact heat produces bilateral evoked potentials in humans (Chen et al. 2006). In fMRI studies in subjects with chronic pain (allodynia due to complex regional pain syndrome), only contralateral activation of SI was observed (Maihofner et al. 2006) which may be due to inhibitory processes affecting the ipsilateral cortex or a methodological issue. One implication of our study is to determine measures in chronic pain patients using DOT since the lack of bilateral activation may provide a useful clinical marker that may reverse with optimal treatment.

We are unaware of any reports of brain activation following pain with DOT in adults. There are a few reports of cortical pain responses in human newborns (Bartocci et al. 2006; Slater et al. 2006) where pain was induced as a result of routine clinical procedures (e.g., venipunctures). Consistent bilateral activation was reported in one study (Bartocci et al. 2006), while the other (Slater et al. 2006) found inconsistent ipsilateral activation. The differences may be attributed to technical issues as well as experimental differences between both studies (Bartocci et al., studied subjects that underwent venipuncture in the hand (Bartocci et al. 2006) while Slater et al. studied subjects undergoing heel sticks (lancet) (Slater et al. 2006)). In non-human primate studies intrinsic optical signals were used to evaluate pain responses in anesthetized squirrel monkeys (Tommerdahl et al., 1998). Painful stimuli that were produced using a contact thermode with temperatures ranging from 48–52°C on the palmar surface of the contralateral hand resulted in a large amplitude reflectance decrease in somatosensory area 3a which was subsequently confirmed by anatomical cytoarchitectural microscopic evaluation in serially sectioned brain slices.

Basis for Bilateral Sensory Pathway Activation—Aside from the functional data for human activation indicating bilateral activation in the SI cortex, other studies have indicated specific pathways that may provide a basis for these. Such pathways may be direct, such as the spino-thalamic cortical pathway (Dong et al. 1978; Burstein et al. 1996; Willis and Westlund 1997) and others may be indirect, such as cortico-cortical pathways or cortical-subcortical pathways. ‘Bilateral’ representation at the level of the cortex may also be due to bilateral receptive fields terminating in the spinal cord or brainstem.

Projections from the spinothalmaic tract originating in laminae 7–10 have bilateral receptive fields and respond to a variety of cutaneous stimuli (Hodge and Apkarian 1990) the termination of these is predominantly in the lateral and medial thalamus and smaller projections to the intralaminar nuclei. The lateral thalamus has a significant projection to the SI cortex. One imaging study suggests the predominant response to noxious pain stimulation is the contralateral thalamus (lateral thalamus) and SI showed contralateral biasing of activation in

response to the stimulus (Bingel et al. 2003). However, other study suggests that nociceptive information reaches distinct thalamic subnuclei eliciting a bilateral cortical response (Tsuji et al. 2006). Interhemispheric connections of the primary somatosensory cortex are reported in rodents and monkeys (Iwamura et al. 1994; Krubitzer et al. 1998). In support of an interhemispheric transfer of sensory information, neurons with bilateral receptive fields of the hands in monkeys, were not present following contralateral lesioning of the postcentral gyrus (Iwamura et al. 1994). In addition to pain, tactile stimulation of the hand results in bilateral SI activation (Hansson and Brismar 1999); this was around 20% less than the contraleral effect, which was similar to that observed in our study for brush stimuli. Anatomical studies of corpus callosum connections indicated relatively sparse connections for the glabarous hand and foot compared with the face and trunk (Killackey et al. 1983). Thus, in humans multiple pathways for noxious information may exist that activate bilateral regions in the cortex (Tsuji et al. 2006).

Temporal Characteristics of Activation—As depicted in Figures 3A and 3B, the hemodynamic response to heat is double peaked compared to the brush response. The early peak in the heat respond resembles the brush response, this could be explained in part as a consequence of the experimental procedure; the thermode was lowered on the hand during stimulation, hence, a sensory (touch) component was present in addition to a thermal one. The second peak might reflect the sensation of pain; there are several lines of evidence to support this: experiments to determine heat pain discrimination found that heat pain tends to summate over time (Oshiro et al. 2007) accordingly a late response in S1 is expected. Becerra et al. (2001) reported responses to a similar painful stimulus and to a non-noxious thermal stimulus (Becerra et al. 2001), the innocuous stimulus produced only one early peak in the hemodynamic response while the noxious heat produced two, these results suggested that the late peak was uniquely associated with pain. Chen et al. (2002) recorded pain perceptions for painful heat stimulation, they also reported a biphasic noxious heat response with fMRI and found good correlation of pain perception and late activation in S1 (Chen et al. 2002).

It is also possible to ascribe in part the biphasic pain response to the recruitment of emotional/cognitive brain structures since expectation, anxiety, aversion play an important role in pain (ref). Such recruitment should also be observed directly in cognitive structures (frontal regions) and were detected in these experiments (see below). Subcortical emotional regions are not observable with DOT and hence cannot be discussed here.

Activation in the Frontal Region

In this study we observed significant activation in the frontal regions of the brain. Activation in this study was bilateral to brush and predominantly ipsilateral to the pain stimulus. Frontal lobe function in pain is considered to be important in cognitive and emotional processing (Lorenz et al., 2003), including the preparatory processing in sensorimotor function (Bonnard et al., 2004) and the placebo response (Wager et al., 2004). Postoperative use of transcranial stimulation over this area reduces the requirement of opioids analgesics (Borckardt et al., 2006). It is thus involve in both pain processing and pain modulation. In this study, the location of the probes measured changes in the dorsal and lateral prefrontal cortex (DLPC). Functional and other imaging studies of pain have suggested an important role of this area of the brain in both acute (Svensson et al., 1997; Becerra et al., 1999; Becerra et al., 2001) and chronic pain conditions (Grachev et al., 2000; Apkarian et al., 2004). A number of projections that are received by the prefrontal cortex originate in visual, auditory, parietal and cingulate regions, as well as subcortical regions such as the amygdala (Barbas, 2000) and hypothalamus (Rempel-Clower and Barbas, 1998). In addition frontal lobe sends inputs to subcortical (Shibata and Naito, 2005) and brainstem nuclei, particularly the periaqueductal gray (Hardy and Haigler,

1985). Of note, however, is that the ventral and medial prefrontal regions seem to contribute to this more so than lateral prefrontal regions.

The prefrontal cortex is also involved in analgesia, both placebo induced (Wager et al., 2004), and control over pain (Wiech et al., 2006). Finally, in fMRI studies of analgesics, including morphine, a decrease signal changes on prefrontal regions (Becerra et al., 2006) and anesthetic such as propofol produce similar decreases in the frontal regions (Kaisti et al., 2002).

Frontal activation was found to have a different valence for brush (positive) and heat (negative) stimuli, similar results have been found in fMRI experiments (Becerra et al, 2001;). This may reflect the contribution of the region to interpreting neutral/pleasant vs. unpleasant stimuli. Its negative change might indicate inhibitory processing taking place as it has been demonstrated with optical imaging (Devor et al., 2007). Taken together with the activation observed in the sensory cortex, the use of DOT allows for the measures of both sensory and emotional components of pain.

CONCLUSIONS

DOT may provide a useful objective measure of pain in a number of clinical conditions including the response to analgesics, the response in patients who cannot communicate (e.g., during surgery for analgesic efficacy while under anesthesia), neonatal/pediatric patients, or patients who are unable to communicate (e.g., coma, stroke). Since DOT measures neural activity in cortical regions with known function, the ability to measure changes in response to pain may provide a mobile, relatively cheap, accessible method for objective measures of pain rather than rely on clinical evaluation of a patient's response to pain (e.g., physiological response in the operating room). A multicortical measure allows sensory-motor (e.g,. SI, MI and premotor cortex) and non-sensory (e.g., dorsolateral prefrontal cortex) systems to be evaluated in the context of useful measure to determine the effects of analgesic and anesthetics on blockade of a painful stimulus.

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References

Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005;9:463–84. [PubMed: 15979027]

Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, Gitelman DR. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci 2004;24:10410–5. [PubMed: 15548656]

Apkarian AV, Darbar A, Krauss BR, Gelnar PA, Szeverenyi NM. Differentiating cortical areas related to pain perception from stimulus identification: temporal analysis of fMRI activity. J Neurophysiol 1999;81:2956–63. [PubMed: 10368412]

Barbas H. Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. Brain Res Bull 2000;52:319–30. [PubMed: 10922509]

Bartocci M, Bergqvist LL, Lagercrantz H, Anand KJ. Pain activates cortical areas in the preterm newborn brain. Pain 2006;122:109–17. [PubMed: 16530965]

Becerra L, Morris S, Bazes S, Gostic R, Sherman S, Gostic J, Pendse G, Moulton E, Scrivani S, Keith D, Chizh B, Borsook D. Trigeminal neuropathic pain alters responses in CNS circuits to mechanical (brush) and thermal (cold and heat) stimuli. J Neurosci 2006;26:10646–57. [PubMed: 17050704]

Becerra L, Breiter HC, Wise R, Gonzalez RG, Borsook D. Reward circuitry activation by noxious thermal stimuli. Neuron 2001;32:927–46. [PubMed: 11738036]

Becerra LR, Breiter HC, Stojanovic M, Fishman S, Edwards A, Comite AR, Gonzalez RG, Borsook D. Human brain activation under controlled thermal stimulation and habituation to noxious heat: an fMRI study. Magn Reson Med 1999;41:1044–57. [PubMed: 10332889]

Beckmann CF, Jenkinson M, Smith SM. General multilevel linear modeling for group analysis in FMRI. Neuroimage 2003;20:1052–63. [PubMed: 14568475]

Bingel U, Quante M, Knab R, Bromm B, Weiller C, Buchel C. Single trial fMRI reveals significant contralateral bias in responses to laser pain within thalamus and somatosensory cortices. Neuroimage 2003;18:740–8. [PubMed: 12667851]

Bonnard M, de Graaf J, Pailhous J. Interactions between cognitive and sensorimotor functions in the motor cortex: evidence from the preparatory motor sets anticipating a perturbation. Rev Neurosci 2004;15:371–82. [PubMed: 15575492]

Borckardt JJ, Weinstein M, Reeves ST, Kozel FA, Nahas Z, Smith AR, Byrne TK, Morgan K, George MS. Postoperative left prefrontal repetitive transcranial magnetic stimulation reduces patient-controlled analgesia use. Anesthesiology 2006;105:557–62. [PubMed: 16931989]

Burstein R, Falkowsky O, Borsook D, Strassman A. Distinct lateral and medial projections of the spinohypothalamic tract of the rat. J Comp Neurol 1996;373:549–74. [PubMed: 8889944]

Bushnell MC, Duncan GH, Hofbauer RK, Ha B, Chen JI, Carrier B. Pain perception: is there a role for primary somatosensory cortex? Proc Natl Acad Sci U S A 1999;96:7705–9. [PubMed: 10393884]

Chen IA, Hung SW, Chen YH, Lim SN, Tsai YT, Hsiao CL, Hsieh HY, Wu T. Contact heat evoked potentials in normal subjects. Acta Neurol Taiwan 2006;15:184–91. [PubMed: 16995598]

Chen JI, Ha B, Bushnell MC, Pike B, Duncan GH. Differentiating noxious- and innocuous-related activation of human somatosensory cortices using temporal analysis of fMRI. J Neurophysiol 2002;88:464–74. [PubMed: 12091568]

Coghill RC, Sang CN, Maisog JM, Iadarola MJ. Pain intensity processing within the human brain: a bilateral, distributed mechanism. J Neurophysiol 1999;82:1934–43. [PubMed: 10515983]

Davis KD, Wood ML, Crawley AP, Mikulis DJ. fMRI of human somatosensory and cingulate cortex during painful electrical nerve stimulation. Neuroreport 1995;7:321–5. [PubMed: 8742480]

Derbyshire SW, Whalley MG, Stenger VA, Oakley DA. Cerebral activation during hypnotically induced and imagined pain. Neuroimage 2004;23:392–401. [PubMed: 15325387]

Devor A, Tian P, Nishimura N, Teng IC, Hillman EM, Narayanan SN, Ulbert I, Boas DA, Kleinfeld D, Dale AM. Suppressed neuronal activity and concurrent arteriolar vasoconstriction may explain negative blood oxygenation level-dependent signal. J Neurosci 2007;27:4452–9. [PubMed: 17442830]

Dong WK, Ryu H, Wagman IH. Nociceptive responses of neurons in medial thalamus and their relationship to spinothalamic pathways. J Neurophysiol 1978;41:1592–1613. [PubMed: 731292]

Fabri M, Polonara G, Mascioli G, Paggi A, Salvolini U, Manzoni T. Contribution of the corpus callosum to bilateral representation of the trunk midline in the human brain: an fMRI study of callosotomized patients. Eur J Neurosci 2006;23:3139–48. [PubMed: 16820004]

Franceschini MA, Fantini S, Thompson JH, Culver JP, Boas DA. Hemodynamic evoked response of the sensorimotor cortex measured noninvasively with near-infrared optical imaging. Psychophysiology 2003;40:548–60. [PubMed: 14570163]

Franceschini MA, Joseph DK, Huppert TJ, Diamond SG, Boas DA. Diffuse optical imaging of the whole head. J Biomed Opt 2006;11:054007. [PubMed: 17092156]

Grachev ID, Fredrickson BE, Apkarian AV. Abnormal brain chemistry in chronic back pain: an in vivo proton magnetic resonance spectroscopy study. Pain 2000;89:7–18. [PubMed: 11113288]

Hansson T, Brismar T. Tactile stimulation of the hand causes bilateral cortical activation: a functional magnetic resonance study in humans. Neurosci Lett 1999;271:29–32. [PubMed: 10471206]

Hardy SG, Haigler HJ. Prefrontal influences upon the midbrain: a possible route for pain modulation. Brain Res 1985;339:285–93. [PubMed: 4027627]

Hlushchuk Y, Hari R. Transient suppression of ipsilateral primary somatosensory cortex during tactile finger stimulation. J Neurosci 2006;26:5819–24. [PubMed: 16723540]

Hodge CJ Jr, Apkarian AV. The spinothalamic tract. Crit Rev Neurobiol 1990;5:363–97. [PubMed: 2204486]

Hoshiyama M, Kakigi R, Koyama S, Watanabe S, Shimojo M. Activity in posterior parietal cortex following somatosensory stimulation in man: magnetoencephalographic study using spatio-temporal source analysis. Brain Topogr 1997;10:23–30. [PubMed: 9358951]

Iwamura Y, Iriki A, Tanaka M. Bilateral hand representation in the postcentral somatosensory cortex. Nature 1994;369:554–6. [PubMed: 8202155]

Jantsch HH, Kemppainen P, Ringler R, Handwerker HO, Forster C. Cortical representation of experimental tooth pain in humans. Pain 2005;118:390–9. [PubMed: 16289801]

Jones AK, Brown WD, Friston KJ, Qi LY, Frackowiak RS. Cortical and subcortical localization of response to pain in man using positron emission tomography. Proc Biol Sci 1991;244:39–44. [PubMed: 1677194]

Kaisti KK, Metsähonkala L, Teräs M, Oikonen V, Aalto S, Jääskeläinen S, Hinkka S, Scheinin H. Effects of surgical levels of propofol and sevoflurane anesthesia on cerebral blood flow in healthy subjects studied with positron emission tomography. Anesthesiology 2002;96:1358–70. [PubMed: 12170048]

Killackey HP, Gould HJ 3rd, Cusick CG, Pons TP, Kaas JH. The relation of corpus callosum connections to architectonic fields and body surface maps in sensorimotor cortex of new and old world monkeys. J Comp Neurol 1983;219:384–419. [PubMed: 6643713]

Krubitzer L, Clarey JC, Tweedale R, Calford MB. Interhemispheric connections of somatosensory cortex in the flying fox. J Comp Neurol 1998;402:538–59. [PubMed: 9862325]

Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. Brain 2003;126:1079–91. [PubMed: 12690048]

Lorenz J, Cross D, Minoshima S, Morrow T, Paulson P, Casey K. A unique representation of heat allodynia in the human brain. Neuron 2002;35:383–93. [PubMed: 12160755]

Maihofner C, Handwerker HO, Birklein F. Functional imaging of allodynia in complex regional pain syndrome. Neurology 2006;66:711–7. [PubMed: 16534108]

Maihöfner C, Schmelz M, Forster C, Neundörfer B, Handwerker HO. Neural activation during experimental allodynia: a functional magnetic resonance imaging study. Eur J Neurosci 2004;19:3211–8. [PubMed: 15217377]

Nihashi T, Naganawa S, Sato C, Kawai H, Nakamura T, Fukatsu H, Ishigaki T, Aoki I. Contralateral and ipsilateral responses in primary somatosensory cortex following electrical median nerve stimulation--an fMRI study. Clin Neurophysiol 2005;116:842–8. [PubMed: 15792893]

Oshiro Y, Quevedo AS, McHaffie JG, Kraft RA, Coghill RC. Brain mechanisms supporting spatial discrimination of pain. J Neurosci 2007;27:3388–94. [PubMed: 17392455]

Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiol Clin 2000;30:263–88. [PubMed: 11126640]

Rempel-Clower NL, Barbas H. Topographic organization of connections between the hypothalamus and prefrontal cortex in the rhesus monkey. J Comp Neurol 1998;398:393–419. [PubMed: 9714151]

Shibata H, Naito J. Organization of anterior cingulate and frontal cortical projections to the anterior and laterodorsal thalamic nuclei in the rat. Brain Res 2005;1059:93–103. [PubMed: 16157311]

Slater R, Cantarella A, Gallella S, Worley A, Boyd S, Meek J, Fitzgerald M. Cortical pain responses in human infants. J Neurosci 2006;26:3662–6. [PubMed: 16597720]

Sutherland MT, Tang AC. Reliable detection of bilateral activation in human primary somatosensory cortex by unilateral median nerve stimulation. Neuroimage 2006;33:1042–54. [PubMed: 16997579]

Suzuki T, Shibukawa Y, Kumai T, Shintani M. Face area representation of primary somatosensory cortex in humans identified by whole-head magnetoencephalography. Jpn J Physiol 2004;54:161–9. [PubMed: 15182423]

Svensson P, Minoshima S, Beydoun A, Morrow TJ, Casey KL. Cerebral processing of acute skin and muscle pain in humans. J Neurophysiol 1997;78:450–60. [PubMed: 9242293]

Talbot JD, Marrett S, Evans AC, Meyer E, Bushnell MC, Duncan GH. Multiple representations of pain in human cerebral cortex. Science 1991;251:1355–8. [PubMed: 2003220]

Tommerdahl M, Delemos KA, Favorov OV, Metz CB, Vierck CJ Jr, Whitsel BL. Response of anterior parietal cortex to different modes of same-site skin stimulation. J Neurophysiol 1998;80:3272–83. [PubMed: 9862921]

Tracey I, Becerra L, Chang I, Breiter H, Jenkins L, Borsook D, Gonzalez RG. Noxious hot and cold stimulation produce common patterns of brain activation in humans: a functional magnetic resonance imaging study. Neurosci Lett 2000;288:159–62. [PubMed: 10876085]

Tsuji T, Inui K, Kojima S, Kakigi R. Multiple pathways for noxious information in the human spinal cord. Pain 2006;123:322–31. [PubMed: 16644130]

Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD. Placebo-induced changes in FMRI in the anticipation and experience of pain. Science 2004;303:1162–7. [PubMed: 14976306]

Wiech K, Kalisch R, Weiskopf N, Pleger B, Stephan KE, Dolan RJ. Anterolateral prefrontal cortex mediates the analgesic effect of expected and perceived control over pain. J Neurosci 2006;26:11501–9. [PubMed: 17079679]

Wilcox T, Bortfeld H, Woods R, Wruck E, Boas DA. Using near-infrared spectroscopy to assess neural activation during object processing in infants. J Biomed Opt 2005;10:11010. [PubMed: 15847576]

Willis WD, Westlund KN. Neuroanatomy of the pain system and of the pathways that modulate pain. J Clin Neurophysiol 1997;14:2–31. [PubMed: 9013357]

Witting N, Kupers RC, Svensson P, Jensen TS. A PET activation study of brush-evoked allodynia in patients with nerve injury pain. Pain 2006;120:145–54. [PubMed: 16368192]

Zhang Q, Brukilacchio TJ, Li A, Stott JJ, Chaves T, Hillman E, Wu T, Chorlton M, Rafferty E, Moore RH, Kopans DB, Boas DA. Coregistered tomographic x-ray and optical breast imaging: initial results. J Biomed Opt 2005;10:024033. [PubMed: 15910106]

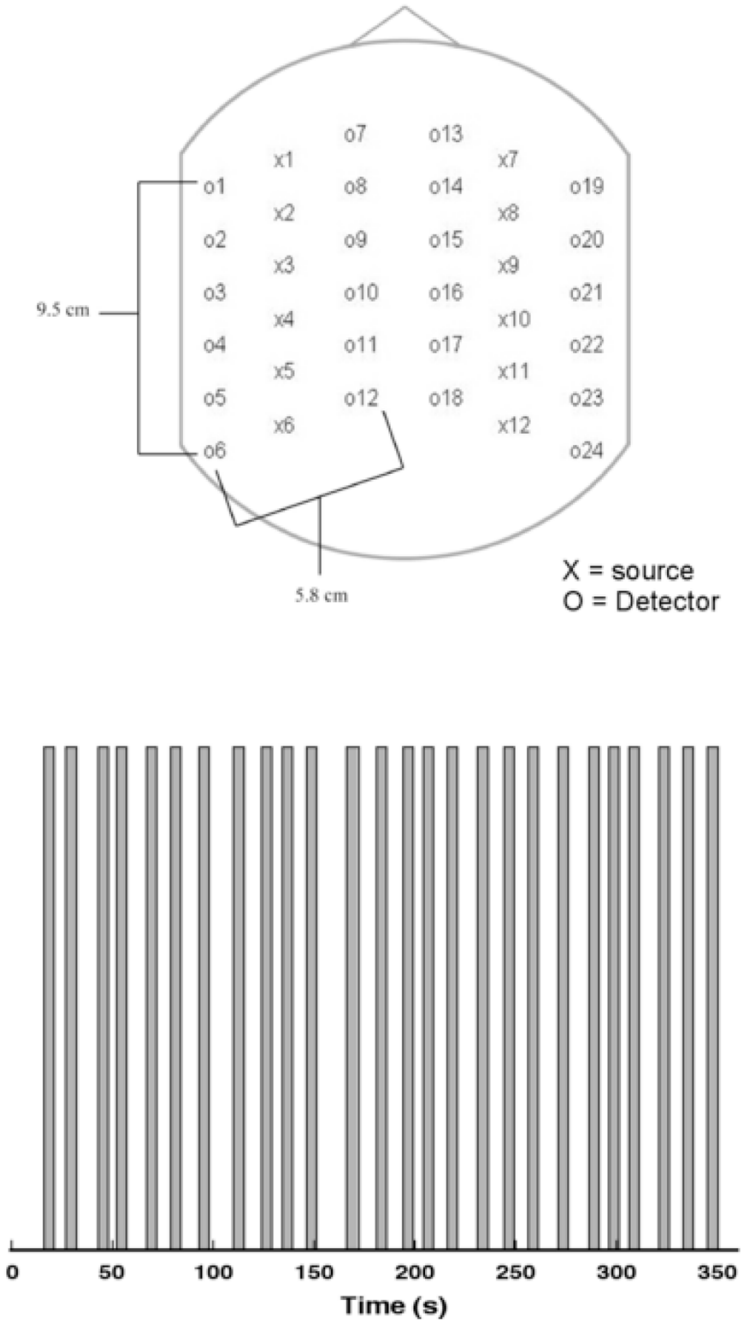

Figure 1. Experimental setup

(A) Localization of source and detectors utilized to measure DOT signals in frontal and sensory cortices. (B) Brush and heat scans consisted of 26 stimuli, with jittered interstimulus intervals (ISI) of 6–13 s with an average ISI of 8.5 s. Stimuli were applied for 5 s. See text.

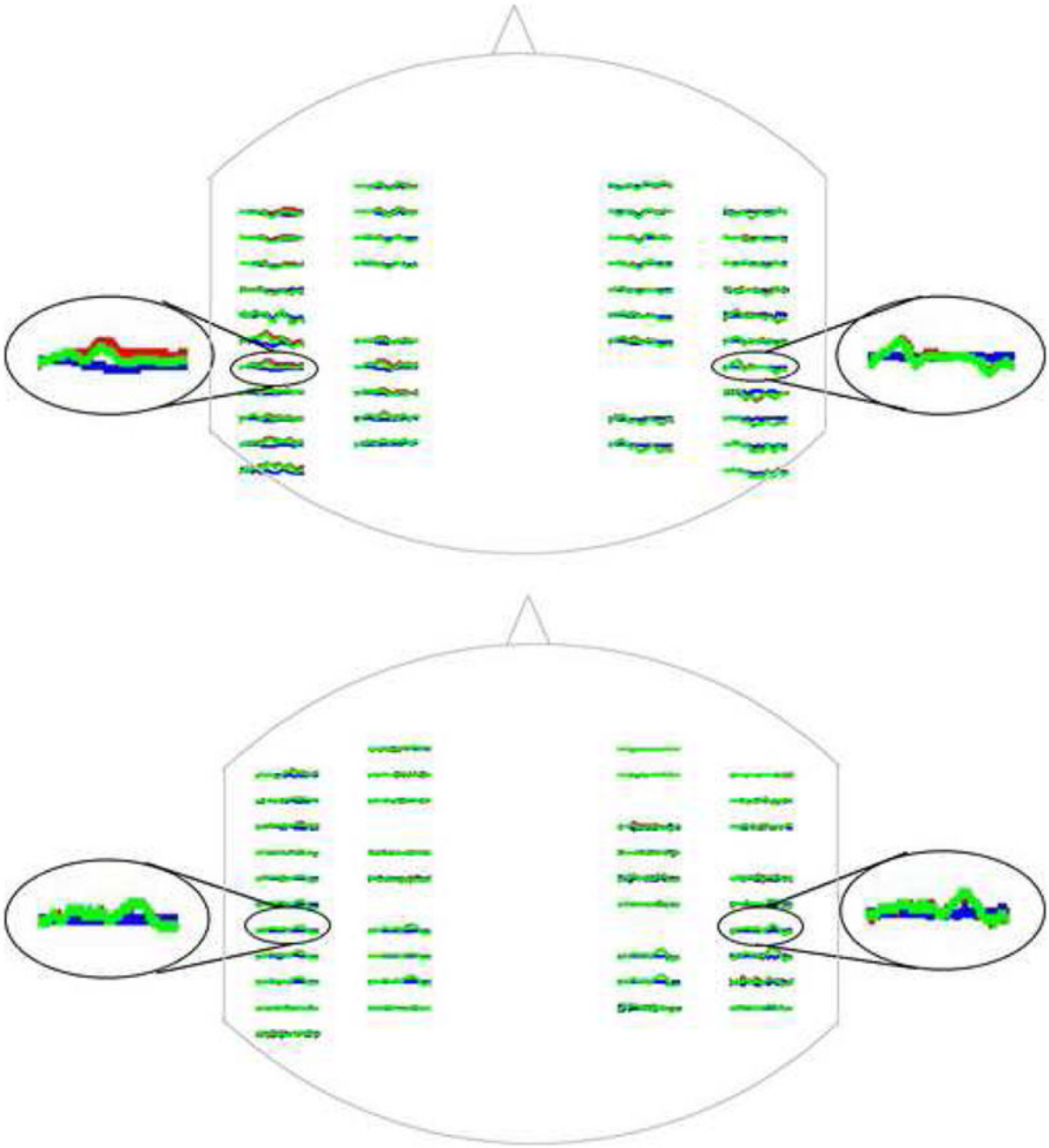

Figure 2. Average detectors responses for Brush (A) and Heat (B) stimulation for one subject
Detectors positioned over the sensorymotor cortex are highlighted depicting oxyhemoglobin (red) deoxyhemoglobin (blue) and total (green) hemodynamic changes. Responses have been processed to remove artifacts and correlates of no interest. See text.

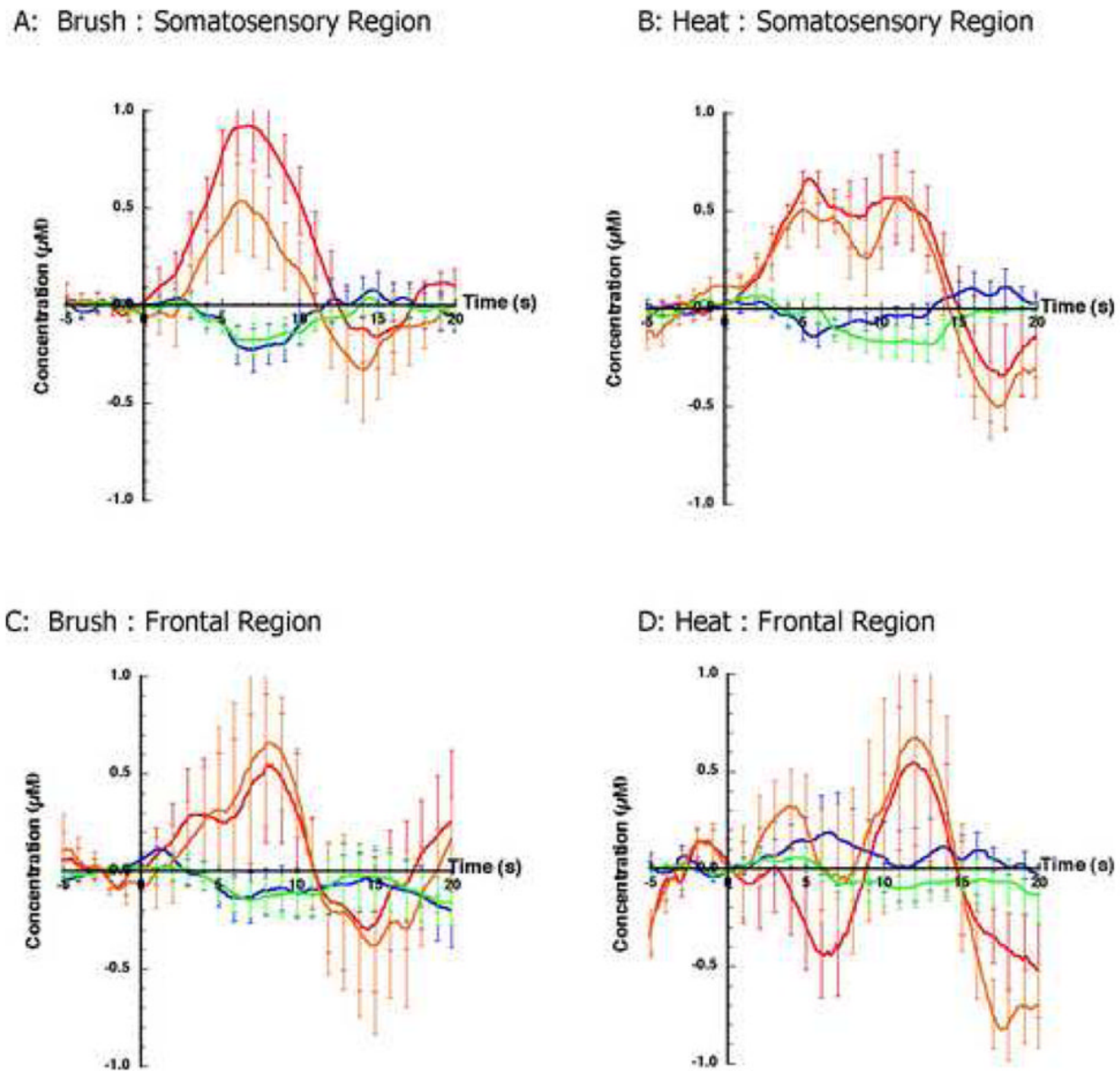

Figure 3. Average response across subjects

Responses to Brush (A) and Heat (B) stimulation in S1 Cortex Region: Brush produced a larger contralateral response than the ipsilateral side. Thermal stimulation produced a biphasic bilateral response, observed also in fMRI studies

Responses to Brush (C) and Heat (D) in Frontal Cortex Region: Bilateral activation to brush was observed while Heat produced a negative contralateral response. See text. Key: HbO: contralateral:red, ipsilateral: orange; Hb: contralateral: blue, ipsilateral: green.

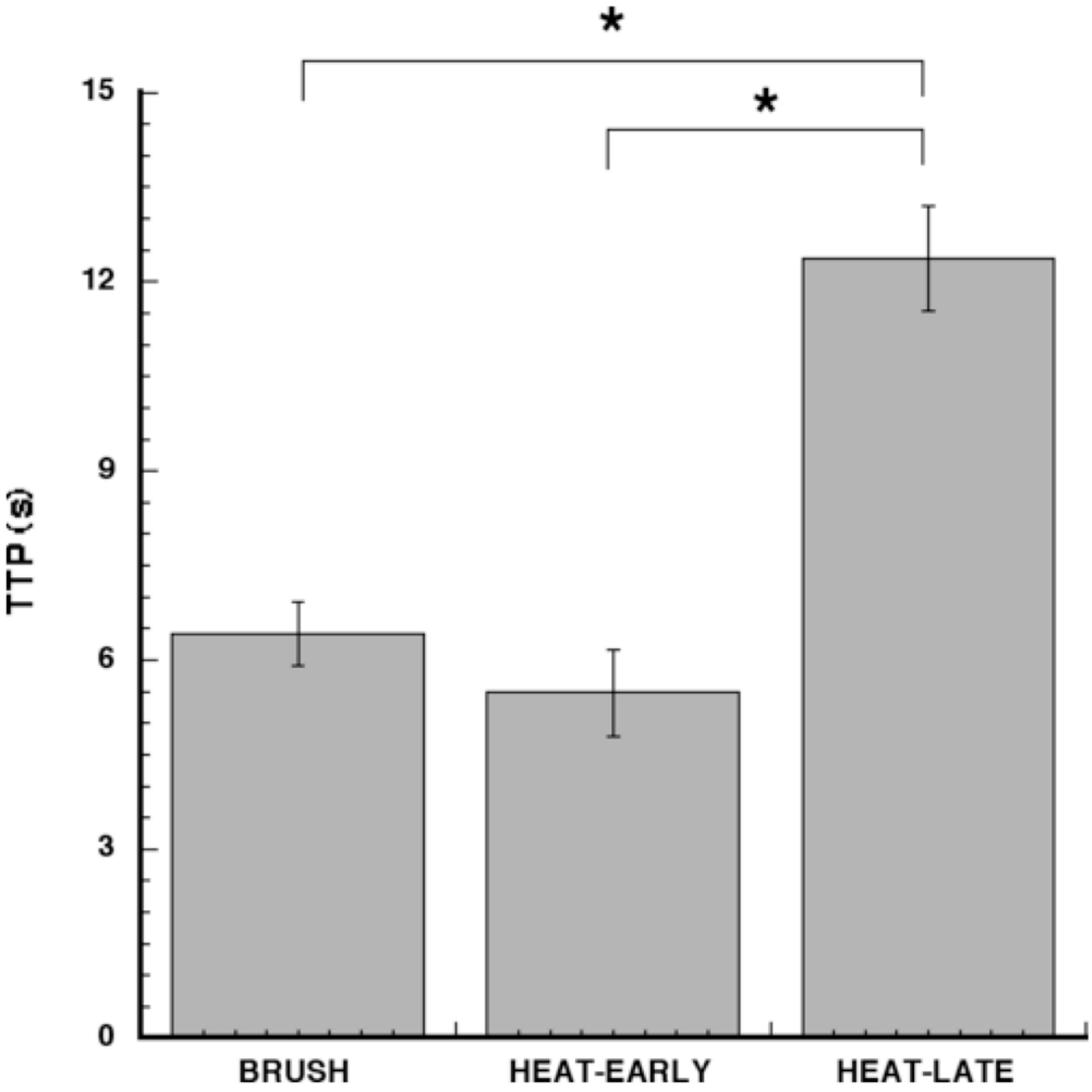

Figure 4. Time-to-Peak

Time to peak from non-linear fits results in a similar TTP for brush and heat early response. The second, late heat response is significantly delayed. See text.