NeuroImage 84 (2014) 383–393

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

The primary somatosensory cortex contributes to the latest part of the cortical response elicited by nociceptive somatosensory stimuli in humans

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ARTICLE INFO

Article history:
Accepted 22 August 2013
Available online 31 August 2013

Keywords:
Event-related potentials (ERPs)
Laser-evoked potentials (LEPs)
Nociceptive system
Functional microstate analysis
Primary somatosensory cortex (S1)

ABSTRACT

Nociceptive laser pulses elicit temporally-distinct cortical responses (the N1, N2 and P2 waves of laser-evoked potentials, LEPs) mainly reflecting the activity of the primary somatosensory cortex (S1) contralateral to the stimulated side, and of the bilateral operculoinsular and cingulate cortices. Here, by performing two different EEG experiments and applying a range of analysis approaches (microstate analysis, scalp topography, single-trial estimation), we describe a distinct component in the last part of the human LEP response (P4 wave). We obtained three main results. First, the LEP is reliably decomposed in four main and distinct functional microstates, corresponding to the N1, N2, P2, and P4 waves, regardless of stimulus territory. Second, the scalp and source configurations of the P4 wave follow a clear somatotopical organization, indicating that this response is likely to be partly generated in contralateral S1. Third, single-trial latencies and amplitudes of the P4 are tightly coupled with those of the N1, and are similarly sensitive to experimental manipulations (e.g., to crossing the hands over the body midline), suggesting that the P4 and N1 may have common neural sources. These results indicate that the P4 wave is a clear and distinct LEP component, which should be considered in LEP studies to achieve a comprehensive understanding of the brain response to nociceptive stimulation.

Introduction

The electroencephalographic (EEG) responses elicited by intense laser heat pulses that selectively excite nociceptive free nerve endings in the epidermis (Bromm and Treede, 1984) are widely used to investigate the peripheral and central processing of nociceptive sensory input (Iannetti et al., 2003; Treede et al., 2003). Such laser-evoked potentials (LEPs) are mediated by the activation of type-II Aδ mechano-heat nociceptors (Treede et al., 1995) and spinothalamic neurons in the anterolateral quadrant of the spinal cord (Treede, 2003), and currently represent the best available tool to assess the spinothalamic function in patients (Haanpaa et al., 2011).

LEPs are composed of three main transient responses detected in the time domain (Carmon et al., 1976). The earliest response is a negative wave (N1) maximal over the central–temporal region contralateral to the stimulated side (Treede et al., 1988) and suggested to mainly reflect the activity of the operculoinsular (Garcia-Larrea et al., 2003) and the primary somatosensory cortices contralateral to the stimulated side (Tarkka and Treede, 1993; Valentini et al., 2012). The N1 wave is followed by a biphasic negative–positive complex (N2 and P2 waves) maximal at the scalp vertex (Bromm and Treede, 1984), and largely reflecting the activity of the bilateral operculoinsular and anterior cingulate cortices (Garcia-Larrea et al., 2003).

While the late N2–P2 waves are functionally similar to other vertex potentials elicited by intense stimuli belonging to non-nociceptive sensory modalities (Mouraux and Iannetti, 2009) and largely reflect saliency-related neural processes possibly related to the detection of relevant changes in the sensory environment (Downar et al., 2000), the early contralateral N1 wave reflects somatosensory-specific activity, more related to the magnitude of the incoming nociceptive input (Lee et al., 2009). Thus, the contribution of somatosensory-specific activities is predominant in the early part of the LEP waveform (i.e., the time interval corresponding to the N1 wave and the onset of the N2 wave; Mouraux and Iannetti, 2009). However, when examining carefully the time course of the respective contribution of somatosensory-specific and multimodal EEG activities to the LEP response (e.g., Fig. 3 in Mouraux and Iannetti, 2009), a small but clear contribution of somatosensory-specific activities to the very last part of the LEP is

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http://dx.doi.org/10.1016/j.neuroimage.2013.08.057

evident. Accordingly, a topographical lateralization of the last part of the LEP response is often anecdotally observed.

Here, using data from two different experiments conducted using multi-channel EEG on 32 healthy subjects (20 for Experiment 1 and 12 for Experiment 2), we describe a distinct component in the last part of the LEP waveform, which we labeled P4. The P4 was isolated as a distinct functional microstate in the LEP response elicited by both hand and foot stimulation. Both topographical distribution and source analysis indicate that primary somatosensory areas contribute at least partly to its generation (Experiment 1). Also, the P4 was not affected by the location of the stimulus in external space, but strongly depended on the somatotopical representation of the stimulated territory (Experiment 2). In addition, its latency and amplitude were significantly more related to the N1 than to the N2 and P2 waves (Experiment 1).

Altogether, both experiments provide compelling evidence of a late, somatosensory-specific component (P4 wave) in the human LEPs.

Materials and methods

Experiment 1

Subjects, experimental paradigm and EEG recording

EEG data were collected from 20 healthy subjects (9 females) aged 27.5 ± 4.4 years (mean ± SD). All subjects gave their written informed consent and were paid for their participation. The local ethics committee approved the procedures.

Nociceptive-specific radiant-heat stimuli were generated by an infrared neodymium yttrium aluminium perovskite (Nd:YAP) laser with a wavelength of 1.34 μm (Electronical Engineering, Italy). At this wavelength the 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 right and left hands and feet, on a squared area (5 × 5 cm) defined prior to the beginning of the experimental session. An 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 5 mm (≈20 mm^2) by focusing lenses. The pulse duration was 3 ms. One energy of stimulation was used in each of the four stimulation sites. The group-average energy values were as follows: right and left hands, 2.35 ± 0.32 J and right and left feet, 2.43 ± 0.32 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 increases of baseline skin temperature, and nociceptor fatigue or sensitization.

Before the EEG 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, LH; right hand, RH; left foot, LF; right foot, RF), 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 sensation, 5 = mild pain, 6 = moderate pain, 7 = high pain; 8 = unbearable pain; Valentini et al., 2012). The energy of laser stimulation needed to achieve a rating of 6 was used in the following Experiment 1.

Laser-evoked EEG responses were obtained following the stimulation of the dorsum of the right and left hands and feet 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, subjects were asked to rate the intensity of the painful sensation elicited by the laser stimuli using a visual analog scale ranging from 0 (not painful) to 100 (extremely painful).

Subjects 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 analysis

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, 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 stimulus onset. This procedure yielded, in each subject, four average waveforms (one waveform for each experimental condition: LH, RH, LF, RF). Single-subject average waveforms were subsequently averaged to obtain group-level waveforms. Group-level scalp topographies were computed by spline interpolation.

For each of the four experimental conditions, group-level scalp topographies were parsed into functional microstates, defined as a temporally consecutive ERP topographies with quasi-stable potential landscape (Lehmann and Skrandies, 1980), using a statistical method based on a modified version of the classical k-means clustering analysis (Pascual-Marqui et al., 1995). The number of microstates was determined using a cross-validation criterion (see Pascual-Marqui et al., 1995 for technical details). Since the aim of the present study was to explore the Aδ-related brain responses, we considered the functional microstates that: (1) were observed within the time-interval from 100 to 500 ms; (2) within this time-interval showed a global field power (GFP) stronger than the GFP within the 0–100 ms time interval (i.e., when there was no LEP); and (3) were observed in all four experimental conditions.

To determine whether the elicited EEG responses were lateralized as a function of the stimulated side, single-subject LEP waveforms elicited by stimulation of the right and left territories were compared using the following procedure. First, for each condition and subject, LEP waveforms were normalized and expressed as z values, by subtracting from each time point the mean of the waveform, and then by dividing the resulting value by the standard deviation of the waveform. Second, a point-by-point paired sample t-test was used to assess the effects of stimulated side for hand and foot stimulation separately. This analysis yielded a time course of P values, representing the significant level of difference between LH and RH, or between LF and RF, for each electrode. Third, to account for multiple comparisons, the significance level (P value) was corrected using a false discovery rate (FDR) procedure (Durka et al., 2004). Fourth, single-subject difference LEP waveforms (LH–RH and LF–RF) were calculated to emphasize the difference of the stimulation in the right and left territories.

To display the differences between LEPs elicited by stimulation of the right and left sides, scalp topographies and corresponding statistical differences (P value) were plotted, in steps of 10 ms, from 390 to 410 ms for hand stimulation, and from 430 to 450 ms for foot stimulation. Scalp topographies of the earliest LEP activity (corresponding to the N1 wave) and their significant differences were also plotted, in steps of 10 ms, from 150 to 170 ms for hand stimulation, and from 190 to 210 ms for foot stimulation.