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Diffuse optical tomography of pain and tactile stimulation: Activation in cortical sensory and emotional systems ☆

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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 double peak similar to results that 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 using 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 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 was 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 (Lorenz et al., 2002); and the placebo response (Wager et al., 2004). In disease (chronic pain), frontal regions have altered acti-

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vation 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 using 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

Nine 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, 690 nm and 830 nm. 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 (Fig. 1A). Source fibers emitting the 690-nm wavelength were paired-off with those emitting the 830-nm 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.

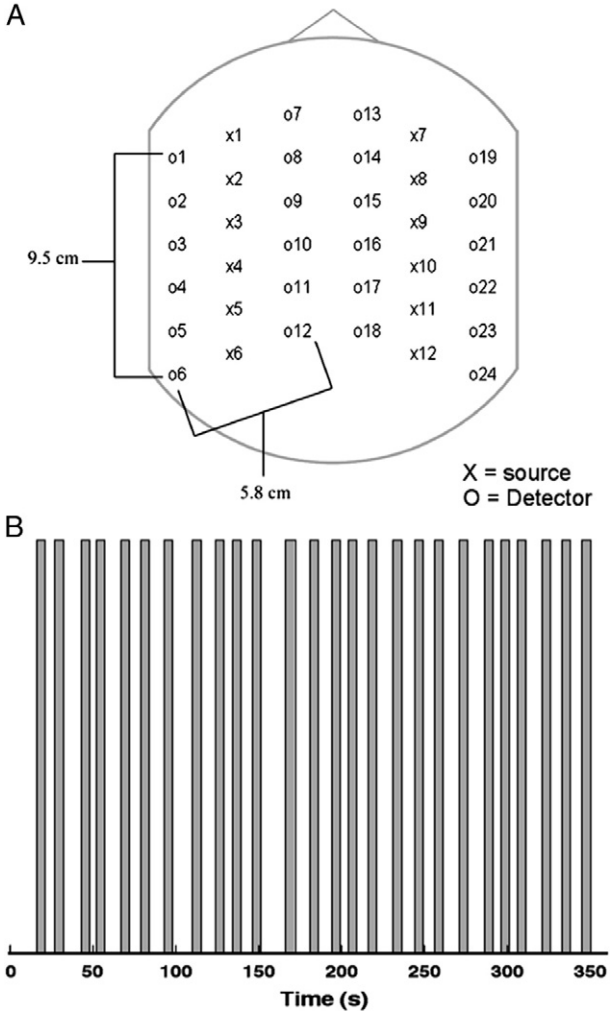

Fig. 1. Experimental setup. (A) Localization of source and detectors used to measure DOT signals in frontal and sensory cortices. (B) Brush and heat scans consisted of 26 stimuli, with jittered inter-stimulus intervals (ISI) of 6–13 s with an average ISI of 8.5 s. Stimuli were applied for 5 s. See text.

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 used 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 lb. For both brush and heat, the paradigm consisted of 26 stimuli of 5-s duration over 6 minutes with a jittered inter-stimulus interval (ISI) of 6–13 s and average ISI of 8.5 s (Fig. 1B). The paradigm was applied twice for