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The primary somatosensory cortex largely contributes to the early part of the cortical response elicited by nociceptive stimuli

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ABSTRACT

Research on the cortical sources of nociceptive laser-evoked brain potentials (LEPs) began almost two decades ago (Tarkka and Treede, 1993). Whereas there is a large consensus on the sources of the late part of the LEP waveform (N2 and P2 waves), the relative contribution of the primary somatosensory cortex (S1) to the early part of the LEP waveform (N1 wave) is still debated.

To address this issue we recorded LEPs elicited by the stimulation of four limbs in a large population (n = 35). Early LEP generators were estimated both at single-subject and group level, using three different approaches: distributed source analysis, dipolar source modeling, and probabilistic independent component analysis (ICA). We show that the scalp distribution of the earliest LEP response to hand stimulation was maximal over the central-parietal electrodes *contralateral* to the stimulated side, while that of the earliest LEP response to foot stimulation was maximal over the central-parietal *midline* electrodes. Crucially, all three approaches indicated hand and foot S1 areas as generators of the earliest LEP response.

Altogether, these findings indicate that the earliest part of the scalp response elicited by a selective nociceptive stimulus is largely explained by activity in the contralateral S1, with negligible contribution from the secondary somatosensory cortex (S2).

Introduction

Brief laser heat pulses selectively excite Aδ- and C-fiber epidermal free nerve endings (Bromm and Treede, 1984). Such stimuli elicit a number of transient brain responses (laser-evoked potentials, LEPs) in the ongoing electroencephalogram (EEG) (Carmon et al., 1976; Mouraux et al., 2003). These responses are mediated by the activation of type-II Aδ mechano-heat nociceptors (II-AMH) (Treede, 1995) and spinothalamic neurons in the anterolateral quadrant of the spinal cord (Treede, 2003). LEPs consist of a number of deflections. The largest of these deflections form a negative–positive complex (N2–P2), peaking at approximately 200–350 ms when stimulating the hand dorsum and maximal at the scalp vertex (Bromm and Treede, 1984). This complex is preceded by a smaller negative deflection (N1) peaking at approximately 160 ms when stimulating the hand dorsum and maximal over the central-temporal region contralateral to the stimulated side (Tarkka and Treede, 1993). Although Aδ-related LEPs are widely used to investigate the peripheral and central processing of nociceptive sensory input (Iannetti et al., 2003; Treede et al., 2003), and are currently considered the best available diagnostic tool to assess the function of Aδ nociceptive pathways in patients (Haanpaa et al., 2011), a full understanding of their functional significance remains to be achieved.

A crucial step in this direction is a compelling description of the cortical sources underlying the earliest part of the LEP response. Indeed, while there is converging evidence from dipolar modeling of both scalp and subdural recordings, as well as from direct intracranial recordings, that the bilateral operculoinsular cortex and the cingulate cortex generate, albeit with different contributions, the late-latency N2 and P2 waves (Frot and Mauguiere, 2003; Frot et al., 2007, 2008; Kakigi et al., 1995; Kanda et al., 2000; Perchet et al., 2008; Tarkka and Treede, 1993; Valeriani et al., 1996, 2000; Vogel et al., 2003), the contribution of the controlateral primary somatosensory cortex (S1) to the early latency N1 wave is much debated. In their seminal study, Tarkka and Treede (1993) indicated that the N1 wave was generated by concomitantly active sources in both the contralateral S1 and the bilateral S2. However, most of the subsequent source analysis studies proposed dipolar modeling solutions that either did not include an S1

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source or did not observe an improvement of the fitting when an S1 source was included in the model (Bentley et al., 2001; Bromm and Chen, 1995; Nakamura et al., 2002; Schlereth et al., 2003; Valeriani et al., 1996, 2000, 2004). This has led some authors to conclude that the parasylvian region, rather than S1, was the earliest cortical structure to respond to nociceptive input in humans (Treede et al., 2000), while others considered that the absence of S1 activation could be only apparent, and due to a combination of technical and physiological factors (e.g., Kakigi et al., 1995). Thus, it is still unclear if and how much S1 contributes to the early part of the cortical response elicited by nociceptive stimuli. This issue is an important one, as the N1 wave of the LEPs has been recently demonstrated to represent somatosensory specific activities maximally reflecting the incoming nociceptive input (Lee et al., 2009; Mouraux and Iannetti, 2009) and to present theoretical advantages for clinical application, such as its lower sensitivity to attention and vigilance as compared to the later vertex complex (Cruccu et al., 2008; Garcia-Larrea et al., 1997).

In the present study we aimed to solve this issue conclusively, by recording 64-channel LEPs elicited by the stimulation of the four limbs, in a large population of healthy volunteers ($n = 35$). In order to compensate for the limited spatial resolution of the techniques used to infer the location of the neural sources underlying scalp ERPs, we analyzed the LEP data both at group and single-subject level, using three different source analysis approaches: distributed source analysis, dipolar source modeling, and probabilistic independent component analysis (PICA).

Material and methods

Subjects

EEG data were collected from 35 healthy volunteers (18 females) aged 27 ± 4.5 (mean $\pm$ SD, range = 22 to 41 years). The present data were collected within a project aiming to investigate the placebo effect (Chakrabarti et al., 2010). All participants gave their written informed consent and were paid for their participation. The local ethics committee approved the procedures.

Nociceptive stimulation

Radiant-heat stimuli were generated by an infrared neodymium yttrium aluminum perovskite (Nd:YAP) laser with a wavelength of 1.34 μm (Electronical Engineering, Italy). Laser pulses activate directly nociceptive terminals in the most superficial skin layers (Baumgartner et al., 2005; Iannetti et al., 2006). Laser pulses were directed at the dorsum of both left and right hand and foot, on a squared area (5×5 cm) defined prior to the beginning of the experimental session. A He–Ne laser pointed to the area to be stimulated. The laser pulse was transmitted via an optic fiber and its diameter was set at approximately 6 mm (28 mm^2) by focusing lenses. The pulse duration was 4 ms. One energy of stimulation was used in each of the four conditions. The average energies were as follows: right and left hand, 2.2 ± 0.3 J; right and left foot, 2.3 ± 0.4 J. At these energies laser pulses elicited a clear pinprick pain, related to the activation of Aδ fibers. After each stimulus, the laser beam target was shifted by approximately 1 cm in a random direction, to avoid nociceptor fatigue or sensitization.

Experimental design

Before the recording session the energy of the laser stimulus was individually adjusted using the method of limits (laser step size: 0.25 J), separately for each of the four stimulated territories (left hand, right hand, left foot, right foot), to ensure that the elicited sensation was in the painful range. During this procedure subjects were asked to report the quality and the intensity of the sensation elicited by each laser pulse using a numerical rating scale (0 = no sensation, 1 = low warmth, 2 = moderate warmth, 3 = high warmth, 4 = non painful pinprick, 5 = mild pinprick pain, 6 = moderate pinprick pain, 7 = high pinprick pain, and 8 = unbearable pinprick pain). The energy of laser stimulation needed to achieve a rating of 6 was used throughout the experiment.

Laser-evoked EEG responses were obtained following the stimulation of the dorsum of the right and left hand and foot in four separate blocks, on the same day. The order of the four blocks was balanced across subjects. In each block we delivered 30 laser pulses, using an inter-stimulus interval (ISI) ranging between 5 and 15 s. At the end of each block, participants were asked to rate the intensity of the painful sensation elicited by the laser stimuli using a visual analogue scale ranging from 0 (not painful) to 100 (extremely painful).

EEG recording

Participants were seated in a comfortable chair in a silent, temperature-controlled room. They wore protective goggles and were asked to focus their attention on the stimuli and relax their muscles. The EEG was recorded using 64 Ag–AgCl scalp electrodes placed according to the International 10–20 system, referenced against the nose. Electro-oculographic (EOG) signals were simultaneously recorded using surface electrodes. Signals were amplified and digitized at a sampling rate of 1000 Hz.

EEG data pre-processing

EEG data were processed using EEGLAB (Delorme and Makeig, 2004), an open source toolbox running in the MATLAB environment. Continuous EEG data were band-pass filtered between 1 and 30 Hz. EEG epochs were extracted using a window analysis time of 1500 ms (500 ms pre-stimulus and 1000 ms post-stimulus) and baseline corrected using the pre-stimulus interval. Trials contaminated by eye-blinks and movements were corrected using an Independent Component Analysis (ICA) algorithm (Delorme and Makeig, 2004; Jung et al., 2001; Makeig et al., 1997). In all datasets, these independent components (ICs) had a large EOG channel contribution and a frontal scalp distribution. After ICA and an additional baseline correction (from −500 ms to 0 ms), EEG epochs were re-referenced to a common average reference.

In each subject, epochs belonging to the same experimental condition were averaged, time-locked to the onset of the stimulus. This procedure yielded, in each subject, four average waveforms (one waveform for each experimental condition: left hand, right hand, left foot, right foot). Single-subject average waveforms were subsequently averaged to obtain group-level average waveforms. Group-level scalp topographies were computed by spline interpolation.

Scalp topographies were first plotted at the peak latency of the N2 and P2 LEP waves, measured at the vertex (Cz) (Fig. 1). The N2 wave was defined as the most negative deflection after stimulus onset. The P2 wave was defined as the most positive deflection after stimulus onset. While N2 and P2 peaks were easily identified in all experimental conditions, N1 peaks were easily identified only in the LEP waveforms elicited by hand stimulation, using the recommended Tc–Fz montage (Kunde and Treede, 1993; Treede et al., 2003). For this reason, scalp topographies capturing the N1 activity were plotted, in steps of 10 ms, for the 60 ms time window preceding the N2 peak (hand stimulation: from 140 ms to 200 ms; foot stimulation: from 180 ms to 240 ms) (Fig. 2). This approach allowed defining better the N1 activity across time in each experimental condition.

Source analysis: group level

Group-level average LEP waveforms were imported in Brain Electrical Source Analysis software (BESA 5.3) (Scherg, 1992; Scherg and Berg, 1996). The aim of the source analysis was to (1) estimate the locations of N1 sources from the group-level average waveforms and