

Steady-state evoked potentials to tag specific components of nociceptive cortical processing

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ABSTRACT

Studies have shown that the periodic repetition of a stimulus induces, at certain stimulation frequencies, a sustained electro-cortical response of corresponding frequency, referred to as steady-state evoked potential (SSEP). Using infrared laser stimulation, we recently showed that SSEPs can be used to explore nociceptive cortical processing. Here, we implemented a novel approach to elicit such responses, using a periodic intra-epidermal electrical stimulation of cutaneous A δ -nociceptors (A δ -SSEPs). Using a wide range of frequencies (3–43 Hz), we compared the scalp topographies and temporal dynamics of these A δ -SSEPs to the A β -SSEPs elicited by non-nociceptive transcutaneous electrical stimulation, as well as to the transient ERPs elicited by the onsets of the 10-s stimulation trains, applied to the left and right hand. At 3 Hz, we found that the topographies of A β - and A δ -SSEPs were both maximal at the scalp vertex, and resembled closely that of the late P2 wave of transient ERPs, suggesting activity originating from the same neuronal populations. The responses also showed marked habituation, suggesting that they were mainly related to unspecific, attention-related processes. In contrast, at frequencies > 3 Hz, the topographies of A β - and A δ -SSEPs were markedly different. A β -SSEPs were maximal over the contralateral parietal region, whereas A δ -SSEPs were maximal over midline frontal regions, thus indicating an entrainment of distinct neuronal populations. Furthermore, the responses showed no habituation, suggesting more obligatory and specific stages of sensory processing. Taken together, our results indicate that A β - and A δ -SSEPs offer a unique opportunity to study the cortical representation of nociception and touch.

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Introduction

For the past 30 years, investigators have relied on the recording of laser-evoked brain potentials (LEPs) to study nociception and pain perception in humans (Carmon et al., 1976; Garcia-Larrea et al., 2003; Treede et al., 1999). It has been suggested that LEPs reflect activity originating from an extensive array of cortical structures, including bilateral operculo-insular and anterior cingulate cortices (Garcia-Larrea et al., 2003). Whether or not LEPs also reflect activity originating from the primary somatosensory cortex remains unclear (Garcia-Larrea et al., 2003). It has been suggested that LEPs reflect, at least partially, the neural processes by which the perception of pain emerges from nociceptive input (Baumgartner et al., 2006; Treede et al., 1988). For this reason, it has been hypothesized that LEPs constitute a reliable approach to study how pain is “represented” in the brain (Treede et al., 2000). However, there is also increasing

evidence indicating that the largest part of LEPs could reflect cortical activity unspecific for nociception, such as multimodal cognitive processes involved in the orientation of attention toward the occurrence of a transient, salient sensory event (Iannetti and Mouraux, 2010; Legrain et al., 2011). Novel approaches are thus needed to progress in our understanding of how nociception is processed in the human brain.

In a recent study (Mouraux et al., 2011), we showed that the rhythmic activation of peripheral nociceptors can be used to elicit steady-state evoked potentials (SSEPs). Unlike conventional transient event-related potentials (ERPs), which reflect a phasic cortical response triggered by the onset of a brief stimulus, SSEPs reflect a sustained cortical response induced by the periodic modulation of a long-lasting stream of sensory input (Regan, 1989; Vialatte et al., 2010). SSEPs are thought to result from the entrainment of a network of neurons responding to the stimulus (Herrmann, 2001; Muller et al., 2001; Vialatte et al., 2010). In other sensory modalities, SSEPs have been shown to reflect, at least in part, activity originating from primary sensory cortices (Giabbiconi et al., 2007; Muller et al., 2006; Plourde, 2006). Hence, SSEPs could constitute a promising approach to study the cortical processes specifically involved in nociception.

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In our first study, nociceptive SSEPs were elicited using a CO₂ laser to activate heat-sensitive nociceptive afferents with a periodicity of 7 Hz. Higher stimulation frequencies could not be achieved because of the time required to displace the laser target between two successive stimuli. The trains of nociceptive stimuli elicited consistent SSEPs. Regardless of stimulus location, the scalp topography of the elicited SSEPs was maximal at the vertex, and symmetrically distributed over both hemispheres. This was markedly different from the scalp topography of the SSEPs elicited by vibro-tactile stimulation, which displayed a clear maximum over the parietal region contralateral to the stimulated side. Taken together, the results of our first study suggested that nociceptive SSEPs reflect the activity of a cortical network that is distinct from the cortical network involved in the perception of vibro-tactile sensations and, hence, that nociceptive SSEPs could reflect cortical activity preferentially involved in nociception and, possibly, the perception of pain.

Here, we aimed to further examine whether nociceptive and non-nociceptive somatosensory SSEPs reflect the entrainment of distinct neuronal populations, by comparing the scalp topography and temporal dynamics of the elicited responses, this time using a wide range of stimulation frequencies. To achieve the selective, rapid and periodic activation of cutaneous nociceptors required to elicit nociceptive SSEPs, we used a novel approach based on intra-epidermal electrical stimulation (IES) (Inui et al., 2002; Mouraux et al., 2010). This approach was justified by the fact that, as compared to the thermal activation of heat-sensitive nociceptors using a laser stimulator, IES can be applied using a wide range of stimulation frequencies. Thus, IES could be used to characterize the frequency tuning curve of nociceptive SSEPs and, thereby, examine whether the scalp topography of the elicited SSEPs varied as a function of stimulation frequency. We hypothesized that different frequencies of stimulation could be used to tag functionally-distinct components of the cortical network involved in nociception, because the different neuronal populations responding to the nociceptive input could be expected to resonate preferentially at certain frequencies.

In addition, we aimed to explore whether nociceptive SSEPs and transient ERPs reflect functionally-distinct cortical processes. For this purpose, the scalp topographies of the obtained SSEPs were compared to those of the transient ERPs elicited by the onset of each stimulation train. Furthermore, it is well known that transient nociceptive ERPs habituate strongly over time. In fact, it is for this reason that nociceptive ERPs are often considered to reflect mainly non-obligatory stage of cortical processing involved in the reorientation of attention (Iannetti et al., 2008). Therefore, we explored the temporal dynamics of nociceptive SSEPs such as to examine whether or not they may reflect more obligatory components of nociceptive processing.

Methods

Participants

Nine healthy volunteers (5 males and 4 females, aged 21 to 35 years, 8 right handed) took part in the study. Written informed consent was obtained from all participants. The study was approved by the local Ethics Committee and conformed to the latest revision of the Declaration of Helsinki.

Stimuli

Non-nociceptive somatosensory stimulation (A β -stimulus)

Trans-cutaneous electrical stimulation (TES) was used to preferentially activate non-nociceptive A β -fibers. The stimuli were delivered over the superficial branch of the radial nerve using a pair of skin electrodes ($\varnothing$: 5 mm, inter-electrode distance: 2 cm) soaked with electrolyte and applied against the left or right wrist. For each stimulus location (left and right hand), the intensity of the stimulus (1.13 ± 0.41 mA; mean $\pm$ sd) was set to twice the perceptual

threshold to a single 0.5 ms pulse, estimated using a staircase procedure. Using such stimulation parameters, TES may be expected to preferentially activate non-nociceptive A β -fibers (Cruccu et al., 2008; Mouraux et al., 2010).

Nociceptive somatosensory stimulation (A δ -stimulus)

Intra-epidermal electrical stimulation (IES) was used to preferentially activate A δ -nociceptors (Inui et al., 2002; Mouraux et al., 2010). The nociceptive stimuli were delivered within the sensory territory of the superficial branch of the radial nerve, using a stainless steel concentric bipolar electrode consisting of a needle cathode (length: 0.1 mm, $\varnothing$: 0.2 mm) surrounded by a cylindrical anode ($\varnothing$: 1.4 mm) (Inui et al., 2002). By gently pressing the device against the skin, the needle electrode was inserted superficially into the epidermis. Before each stimulation block, the electrode was displaced and the intensity of the stimulus (0.24 ± 0.08 mA) was set to twice the perceptual threshold to a single 0.5 ms pulse, estimated using a staircase procedure. Using such stimulation parameters, we have previously shown that IES preferentially activates A δ -nociceptors (Mouraux et al., 2010). Although nociceptive, these stimuli do not necessarily elicit a percept qualified as painful. This could be due to the very spatially-restricted nature of the stimulus. Supporting this view, spatial summation has been shown to be an important factor contributing to the quality of percepts elicited by nociceptive input (Opsommer et al., 2001).

Procedure

Experiments were conducted in a dim, silent, temperature-controlled room. Participants lay semi-supine in a comfortable arm-chair. Non-nociceptive and nociceptive somatosensory stimuli were applied to the left and right hand in separate blocks. These four different blocks were repeated 5 times, resulting in a total of 20 blocks. The order of the blocks was randomized across participants. Each block consisted in 10 trains of electrical pulses lasting 10 s, separated by a 10 s inter-train interval. Each train consisted of constant-current electrical pulses lasting 0.5 ms, separated by an inter-pulse interval of 5 ms. The trains of stimuli were modulated by a repeating boxcar function, such that within each train, periods of stimulation were alternated with periods without stimulation of equal duration, with a periodicity of 3, 7, 13, 23 or 43 Hz. These modulation frequencies were chosen to explore a large range of frequencies and to avoid a possible overlap between the responses to the elicited SSEPs at the different frequencies and their possible harmonics. Within each block, each of the five stimulation frequencies was repeated two times, delivered in random order. Each block was separated by a short-lasting rest period of 3–4 min. The entire recording lasted approximately 1.5 h (Fig. 1).

Measures

Behavioral measures

After each train of stimulation, participants were asked to rate the perceived stimulus intensity using a numerical rating scale ranging from 0 to 10 and defined as follows: NRS = 0: stimulus not perceived, NRS > 5: stimulus perceived as painful, NRS = 10: maximum pain.

Electrophysiological measures

The EEG was recorded using 64 Ag–AgCl electrodes placed on the scalp according to the international 10/10 system (Waveguard64 cap, Cephalon A/S, Denmark). Electrode impedances were kept below 10 k Ω . Ocular movements and eye blinks were recorded using two additional surface electrodes placed at the upper-left and the lower-right sides of the right eye. Two additional electrodes were placed on the left and right forearms with the aim of identifying and possibly removing electrical stimulation artifacts. Signals were amplified and digitized using a sampling rate of 1000 Hz, using an average reference

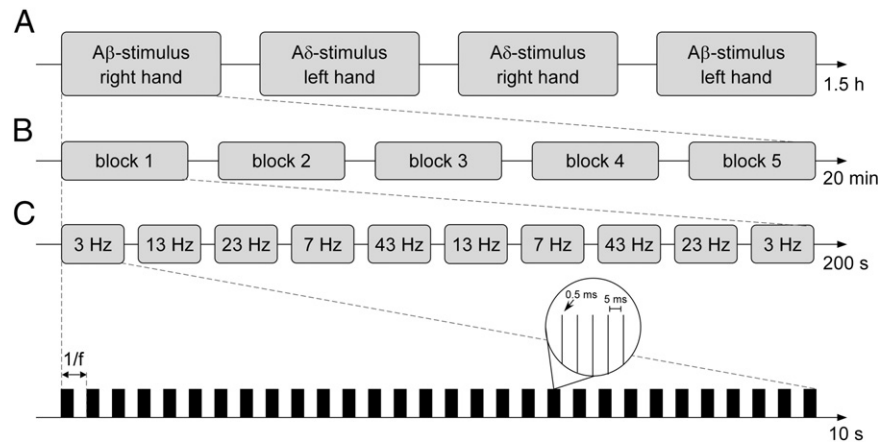


Fig. 1. Experimental design. A. Non-nociceptive somatosensory stimuli (Aβ-stimuli) and nociceptive somatosensory stimuli (Aδ-stimuli) were applied to the left and right hand in 4 separate blocks. The order of the blocks was randomized across participants. B. Each block was repeated 5 times, resulting in a total of 20 blocks. C. Each block consisted in 10 stimulation trains lasting 10 s, separated by a 10-s inter-train interval. The trains of stimuli were modulated by a repeating boxcar function with a periodicity of 3, 7, 13, 23 or 43 Hz. Each individual pulse lasted 0.5 ms, and was separated by a 5-ms inter-pulse interval. Within each block, each of the 5 types of stimulation trains was repeated 2 times. The order of the trains was randomized across blocks.

(64-channel high-speed amplifier, Advanced Neuro Technology, The Netherlands).

Data analysis

All EEG processing steps were carried out using Analyzer 1.05 (Brain Products, Germany), Letswave (<http://nocions.webnode.com/letswave>; see also (Mouraux and Iannetti, 2008)) and Matlab (The MathWorks, USA). Statistical analyses were performed using SPSS 18 (IBM, USA).

Continuous EEG recordings were filtered using a 0.5–250 Hz band-pass Butterworth zero-phase filter to remove slow drifts in the recorded signals and high frequency signal components non relevant to the present study. Non-overlapping EEG epochs were obtained by segmenting the recordings from 0 to 10 s relative to the onset of each stimulus train, thus yielding a total of 200 epochs per subject (10 stimulation trains $\times$ 5 blocks of stimulation $\times$ 2 locations $\times$ 2 modalities). Each EEG epoch was demeaned using the time-interval ranging from 0 to 10 s. Artifacts due to eye blinks or eye movements were then removed using a validated method based on an independent-component analysis (FastICA algorithm) (Hyvarinen and Oja, 2000). Finally, epochs containing artifacts exceeding 500 μ V were rejected from further analysis. Based on this criterion, the rejection rate was $3.9 \pm 4.5\%$.

For each subject, modality, stimulus location and stimulation frequency, artifact-free EEG epochs were averaged such as to attenuate the contribution of activities non phase-locked to the stimulation train. When present, electrical stimulation artifacts were then removed using the same method as was used to remove eye-movement artifacts. Finally, the obtained average waveforms were transformed in the frequency domain using a discrete Fourier Transform (FFT) (Frigo and Johnson, 1998), yielding an amplitude spectrum (μ V) ranging from 0 to 500 Hz with a frequency resolution of 0.1 Hz (Bach and Meigen, 1999).

Within the obtained frequency spectra (Fig. 2), the signal amplitude at the frequencies of 3, 7, 13, 23 and 43 Hz was measured. These signal amplitude values may be expected to correspond to the sum of the stimulus-evoked steady-state response (i.e. the SSEP, if present) and unrelated residual background noise. Therefore, to obtain valid estimates of the magnitude of the recorded SSEPs, the contribution of this residual noise was removed by subtracting, at each electrode and at each frequency bin, the average amplitude of the signal measured at neighboring frequencies (± 0.2 to ± 0.5 Hz) (Mouraux et al., 2011).

Statistical evaluation of the elicited SSEPs

In the absence of a steady-state response, the average subtracted signal amplitude may be expected to tend towards zero. Hence, to assess the significance of the responses measured at each electrode, and for each stimulus location, modality and stimulation frequency, it was examined whether the magnitude of the noise-subtracted signal amplitude was significantly greater than zero, using a *t*-test against zero (significance level: $p < 0.05$).

Effect of stimulation frequency on the magnitude of non-nociceptive and nociceptive SSEPs and on the intensity of perception

A repeated-measures ANOVA with three factors was used to assess the effect of modality (Aβ- vs. Aδ-stimulus), stimulus location (left vs. right hand) and stimulation frequency (3, 7, 13, 23 vs. 43 Hz) on the noise-subtracted magnitude of the elicited SSEPs averaged across all scalp channels, as well as on the elicited intensity of perception. Degrees of freedom were adjusted using Greenhouse–Geisser correction when necessary (sphericity assumption). When significant, planned pairwise comparisons were performed using paired-sample *t* tests. Significance level was set at $p < 0.05$, uncorrected for multiple comparisons.

Effect of repetition on the magnitude of non-nociceptive and nociceptive SSEPs and on the intensity of perception

The effect of stimulus repetition was examined at the following levels: (1) stimulus repetition within a single train, and (2) repetition of blocks across the entire experiment. To assess the temporal dynamics of the elicited SSEPs within stimulation trains, an additional set of epochs was computed by segmenting, for each modality, stimulus location and stimulation frequency, the 10-s average waveforms into five successive 2-s segments. After applying the same analysis procedures, the magnitude of the elicited SSEPs was compared using a repeated-measures ANOVA with modality (Aβ- vs. Aδ-stimulus), stimulation frequency (3, 7, 13, 23 vs. 43 Hz), and time (first segment vs. last segment) as experimental factors. To assess the effect of block repetition on the magnitude of the elicited SSEPs and on the intensity of perception, a repeated-measures ANOVA was conducted using modality (Aβ- vs. Aδ-stimulus), stimulation frequency (3, 7, 13, 23 vs. 43 Hz), and block order (1–5) as experimental factors. Five subjects were excluded from this additional analysis, because the SSEP peaks could not be clearly identified at the level of single blocks. Degrees of freedom were adjusted using Greenhouse–Geisser correction when necessary (sphericity assumption). When significant, planned pairwise comparisons were

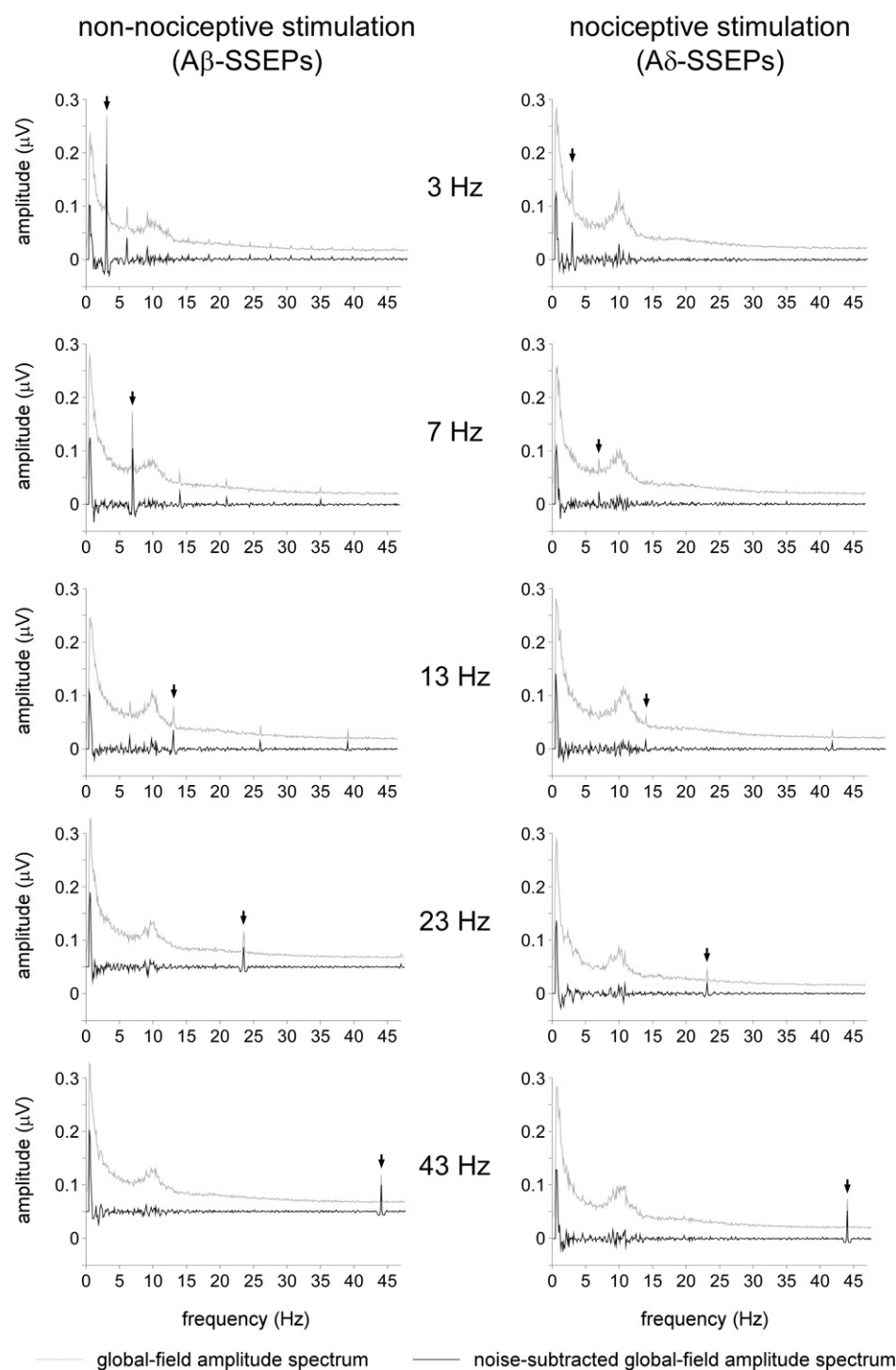


Fig. 2. Group-level average of non-nociceptive and nociceptive SSEPs elicited by 3, 7, 13, 23 and 43 Hz periodic electrical stimulation of A δ - and A β -fibers innervating the hand dorsum. The light gray frequency spectra represent the amplitude of the EEG signal averaged across all scalp channels and stimulation sites (left and right hand). The black frequency spectra represent the noise-subtracted amplitude (see Methods). The vertical arrows mark the frequency of the expected SSEPs. x-axis: frequency (Hz), y-axis: average amplitude (μ V). Note that, at all stimulation frequencies, both non-nociceptive and nociceptive somatosensory stimulation elicited consistent SSEPs.

performed using paired-sample *t* tests. Significance level was set at $p < 0.05$, uncorrected for multiple comparisons.

Scalp topography of non-nociceptive and nociceptive SSEPs

In previous studies, it was shown that the scalp topography of the SSEPs elicited by innocuous tactile stimulation displays a clear maximum over the parietal region contralateral to the stimulated side (Mouraux et al., 2011). Therefore, we assessed a possible hemispheric lateralization of the scalp topography of non-nociceptive and

nociceptive SSEPs by comparing the magnitude of the signals measured at C3 and C4 using a repeated-measures ANOVA with stimulus modality (A β - vs. A δ -stimulus), stimulation frequency (3, 7, 13, 23 vs. 43 Hz) and electrodes (ipsilateral vs. contralateral central electrode relative to the stimulated side) as experimental factors. Degrees of freedom were adjusted using Greenhouse–Geisser correction when necessary (sphericity assumption). When significant, planned pairwise comparisons were performed using paired-sample *t* tests. Significance level was set at $p < 0.05$, uncorrected for multiple comparisons.

Scalp topographies computed using the magnitude of the SSEP measured in the frequency domain do not allow identifying the possible occurrence of phase reversal across channels. For this reason, additional scalp topographies were computed as follows. First, for each stimulation frequency, continuous EEG recordings were filtered using a narrow band-pass Butterworth zero-phase filter centered at the SSEP frequency (3 Hz: 2.5–3.5 Hz; 7 Hz: 6.5–7.5 Hz, 13 Hz: 12.5–13.5 Hz; 23 Hz: 22.5–23.5 Hz; 43 Hz: 42.5–43.5 Hz), such as to filter-out signal changes unrelated to the steady-state response. Second, the obtained EEG recordings were segmented into a series of epochs time-locked to the periodicity of the stimulation trains which, when averaged across trials, revealed the SSEP time course in the time domain. Third, for each modality, stimulus location and stimulation frequency, topographical maps were computed using the signal amplitude measured within these average waveforms, at the latency corresponding to the most positive peak at electrode Fz (this midline electrode was chosen to avoid biasing estimates towards the left or right hemisphere).

Transient non-nociceptive and nociceptive somatosensory ERPs

In order to examine whether the trains of A β - and A δ -stimulation elicited transient ERPs, significant time-locked deflections were searched for in the 10-s average waveforms computed for each subject, modality, stimulus location and stimulation frequency.

Results

Non-nociceptive A β -SSEPs and nociceptive A δ -SSEPs

For all stimulus locations (left vs. right hand) and for all stimulation frequencies (3, 7, 13, 23 vs. 43 Hz), both the stimulation of non-nociceptive A β -fibers and the stimulation of nociceptive A δ -fibers elicited a marked increase of EEG power centered at the frequency corresponding to the frequency of stimulation (Fig. 2). For all stimulus locations and for all stimulation frequencies, after subtraction of the surrounding frequency bins to account for residual background noise, the magnitude of both non-nociceptive A β -SSEPs and nociceptive A δ -SSEPs, averaged across all scalp channels, was significantly greater than zero (all $t \geq 2.42$, $p \leq 0.04$).

Effect of stimulus modality, frequency and location

On average, the magnitude of non-nociceptive A β -SSEPs was greater than the magnitude of nociceptive A δ -SSEPs. The magnitude of both A β -SSEPs and A δ -SSEPs appeared to be dependent on the frequency of stimulation, being greater at both low (e.g. 3 Hz) and high (e.g. 23 and 43 Hz) frequencies of stimulation (Fig. 3). To assess the effect of stimulus modality, frequency and location on the magnitude of the elicited SSEPs, a repeated-measures ANOVA was performed, with 'modality' (A β - vs. A δ -stimulus), 'frequency' (3, 7, 13, 23 vs. 43 Hz) and 'location' (left vs. right hand) as experimental factors. The analysis confirmed a significant main effect of 'modality' ($F = 10.64$, $p = 0.01$): on average, the magnitude of non-nociceptive A β -SSEPs was significantly greater than the magnitude of nociceptive A δ -SSEPs. The analysis also confirmed a significant main effect of 'frequency' ($F = 16.49$, $p = 0.01$), as well as a significant interaction between the factors 'modality' and 'frequency' ($F = 7.93$, $p = 0.01$). As detailed in Table 1, planned pairwise comparisons confirmed that, for both A β - and A δ -SSEPs, greater responses were elicited at low and high stimulation frequencies. There was no significant main effect of the factor 'location' ($F = 0.03$, $p = 0.88$) on the magnitude of A β - and A δ -SSEPs, and no significant interaction between this factor and the factors 'modality' or 'frequency' ($F = 0.001$, $p = 0.97$; $F = 0.82$, $p = 0.52$).

The same repeated-measures ANOVA was used to assess the effect of stimulus modality, frequency and location on the intensity of

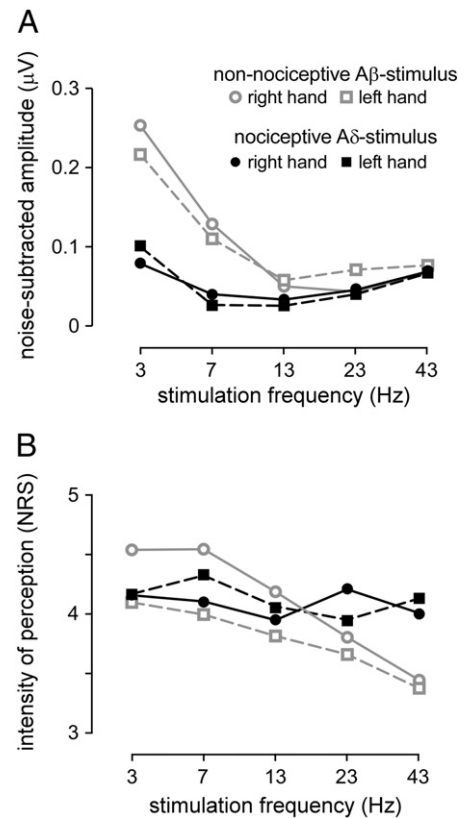


Fig. 3. A. Group-level average amplitude (μ V) of non-nociceptive and nociceptive somatosensory SSEPs elicited by left and right hand stimulation, as a function of stimulation frequency. B. Group-level average intensity of the perception elicited by non-nociceptive and nociceptive somatosensory stimulation of the left and right hand, as a function of stimulation frequency.

perception. There was no significant main effect of the factor 'modality' ($F = 0.41$, $p = 0.54$): on average, the intensity of perception elicited by non-nociceptive A β stimulation was not significantly different from the intensity of perception elicited by nociceptive A δ stimulation. In contrast, there was a significant main effect of 'frequency' ($F = 23.21$, $p = 0.001$) as well as a significant interaction between the factors 'modality' and 'frequency' ($F = 10.02$, $p = 0.001$). Planned pairwise comparisons of the intensity of perception elicited at different frequencies of stimulation revealed that, for non-nociceptive A β -stimulation, low-frequency stimulation was perceived as more intense than high-frequency stimulation (all $t \geq 2.99$, $p \leq 0.02$, except between 3 and 7 Hz: $t = 1.09$, $p = 0.31$) (Fig. 3). In contrast, the frequency of stimulation had little or no effect on the intensity

Table 1

Planned pairwise comparisons of the noise-subtracted amplitude of the SSEPs elicited by the different frequencies of nociceptive (A δ) and non-nociceptive (A β) stimulation.

		3 Hz		7 Hz		13 Hz		23 Hz	
		t	p-value	t	p-value	t	p-value	t	p-value
A δ	7 Hz	3.18	0.01**						
	13 Hz	3.09	0.01**	0.87	0.41				
	23 Hz	2.48	0.04*	−1.52	0.17	−3.14	0.01**		
	43 Hz	1.26	0.24	−3.51	0.008**	−4.02	0.004***	−3.60	0.007**
A β	7 Hz	2.35	0.05*						
	13 Hz	4.49	0.002***	3.75	0.006**				
	23 Hz	4.57	0.002***	3.27	0.01*	−0.70	0.50		
	43 Hz	3.83	0.005**	2.79	0.02*	−3.55	0.008**	−2.05	0.07

** $p < 0.01$.

* $p < 0.05$.

*** $p < 0.005$.

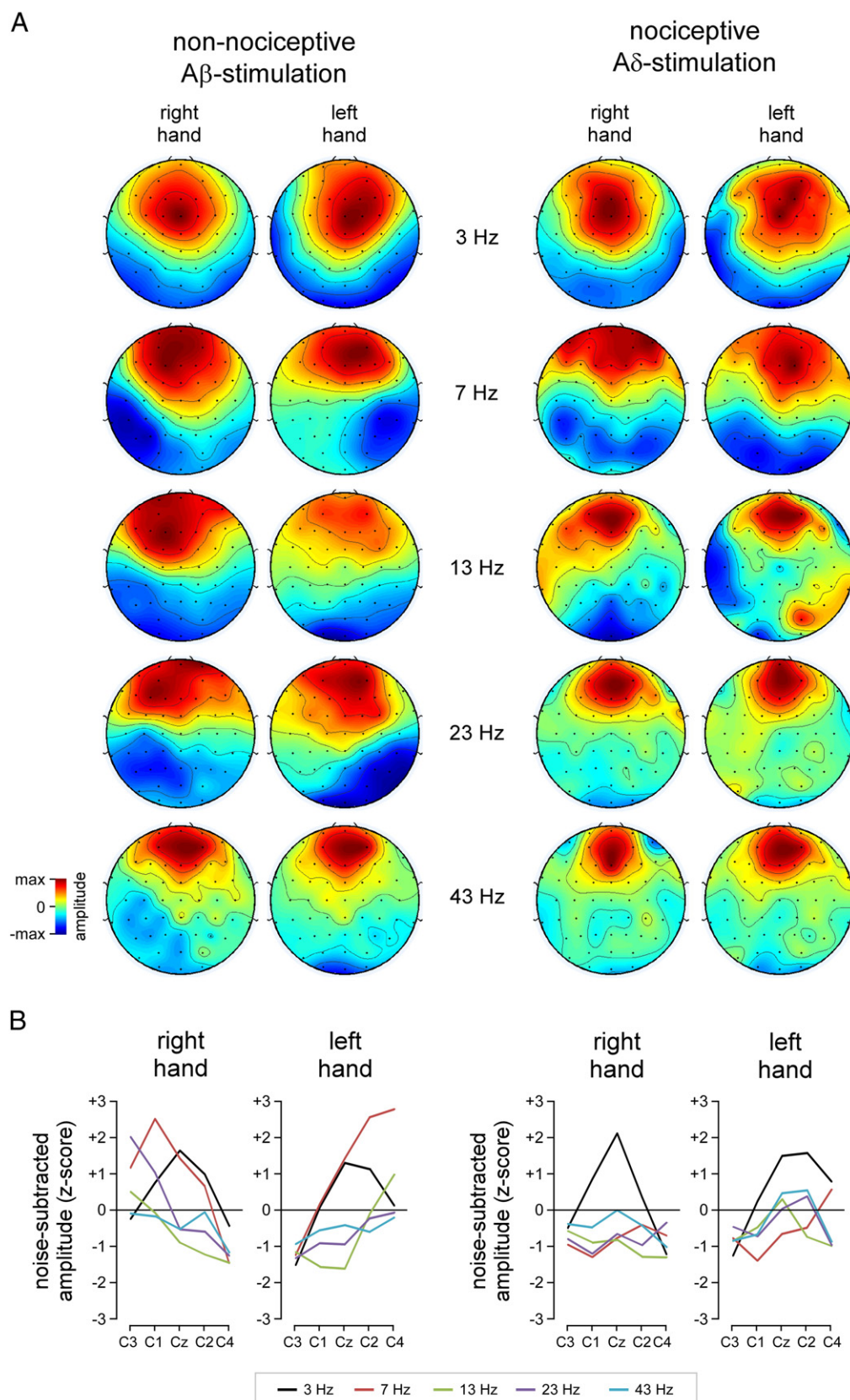


Fig. 4. A. Group-level average scalp topographies of non-nociceptive and nociceptive somatosensory SSEPs elicited by stimulation of the left and right hand, as a function of stimulation frequency. The color maps represent the amplitude of the elicited SSEPs obtained at each scalp electrode (see [Methods](#)). B. Group-level average amplitude of non-nociceptive and nociceptive somatosensory SSEPs elicited by stimulation of the left and right hand, recorded over left (C3, C1), midline (Cz) and right (C2, C4) central electrodes, as a function of stimulation frequency. For each stimulation frequency, amplitudes are expressed as standard deviations from the mean amplitude measured at all scalp channels. Note that, at 3 Hz, the scalp topographies of $A\beta$ - and $A\delta$ -SSEPs are very similar, and maximal over the scalp vertex. In contrast, for frequency higher than 3 Hz, the scalp topographies of non-nociceptive $A\beta$ -SSEPs are maximal over the hemisphere contralateral to the stimulated side, whereas the scalp topographies of nociceptive $A\delta$ -SSEPs are maximal over fronto-central electrodes, and symmetrically distributed over both hemispheres.

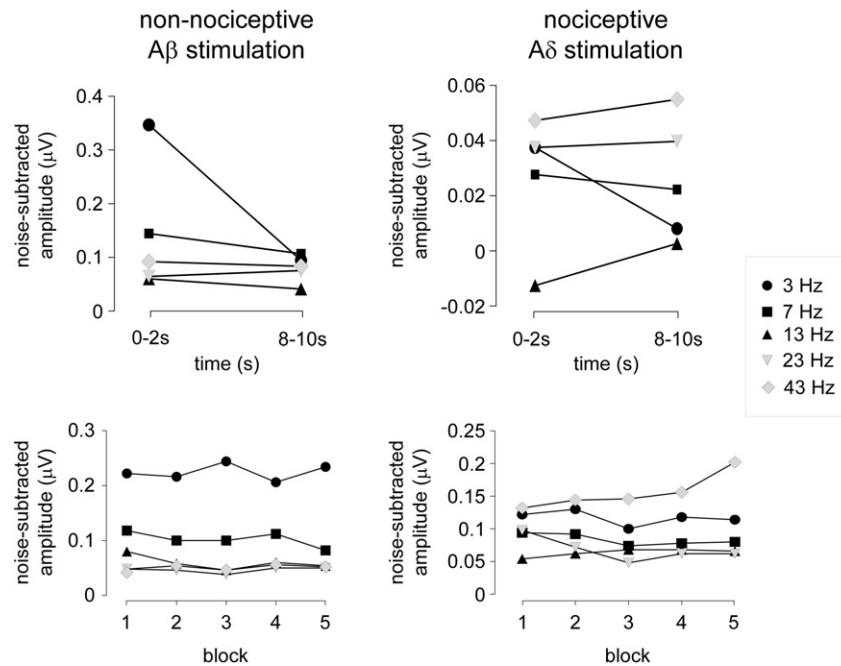


Fig. 5. Temporal dynamics of non-nociceptive and nociceptive somatosensory SSEPs. The upper graphs represent the group-level average amplitude of non-nociceptive and nociceptive SSEPs estimated within the first (0–2 s) and last (8–10 s) two seconds of the 10-s stimulation trains, as function of stimulation frequency. The lower graphs represent the group-level average amplitude of non-nociceptive and nociceptive SSEPs estimated within each of the five consecutive stimulation blocks, as function of stimulation frequency. In all graphs, amplitudes are averaged across all scalp channels and stimulation sites.

of the perception elicited by nociceptive A δ -stimulation (all $t \leq 1.72$, $p \geq 0.12$). There was no significant main effect of the factor 'location' ($F = 1.39$, $p = 0.27$). The other ANOVA comparisons were not significant (all $F < 1.39$; $p > 0.23$).

Scalp topography

For stimulation frequencies greater than 3 Hz, the scalp topographies of non-nociceptive A β -SSEPs were markedly different from the scalp topographies of nociceptive A δ -SSEPs. As shown in Fig. 4, the scalp topographies of non-nociceptive A β -SSEPs were maximal over the hemisphere contralateral to the stimulated side, and exhibited a clear polarity reversal over the contralateral central sulcus. Contrasting with this asymmetrical scalp distribution, nociceptive A δ -SSEPs were maximal over fronto-central electrodes, and symmetrically distributed over both hemispheres, regardless of the stimulated side (left vs. right hand). Finally, the scalp topographies of the A β - and A δ -SSEPs elicited by 3 Hz stimulation were much more similar, displaying a fairly symmetrical scalp topography, maximal over the scalp vertex. To assess the hemispheric lateralization of A β - and A δ -SSEPs, a repeated-measures ANOVA was conducted using 'modality' (A β - vs. A δ -stimulus), 'frequency' (3, 7, 13, 23 vs. 43 Hz) and 'electrode' (ipsilateral vs. contralateral central electrodes C3 or C4) as experimental factors. The analysis revealed a main effect of the factors 'modality' ($F = 43.63$, $p = 0.001$), 'frequency' ($F = 15.26$, $p = 0.001$) and 'electrode' ($F = 36.47$, $p = 0.001$). The analysis also showed a significant interaction between the factors 'modality' and 'frequency' ($F = 10.74$, $p = 0.002$) and, most importantly, a significant interaction between the factors 'modality' and 'electrode' ($F = 13.84$, $p = 0.006$), thus confirming that the scalp topographies of non-nociceptive A β -SSEPs and nociceptive A δ -SSEPs were distinct. Planned pairwise comparisons showed that, for all frequencies of stimulation except 3 Hz, the magnitude of non-nociceptive A β -SSEPs was significantly greater at the contralateral vs. the ipsilateral central electrode (all $t \geq 3.13$, $p \leq 0.01$, except at 3 Hz $t = 1.99$, $p = 0.08$). Such a systematic lateralization was

not found when examining nociceptive A δ -SSEPs (all $t \leq 1.87$, $p \geq 0.09$, except at 7 Hz $t = 3.9$, $p = 0.005$) (Fig. 4).

Temporal dynamics

To explore the temporal dynamics of non-nociceptive and nociceptive SSEPs, for each stimulation frequency, the magnitude of the elicited A β - and A δ -SSEPs was compared at two different levels: (1) within the train of stimulation lasting 10 s and (2) between successive blocks of stimulation. To increase the signal-to-noise ratio of the elicited responses, and to reduce the number of experimental factors, the comparisons were performed using the estimates of SEP amplitude, averaged for left and right hand stimulation.

Within-train temporal dynamics of A β - and A δ -SSEPs

EEG epochs spanning the entire 10-s trial duration were epoched into five consecutive 2-s segments (Fig. 5). For all stimulation frequencies but 3 Hz, the magnitude of non-nociceptive A β -SSEPs appeared to remain constant across segments. Similarly, for all stimulation frequencies, the magnitude of nociceptive A δ -SSEPs appeared to remain constant across segments. In contrast, the magnitude of the non-nociceptive A β -SSEPs elicited by 3 Hz stimulation elicited a response of much greater magnitude during the first segment as compared to the last segment (Fig. 5). To assess the significance of these observations, a repeated-measures ANOVA was conducted on the magnitude of the A β - and A δ -SSEPs using 'time' (first vs. last segment), 'modality' (A β - vs. A δ -stimulus) and 'frequency' (3, 7, 13, 23 vs. 43 Hz) as experimental factors. The analysis showed a significant main effect of 'time' ($F = 6.28$, $p = 0.04$), a significant interaction between the factors 'time' and 'modality' ($F = 11.18$, $p = 0.01$), an interaction between the factors 'time' and 'frequency' ($F = 8.21$, $p = 0.006$), as well as between the factors 'time', 'modality' and 'frequency' ($F = 7.27$, $p = 0.01$). The other ANOVA factors and comparison ('modality', 'frequency' and 'modality' and 'frequency'), were also significant (all $F \geq 5.39$; $p \leq 0.03$). Planned pairwise comparisons showed that only the magnitude of the A β -SSEP obtained during 3 Hz

stimulation was significantly greater during the first segment as compared to the last segment ($t = 3.65$, $p = 0.006$). All other paired comparisons were not significant (all $t \leq 1.43$, $p \geq 0.19$).

Between-blocks temporal dynamics of A β - and A δ -SSEPs

As shown in Fig. 5, the magnitude of both A β - and A δ -SSEPs appeared to be largely unaffected by stimulus repetition across blocks. A repeated-measures ANOVA was conducted on the magnitude of the elicited SSEPs with 'block order' (1–5), 'modality' (A β - vs. A δ -stimulus) and 'frequency' (3, 7, 13, 23 vs. 43 Hz) as experimental factors. There was no significant main effect of the factor 'block order' ($F = 0.46$, $p = 0.77$), and no significant interaction involving that factor (all $F \leq 1.16$, $p \geq 0.36$). The same repeated-measures ANOVA was conducted on the intensity of perception elicited by A β and A δ stimulation across blocks. Such as for the magnitude of the elicited SSEPs, there was no significant main effect of the factor 'block order' ($F = 0.41$, $p = 0.81$), and no significant interaction involving that factor (all $F \leq 1.71$, $p \geq 0.16$).

Transient nociceptive and non-nociceptive event-related potentials

In order to examine whether the trains of A β and A δ stimulation elicited transient event-related potentials (ERPs), 10-s average waveforms were computed in the time domain. As shown in Fig. 6, the onset of the trains elicited, at all frequencies of stimulation, a clear ERP. Regardless of the type of stimulus (A β vs. A δ), the ERP consisted of a large negative-positive biphasic wave that was maximal at the scalp vertex (electrode Cz). The latency of both the negative and positive peaks of the ERP elicited by A β stimulation appeared to be shorter than that elicited by A δ stimulation. In order to examine this difference in latency, a repeated-measures ANOVA was conducted with 'modality' (A β - vs. A δ -stimulus) and 'frequency' (3, 7, 13, 23 vs. 43 Hz) as experimental factors. Considering the peak latency of the negative wave, the analysis confirmed a significant main effect of the factor 'modality' ($F = 17.75$, $p = 0.003$). Planned pairwise comparisons showed that the latency of the negative peak was significantly greater following nociceptive stimulation vs. non-nociceptive stimulation, at all frequencies (all $t \geq 2.38$, $p \leq 0.04$) except 13 Hz ($t = 1.06$, $p = 0.32$). Considering the peak latency of the positive wave, the analysis also confirmed a significant main effect of the factor 'modality' ($F = 65.19$, $p < 0.001$). Planned pairwise comparisons showed that the latency of the positive peak was significantly greater following nociceptive stimulation vs. non-nociceptive stimulation, at all frequencies (all $t \geq 2.31$, $p \leq 0.05$) except 7 Hz ($t = 1.46$, $p = 0.18$).

For all stimulation frequencies greater than 3 Hz, no later ERPs could be identified within the 10-s average waveforms, thus indicating that nociceptive and non-nociceptive ERPs were triggered only by the train onset. In contrast, when non-nociceptive stimuli were repeated at 3 Hz frequency, the average waveforms obtained after A β stimulation appeared to be composed of a succession of ERPs, whose magnitude decayed rapidly as a function of time, but which were still clearly visible during the first seconds of stimulation (Fig. 6).

Discussion

Our results show that consistent nociceptive SSEPs can be obtained by the selective, rapid and periodic intra-epidermal electrical stimulation of nociceptive free nerve endings, using a wide range of frequencies (3–43 Hz).

Importantly, both for non-nociceptive and nociceptive SSEPs, low and high frequencies of stimulation appeared to reflect the entrainment of distinct neuronal populations. Indeed, the scalp topographies of A β - and A δ -SSEPs obtained when stimulating at 3 Hz were markedly different from the scalp topographies of A β - and A δ -SSEPs obtained when stimulating at frequencies greater than 3 Hz.

In fact, at 3 Hz, the scalp topographies of the SSEPs elicited by non-nociceptive and nociceptive somatosensory stimulation were very

similar. Both responses displayed a maximum over the vertex and fronto-central regions, and were fairly symmetrically distributed over both hemispheres. Importantly, their scalp topographies were also comparable to the scalp topographies of the late P2 component of the transient ERPs elicited by the train onset, thus suggesting that all these responses reflected activity originating from common cortical structures. Taking into consideration previous source analysis studies of the late P2 component of transient ERPs, it is likely that these responses reflected a combination of activity originating from multiple sources, located in bilateral opercular-insular areas, as well as the anterior cingulate cortex (Garcia-Larrea et al., 2003).

Moreover, such as the late P2 component of ERPs, the magnitude of the 3-Hz A β -SSEPs showed a marked habituation: within the 10-second trains of stimulation, the magnitude of the 3-Hz A β -SSEP, such as the magnitude of the late P2 components of A β - and A δ -ERPs, decayed rapidly as a function of time, being maximal only during the first seconds of stimulation. This similar behavior suggests that all these responses reflect unspecific and non-obligatory stages of sensory processing, strongly dependent on the context within which the afferent sensory input occurred. Indeed, the fact that the magnitude of these responses was markedly reduced by stimulus repetition indicates that they reflect cortical processes that are determined, at least in part, by the saliency of the afferent input. Hence, these responses could reflect brain processes involved mainly in the reorientation of attention that may be expected to be triggered by the sudden onset of the stimulation trains. In other words, our results indicate that, at 3 Hz, non-nociceptive somatosensory stimulation elicits SSEPs reflecting mainly late, unspecific and possibly attention-related cortical processes, similar to those thought to underlie the late positive component of somatosensory vertex potentials (Iannetti et al., 2008; Legrain et al., 2011; Lorenz and Garcia-Larrea, 2003). Conversely to the 3-Hz A β -SSEPs, the magnitude of the 3-Hz A δ -SSEPs did not show such a habituation within the 10-second train, thus suggesting that these responses could reflect cortical processes that are more obligatory to the processing of nociceptive input, than to the processing of non-nociceptive input.

Stimulating at frequencies greater than 3 Hz yielded entirely different results. Indeed, at stimulation frequencies > 3 Hz, the scalp topographies of the SSEPs elicited by non-nociceptive and nociceptive somatosensory stimulation differed from one another, and differed from the scalp topographies of the late transient ERPs. Non-nociceptive somatosensory stimulation elicited a lateralized response, maximal over the hemisphere contralateral to the stimulated side. Such as the scalp topographies of the early components of transient non-nociceptive somatosensory ERPs (Crucchi et al., 2008; Regan, 1989), the scalp topographies of the A β -SSEPs displayed a reversal of polarity over the contralateral parietal region, thus suggesting a tangential source originating from the primary somatosensory cortex (S1). Supporting this interpretation, a number of previous studies showed that SSEPs elicited by vibrotactile stimulation reflect mainly activity originating from the primary somatosensory cortex (Giabbiconi et al., 2007; Mouraux et al., 2011; Snyder, 1992). In contrast, intra-epidermal electrical stimulation of nociceptive fibers elicited SSEPs symmetrically distributed over both hemispheres, and focused over frontal areas; suggesting a radial source originating from anterior midline brain structures. The obtained scalp topographies were similar to the scalp topographies of the nociceptive SSEPs elicited by infrared laser stimulation of heat-sensitive nociceptors (Mouraux et al., 2011), which were best modeled as sources originating from the anterior cingulate cortex. Taken together, this indicates that, at frequencies greater than 3 Hz, nociceptive SSEPs reflect the activity of neuronal populations that are distinct from the neuronal populations involved in the processing of non-nociceptive vibrotactile input. Indeed, whereas the contralateral tangential source probably originating from the primary somatosensory cortex which constitutes the bulk of A β -SSEPs does not appear to contribute significantly to A δ -SSEPs, the midline radial

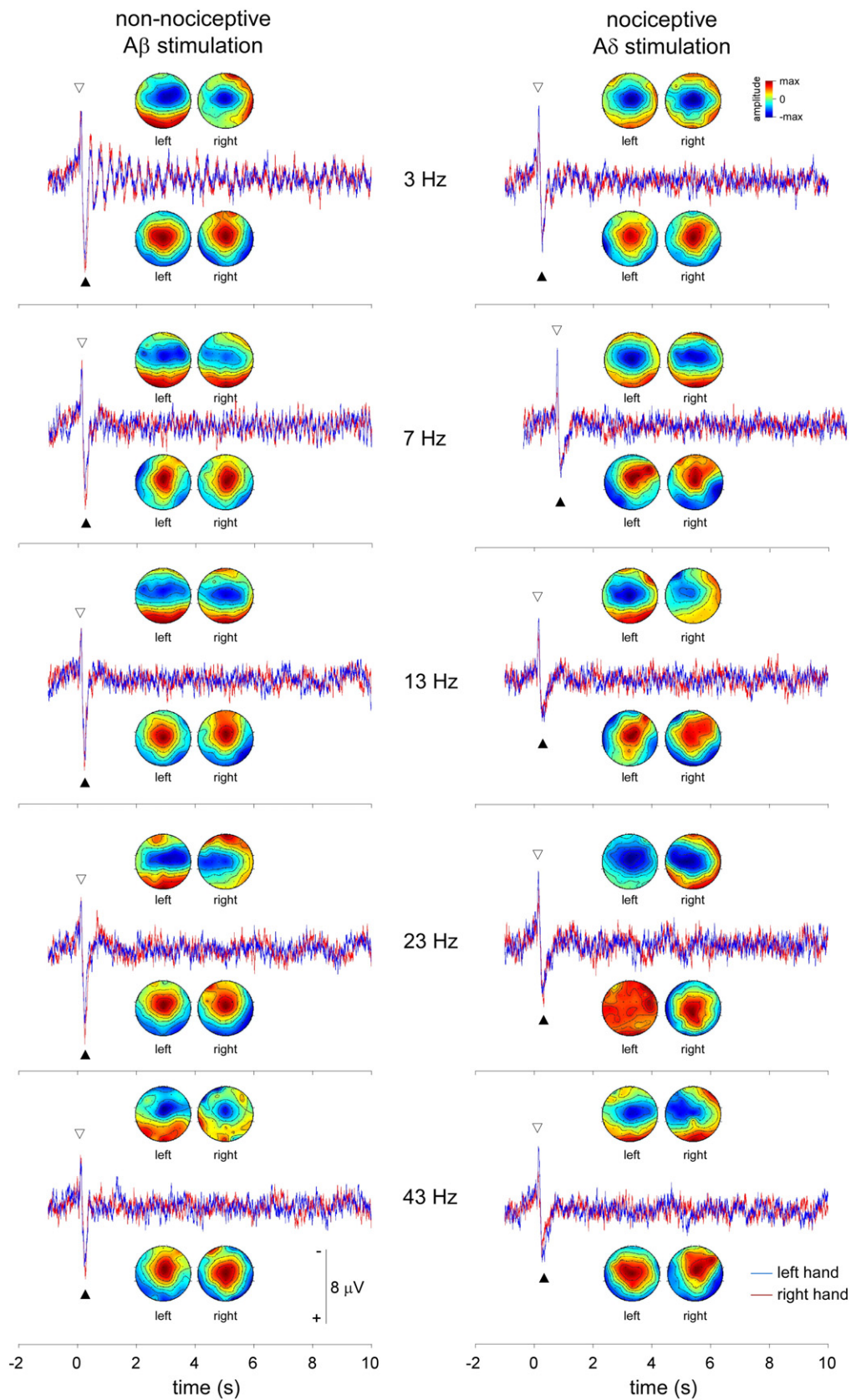


Fig. 6. Transient event-related potentials (ERPs) elicited by the 10-s trains of non-nociceptive and nociceptive stimulation presented at 3, 7, 13, 23 and 43 Hz. Waveforms obtained following left and right hand stimulation are shown in blue and red, respectively (group-level average waveforms recorded at electrode Cz). Regardless of the type of stimulus, the onset of the stimulation train elicited a clear ERP consisting of a large negative wave (white marker) followed by a positive wave (black marker) whose scalp topographies following stimulation of the left and right hand are shown in the corresponding scalp maps.

source probably originating from the anterior cingulate cortex which constitutes the bulk of A δ -SSEPs does not appear to contribute significantly to A β -SSEPs.

Although not significant, a slight lateralization of A δ -SSEPs cannot be entirely excluded, in particular, at 7 and 13 Hz (Fig. 4). If present, this lateralization could be explained by the fact that, in a small number of subjects and/or trials, in addition to activating nociceptive A δ -fibers, IES could have also activated non-nociceptive A β -fibers, as the difference in electrical activation threshold of A δ - and A β -fibers can be relatively narrow (Mouraux et al., 2010). However, a more likely interpretation would be that, such as non-nociceptive A β -fiber input, nociceptive A δ -fiber input also elicits activity within the parietal region contralateral to the stimulated side. Compatible with this hypothesis, it has been shown that the early components of nociceptive laser-evoked brain potentials are lateralized, and could at least partly reflect activity originating from the contralateral S1 (Valentini et al., 2011). Nevertheless, the scalp topographies of A β - and A δ -SSEPs were different (in particular, only A β -SSEPs clearly showed a reversal of polarity observed over the contralateral parietal region). Hence, our results indicate that the bulk of A β - and A δ -SSEPs reflects activity originating from distinct cortical areas.

Consistent with these findings, Dum et al. (2009) using anterograde viral tracing in monkeys, showed that unlike non-nociceptive somatosensory input, the primary target of nociceptive spino-thalamic input is not the primary somatosensory cortex (S1), but the insular cortex, the secondary somatosensory cortex and, most importantly, the cingulate cortex. Other studies performed in humans and monkeys have suggested that S1 is involved in processing both non-nociceptive and nociceptive somatosensory inputs, but that both types of inputs are represented differently within the S1 cortex (Kenshalo et al., 2000; Tommerdahl et al., 1998; Whitsel et al., 2009): unlike non-nociceptive somatosensory input which predominantly elicits responses in area 3b (Nangini et al., 2006) showed that although the spatial location of early components A β -fiber ERPs and vibrotactile A β -SSEPs within S1 are slightly different, both probably originate from area 3b), nociceptive somatosensory inputs predominantly elicit responses in area 3a and/or area 1 (Baumgartner et al., 2011). Because activity originating from these different sub-regions of S1 may be expected to project differently onto the scalp, this could also contribute to explaining the difference in scalp topography of A β - and A δ -SSEPs.

Most importantly, whereas late nociceptive and non-nociceptive transient ERPs were identifiable only at the onset of the stimulation train, nociceptive and non-nociceptive SSEPs elicited by > 3 Hz stimulation were present during the entire duration of the stimulation train. The fact that these SSEPs were entirely unaffected by stimulus repetition suggests that, unlike the transient ERPs, they reflect cortical processes that do not habituate. In other words, our observations indicate that nociceptive and non-nociceptive SSEPs elicited by > 3 Hz stimulation and the late components of transient nociceptive and non-nociceptive ERPs reflect functionally distinct cortical processes. What is therefore their functional significance? Recent studies have suggested that the marked habituation of transient nociceptive ERPs is due to the fact that these EEG responses reflect mainly non nociceptive-specific cognitive processes involved in the detection and reaction to the occurrence of a sudden and thus salient change in the sensory environment (Bromm and Treede, 1984; Garcia-Larrea, 2004; Iannetti et al., 2008; Mouraux and Plaghki, 2006). This hypothesis is supported by our own observation that transient nociceptive ERPs – as well as the late components of non-nociceptive ERPs – were elicited only by the sudden onset of the 10-s stimulation trains. Conversely, the lack of habituation of > 3 Hz A β - and A δ -SSEPs indicates they are less imprinted by stimulus-driven attentional processes and, hence, that they reflect more obligatory stages of sensory processing.

SSEPs are often considered to be the consequence of a stimulus-driven entrainment of neurons responding to the periodically-modulated feature of the eliciting stimulus. At preferred frequencies

of stimulation, the network – or part of the network – of neurons responding to that stimulus feature is thus thought to “resonate” to the stimulus (Herrmann, 2001; Vialatte et al., 2010). According to Herrmann (2001), the preferred response frequencies of SSEPs could be related to the temporal characteristics of the connections constituting the resonating network of interconnected neurons. For non-nociceptive vibrotactile stimulation, Tobimatsu et al. (1999) found maximal SSEP amplitudes for stimulation frequencies around 20 Hz. In the present study, considering SSEPs elicited by > 3 Hz stimulation, we found maximal A β -SSEP amplitudes at higher stimulation frequencies (43 Hz). This could be explained by the fact that Tobimatsu et al. relied on mechanical vibrotactile stimulation while we relied on transcutaneous electrical stimulation: the afferent volley generated by the mechanical activation of touch-sensitive afferents is probably less synchronous than the afferent volley generated by the direct electrical activation of nerve fibers. Hence, at high stimulation frequencies, the afferent input generated by mechanical stimulation may lose most of its periodicity.

In conclusion, the present study shows that nociceptive SSEPs elicited by the direct and selective activation of nociceptive afferents using intra-epidermal electrical stimulation reflect cortical processes that are clearly distinct from those underlying transient nociceptive ERPs and, possibly, more specifically related to the processing of nociceptive input.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at [doi:10.1016/j.neuroimage.2011.12.015](https://doi.org/10.1016/j.neuroimage.2011.12.015).

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