EEG Frequency Tagging to Dissociate the Cortical Responses to Nociceptive and Nonnociceptive Stimuli

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Abstract

■ Whether the cortical processing of nociceptive input relies on the activity of nociceptive-specific neurons or whether it relies on the activity of neurons also involved in processing nonnociceptive sensory input remains a matter of debate. Here, we combined EEG "frequency tagging" of steady-state evoked potentials (SS-EPs) with an intermodal selective attention paradigm to test whether the cortical processing of nociceptive input relies on nociceptive-specific neuronal populations that can be selectively modulated by top–down attention. Trains of nociceptive and vibrotactile stimuli (Experiment 1) and trains of nociceptive and visual stimuli (Experiment 2) were applied concomitantly to the same hand, thus eliciting nociceptive, vibrotactile, and visual SS-EPs. In each experiment, a target detection task was used to focus attention toward one of the two concurrent streams of sensory input. We found that selectively attending to nociceptive or vibrotactile somatosensory input indistinctly enhances the magnitude of nociceptive and vibrotactile SS-EPs, whereas selectively attending to nociceptive or visual input independently enhances the magnitude of the SS-EP elicited by the attended sensory input. This differential effect indicates that the processing of nociceptive input involves neuronal populations also involved in the processing of touch, but distinct from the neuronal populations involved in vision. ■

INTRODUCTION

Conscious perception of an external stimulus requires encoding by sensory organs, transmission and processing within a dedicated sensory system, and activation of appropriate sensory cortical areas (Treede & Apkarian, 2008). In healthy individuals, it is clearly established that the perception of pain relies on the encoding of nociceptive input by specific receptors, that is, Aδ and C fiber nociceptors, and on the transmission of this nociceptive input to the thalamus and cortex through specific ascending pathways, that is, the spinothalamic tracts (McMahon & Wall, 2013). It is also clearly established that transient painful stimuli activate a vast network of cortical areas, including the primary (S1) and secondary (S2) somatosensory cortices, the insula, the posterior parietal cortex, the ACC, and parts of the pFC (Apkarian, Bushnell, Treede, & Zubieta, 2005; Garcia-Larrea, Frot, & Valeriani, 2003; Peyron, Laurent, & Garcia-Larrea, 2000). However and contrasting with other sensory systems, there appears to be no spatially segregated cortical area devoted specifically to the processing of nociceptive input, that is, a cortical area that could be considered as a "primary nociceptive cortex" (Iannetti & Mouraux, 2010; Andersson & Rydenhag, 1985). Indeed, the brain areas responding to nociceptive input are all also involved in other sensory, emotional, cognitive, motor, or autonomic functions (Legrain, Iannetti, Plaghki, & Mouraux, 2011; Iannetti & Mouraux, 2010; Treede & Apkarian, 2008).

Whether the cortical processing of nociceptive input relies on the activity of nociceptive-specific neurons or whether it relies on neurons also processing other types of sensory input—in particular innocuous somatosensory input (Iannetti & Mouraux, 2010)—thus remains a crucial open question in pain neuroscience.

In favor of the view that perceiving pain involves the activity of nociceptive-specific neurons, single-cell recordings in animals have shown the existence of neurons responding specifically to nociceptive stimuli, especially in S1 (Whitsel, Favorov, Li, Quibrera, & Tommerdahl, 2009; Apkarian et al., 2005; Kenshalo, Iwata, Sholas, & Thomas, 2000; Bushnell et al., 1999) and the parasylvian cortex (Apkarian et al., 2005; Treede, Apkarian, Bromm, Greenspan, & Lenz, 2000). Some of these neurons exhibit punctate receptive fields and/or their frequency of discharge appears to encode the intensity of the stimulus, suggesting a specific role in the sensoridiscriminative representation of pain (Hofbauer, Rainville, Duncan, & Bushnell, 2001; Timmermann et al., 2001; Kenshalo, Chudler, Anton, & Dubner, 1988). Moreover, whereas vibrotactile afferents primarily project to Area 3b of S1, neurons responding to nociceptive stimuli have been mainly identified in Area 1 and/or Area 3a, suggesting that the processing of nociceptive and vibrotactile inputs within S1 may involve spatially distinct subregions (Vierck, Whitsel, Favorov, Brown, & Tommerdahl, 2013; Baumgartner, Vogel, Ohara, Treede,

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& Lenz, 2011; Whitsel et al., 2009; Kenshalo et al., 2000; Tommerdahl et al., 1998; Mountcastle, Steinmetz, & Romo, 1990). Furthermore, lesions of the parasylvian cortex, in particular, lesions including the posterior insula, have been reported to cause a deficit in pain perception (Garcia-Larrea, 2012; Greenspan, Lee, & Lenz, 1999), and epileptic activity or direct electrical stimulation of this region can, among other things, cause painful experiences (Ostrowsky et al., 2002), suggesting that parts of the parasylvian cortex may contain neuronal populations preferentially involved in the perception of pain (Treede & Apkarian, 2008; Greenspan et al., 1999).

However, one main common feature of nociceptive-specific neurons throughout the cortex is their scarcity (reviewed in Iannetti & Mouraux, 2010). Furthermore, because of the intrinsic significance of nociceptive input (Belmonte & Viana, 2008), brain activity that has been interpreted as "nociceptive-specific" could, at least in some cases, reflect the activity of neurons that are unspecific for nociception and, instead, mainly be involved in the detection of salient sensory input regardless of whether that input is conveyed through nociceptive pathways (Legrain et al., 2011). Supporting this view, several studies have shown the existence of neurons responding to both nociceptive stimuli and stimuli belonging to another sensory modality, especially if the stimuli convey information signaling a potential impact on the body (e.g., a visual stimulus moving toward the body; Hutchison, Davis, Lozano, Tasker, & Dostrovsky, 1999; Kenshalo & Douglass, 1995; Dong, Chudler, Sugiyama, Roberts, & Hayashi, 1994).

Nonetheless, one cannot rule out the possibility that nociceptive stimuli activate sparse and intermingled clusters of nociceptive-specific neurons, whose synaptic activity cannot be spatially distinguished from that of non-nociceptive-specific neurons, especially when using conventional functional neuroimaging techniques that sample human brain activity at population level.

For this reason, this study aimed to explore nociceptive processing in the human cortex using a different approach, referred to as "frequency tagging" with steady-state evoked potentials (SS-EP; Regan, 1989). It has been shown, for example, that if one presents simultaneously an auditory stimulus modulated at frequency f_1 and a visual stimulus modulated at frequency f_2, this elicits two distinct peaks in the EEG frequency spectrum at frequencies f_1 and f_2, respectively, tagging the cortical activity elicited by the auditory and visual stimuli (Colon, Legrain, & Mouraux, 2012; Giani et al., 2012; Keitel, Schroger, Saupe, & Muller, 2011; Nozaradan, Peretz, & Mouraux, 2011; de Jong, Toffanin, & Harbers, 2010; Saupe, Schroger, Andersen, & Muller, 2009; Talsma, Doty, Strowd, & Woldorff, 2006). Most interestingly, discrimination between the activities elicited by each of the two streams of sensory input is not dependent on the spatial resolution of the brain sampling technique, as they will be isolated in the frequency domain even if the eliciting neuronal populations are spatially intermingled. Furthermore, using the "frequency tagging" approach, previous studies on intermodal selective attention have shown that selectively attending one of several concurrent streams of sensory input belonging to different sensory modalities increases the magnitude of the SS-EP elicited by the sensory inputs of the attended modality (Giani et al., 2012; Keitel et al., 2011; Nozaradan et al., 2011; de Jong et al., 2010; Saupe et al., 2009; Talsma et al., 2006), probably through a selective enhancement of the responsiveness of the neuronal populations responding to the attended input. The approach has also been used within a given sensory modality. For example, it was shown that selectively attending to a given color selectively increases the magnitude of the visual SS-EP elicited by flickering dots of the attended color, probably through a top–down enhancement of the responsiveness of neurons responding preferentially to the attended visual feature (Muller et al., 2006; see also Hillyard, Vogel, & Luck, 1998; Morgan, Hansen, & Hillyard, 1996). Hence, it can be hypothesized that if the processing of nociceptive and nonnociceptive somatosensory inputs at least partly relies on neuronal populations preferentially responding to one of the two types of somatosensory inputs, SS-EPs elicited by combined nociceptive and nonnociceptive somatosensory stimulation while participants selectively attend one of the two streams of somatosensory input will show a selective enhancement of the SS-EP elicited by the attended input (Legrain et al., 2012; Legrain, Guerit, Bruyer, & Plaghki, 2002). Conversely, if the processing of nociceptive and nonnociceptive somatosensory inputs does not involve neuronal populations selective for nociceptive or nonnociceptive somatosensory input, selectively attending to the noxious or the innocuous stream of somatosensory input will indistinctly enhance the SS-EPs elicited by both types of stimuli.

Finally, a small number of studies have suggested that cortical integration of different streams of sensory input can be revealed by the appearance of additional SS-EPs, appearing at nonlinear cross-modulation frequencies corresponding to the sum or differences of the eliciting frequencies or their harmonics (i.e., $nf_1 \pm mf_2$, where n and m are integers) and reflecting the activity of multisensory neurons onto which the different sensory inputs converge (Giani et al., 2012; Regan, He, & Regan, 1995).

These different hypotheses were tested in this study, in which we compared the effect of intermodal selective attention on the SS-EPs elicited by concomitant nociceptive and tactile stimulation (Experiment 1) and concomitant nociceptive and visual stimulation (Experiment 2).

METHODS

Participants

Sixteen healthy volunteers (10 men, aged 19–35 years, 13 right-handed) took part in the nociceptive–tactile experiment (Experiment 1). Twelve healthy volunteers

(six men, aged 23–33 years, 10 right-handed) took part in the nociceptive–visual experiment (Experiment 2). All participants had normal or corrected-to-normal vision and no prior history of neurological, psychiatric, and chronic pain disorders. Before the experiments, participants were familiarized with the experimental setup and task and exposed to a small number of test stimuli. Written informed consent was obtained from all participants, and they were paid for their participation. The study was approved by the local ethics committee and conformed to the latest revision of the Declaration of Helsinki.

Stimuli

Nociceptive Somatosensory Stimulation

Infrared laser stimulation was used to selectively activate heat-sensitive nociceptive free nerve endings of the skin (Plaghki & Mouraux, 2003, 2005). The CO_2 laser (wavelength, 10.6 μm) was designed and built in the Department of Physics of the Université catholique de Louvain. Brief (20 msec) and focal (5 mm beam diameter) laser pulses were delivered to the left- or right-hand dorsum, as follows. The participants were seated in a chair with one of the two hands resting on a table (Figure 1). Before the experimental session, the energy of the laser stimulus was defined for each hand, such as to slightly exceed the thermal activation threshold of Aδ nociceptors, defined as the energy at which a single laser pulse was detected with an RT shorter than 650 msec (i.e., compatible with the conduction velocity of Aδ fibers; Churyukanov, Plaghki, Legrain, & Mouraux, 2012). The average energy density of the stimulus was 12.6 ± 2.1 mJ/mm^2. This energy density was similar to the energy density used in our previous studies using single stimuli (e.g., Mouraux & Plaghki, 2007a, 2007b) or trains of stimuli (e.g., Mouraux et al., 2011). Participants described the sensation elicited by these stimuli as a short-lasting pricking/burning sensation. Thirty points were then defined on each hand dorsum at locations where the laser beam was close to orthogonal relative to the skin surface. The distance between two points was approximately 5 mm. The target of the laser stimulus was displaced using a dual-axis galvanometer mirror positioning system with switching times as short as a few microseconds (LSST-10.6-12-105-8062-3A, Sintec Optronics, Singapore). The distance between the mirrors and the hand dorsum was approximately 35 cm. The stimuli were delivered as trains lasting 5 sec and consisting in 30 laser pulses delivered at a rate of 6 Hz to each of the 30 predefined locations. The target of the laser stimulus was displaced after each pulse to avoid skin overheating and possible sensitization or habituation of the activated nociceptors. The displacement followed a zigzag path of points beginning on the left side of the hand dorsum and ending on the right side of the

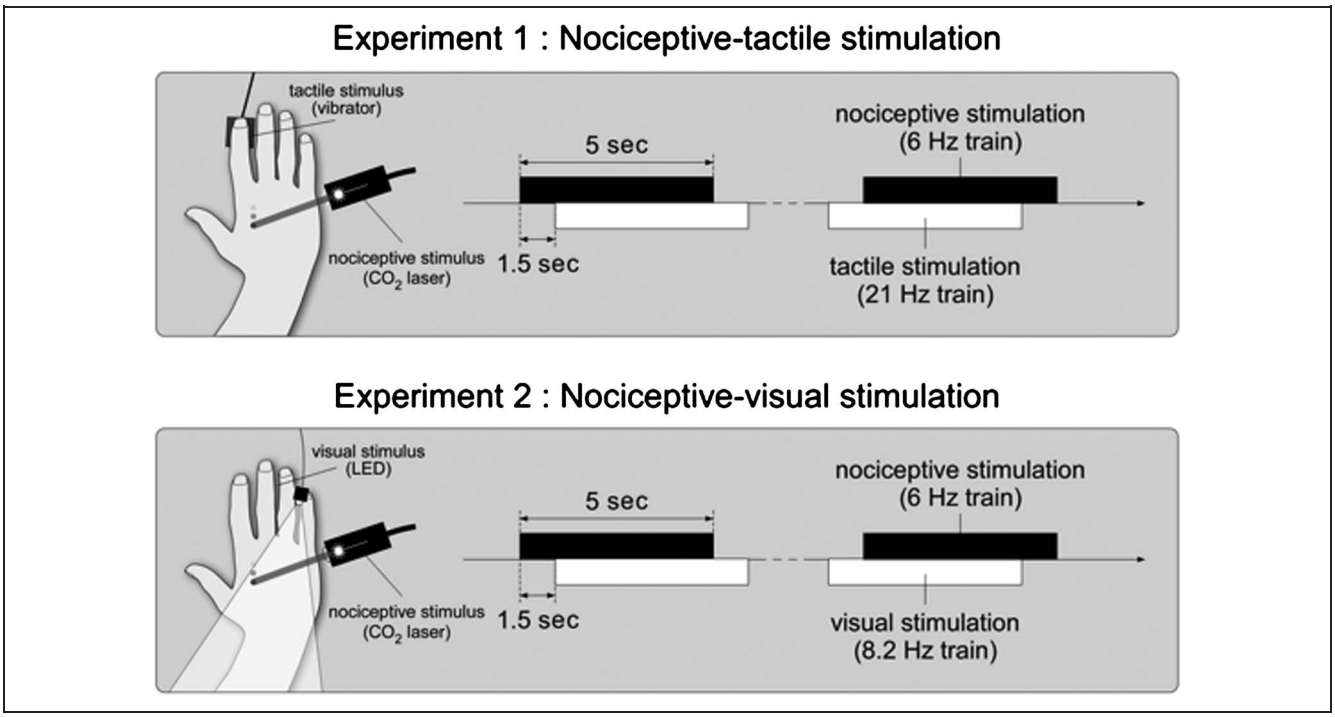

Figure 1. In the nociceptive–tactile experiment (Experiment 1), nociceptive and vibrotactile stimuli were applied to the left- or right-hand dorsum. The nociceptive stimuli consisted in 30 laser pulses delivered at a rate of 6 Hz to predefined locations on the hand. The vibrotactile stimuli consisted in a 128-Hz carrier frequency periodically modulated at 21 Hz, generated by a recoil-type vibrotactile transducer positioned on the index fingertip. Each stimulation train lasted 5 sec. A 1.5-sec delay separated the onsets of the two trains. In the nociceptive–visual experiment (Experiment 2), the vibrotactile stimulus was replaced by a visual stimulus, consisting in LED placed close to the fifth finger, flickering at 8.2 Hz.

hand dorsum. The frequency of 6 Hz was chosen relative to previous studies using nociceptive SS-EPs (Colon, Nozaradan, Legrain, & Mouraux, 2012; Mouraux et al., 2011). The stimulation trains were perceived by the participants as a continuous burning/pricking sensation.

Vibrotactile Stimulation

Vibrotactile stimuli were generated by a recoil-type vibrotactile transducer driven by a standard audio amplifier (Haptuator, Tactile Labs, Inc., Montreal, Canada) and positioned on the left or right index fingertip. The vibrotactile stimulus lasted 5 sec and consisted in a 128-Hz carrier frequency periodically modulated at 21 Hz (previous studies have shown that the optimal modulation frequency to elicit vibrotactile SS-EPs lies within the range of 20–30 Hz; Colon, Legrain, et al., 2012; Snyder, 1992). The same maximum output voltage was used in all participants (3 V). At this output voltage, the carrier frequency (128 Hz) may be expected to generate forces of up to 0.45 N. The stimulation trains were perceived by the participants as a clear continuous vibration. The vibration was neither qualified as painful or as unpleasant by the participants.

Visual Stimulation

Visual stimuli were continuous flashes generated by means of a white light-emitting diode (LED) with a 12-lm luminous flux, a 5.10-cd luminous intensity, and a 120° visual angle (GM5BW97333A, Sharp Corporation, Osaka, Japan). The LED was placed on the fifth finger of the right or left hand, according to the stimulation block. The visual stimuli were delivered as trains lasting 5 sec during which the LED was switched on and off with a periodicity of 8.2 Hz. The frequency of 8.2 Hz was chosen in relation with the preferred range of stimulation frequencies to elicit visual SS-EPs (Vialatte, Maurice, Dauwels, & Cichocki, 2010). The stimulation trains were perceived by the as a continuous flashing white light.

Procedures

Both experiments were conducted in a dim and silent room. During the recordings, participants wore protective goggles. White noise was presented continuously through headphones, at a comfortable listening level, to mask any sounds produced by the laser stimulator as well as the vibrotactile stimulator. In the nociceptive–tactile experiment, participants were asked to maintain their gaze on a central fixation cross in front of them. In the nociceptive–visual experiment, they were asked to maintain their gaze on a fixation cross placed on the right side of the table when the left hand was stimulated and on the left side of the table when the right hand was stimulated.

In the nociceptive–tactile experiment, participants received nociceptive and tactile stimuli. The two types of stimuli were concomitantly applied to the left hand and to the right hand in separate blocks. Participants were asked to direct their attention toward one of the two sensory modalities such as to detect the occasional occurrence of a target (change within the stimulation train) in the attended modality, also in separate blocks.

In the nociceptive modality, the target consisted in a jump of stimulus location at the beginning of the train (rather than beginning on the left side of the hand, the predefined zigzag path began on the middle of the hand dorsum). In the tactile modality, the target consisted in a 70-msec interruption of the vibrator and could occur at any time during the 5-sec stimulation train. These targets were defined after several pilot experiments to ensure that the task was feasible but sufficiently difficult to require attention to be fully focused toward the attended modality. At the end of each trial, participants had to report whether a target was present or not in the attended modality by responding "yes" or "no." No target was presented in the unattended modality. To ease selection of the sensory input belonging to the attended modality, the onsets of the nociceptive and tactile stimulation trains were asynchronous with an interonset delay of 1.5 sec. Therefore, each stimulation train lasted 5 sec but an entire trial lasted 6.5 sec (Figure 1). The order of the trains (nociceptive–tactile, tactile–nociceptive) was randomized across trials. A 10-sec intertrial interval separated each trial. The experiment consisted in eight blocks of stimulation presented in random order: four different block types according to the selective attention task (attend nociceptive vs. attend tactile) and stimulus location (left hand vs. right hand), repeated twice. Each block contained 12 trials (including two or three target trials that were discarded from the analysis). Therefore, in each participant, 20 trials were collected for each condition. The entire recording lasted approximately 1.3 hr.

The nociceptive–visual experiment was identical to the nociceptive–tactile experiment, except for the fact that the tactile stimulus was replaced by a visual stimulus. In the visual modality, the change consisted in a 70-msec interruption of the flashing LED, which could occur at any time during the 5-sec stimulation train.

Measures

Behavioral Measures

For each experiment and each attention condition, behavioral performance, merged for left and right hands, was estimated by an accuracy index computed as follows: (number of true positives + number of true negatives)/(number of true positives + number of true negatives + number of false negatives + number of false positives; Macmillan & Creelman, 2005), where true positives are defined as a correct detection of a target stimulus in the

attended stream, true negatives as a correct rejection of an attended nontarget stimulus, false positives as a false alarm to an attended nontarget stimulus, and false negatives as a missed response to an attended target stimulus. In each experiment, the accuracy indexes to the two selective attention conditions were compared using a paired *t* test (SPSS 18, IBM).

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 kΩ. 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. Signals were amplified and digitized using a sampling rate of 1000 Hz and an average reference (64-channel high-speed amplifier, Advanced Neuro Technology, The Netherlands).

Analysis of the EEG data was carried out using Analyzer 1.05 (Brain Products, Germany) and Letswave 5 (nocions.webnode.com/letswave; see also Mouraux & Iannetti, 2008). The continuous EEG recordings were filtered using a 0.01–0.3 Hz high-pass Butterworth filter to remove slow drifts in the recorded signals. Nonoverlapping EEG epochs were then obtained by segmenting the recordings from 0 to 6.5 sec relative to the onset of the first stimulation train. Each EEG epoch was demeaned using the time interval ranging from 0 to 6.5 sec. Artifacts due to eye blinks or eye movements were then removed using a validated method based on an independent-component analysis (FastICA algorithm; Hyvarinen & Oja, 2000). In addition, epochs with amplitude values exceeding ±500 μV (i.e., epochs likely to be contaminated by an artifact) were rejected. These epochs constituted 4.8 ± 6.6% of the total number of epochs in the nociceptive–tactile experiment and 3.3 ± 3.3% of the total number of epochs in the nociceptive–visual experiment. Finally, the 6.5-sec epochs were segmented in 5-sec epochs relative to the onset of each stimulation train, and separate average waveforms were computed for each modality (nociceptive and tactile in the nociceptive–tactile experiment; nociceptive and visual in the nociceptive–visual experiment), attended condition (attend nociceptive vs. tactile in the nociceptive–tactile experiment; attend nociceptive vs. visual in the nociceptive–visual experiment), and stimulated hand (left vs. right hand). Finally, the obtained average waveforms were transformed in the frequency domain using a discrete Fourier transform (FFTW; Frigo & Johnson, 1998), yielding an amplitude spectrum (μV) ranging from 0 to 500 Hz with a frequency resolution of 0.1 Hz (Bach & Meigen, 1999).

Within the obtained frequency spectra, the signal amplitude at 6 Hz (nociceptive stimulus) and 21 Hz (tactile stimulus) in the nociceptive–tactile experiment and at 6 Hz (nociceptive stimulus) and 8.2 Hz (visual stimulus) in the nociceptive–visual experiment was measured at each EEG electrode. These measures may be expected to correspond to the sum of the stimulus-evoked steady-state response (i.e., the nociceptive, tactile, or visual SS-EP) and unrelated residual background noise. Therefore, to obtain valid estimates of the magnitude of the elicited SS-EPs, 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 (±0.3–0.5 Hz relative to the expected SS-EP frequency; Mouraux et al., 2011). In the absence of a steady-state response, this noise-subtracted average signal amplitude may be expected to tend toward zero. Hence, to assess the significance of the responses measured at each frequency, experimental condition, and electrode, a *t* test against zero was used to determine whether the magnitude of the noise-subtracted signal amplitude was significantly greater than zero (SPSS 18, IBM).

Estimation of SS-EP Amplitude

To avoid any bias related to an arbitrary selection of electrodes, the analyses were performed using the estimates of noise-subtracted SS-EP amplitudes averaged across all scalp channels. As there was no statistical difference between the SS-EP amplitude measures obtained from stimulation of the left and right hands in the two experiments and the two conditions (nociceptive–visual experiment: all $t(11) > -2.11$, $p > .06$; nociceptive–tactile experiment: all $t(15) > -0.9$, $p > .38$), the noise-subtracted SS-EP amplitudes were averaged for left- and right-hand stimulation to reduce the number of experimental factors and to increase the signal-to-noise ratio.

Effect of Selective Attention on the Magnitude of SS-EPs

To assess whether the magnitude of the nociceptive SS-EP was differently affected by selectively attending to tactile input versus selectively attending to visual input, an ANOVA with one within-subject factor (Attention: attend the nociceptive modality vs. attend another modality) and one between-subject factor (Experiment: nociceptive–tactile vs. nociceptive–visual) was performed (SPSS 18, IBM). Next, a repeated-measures ANOVA was used to assess the effect of selective attention on the amplitude of the nociceptive, tactile, and visual SS-EPs obtained in each of the two experiments, with the following two factors: Modality (nociceptive vs. tactile in the nociceptive–tactile experiment; nociceptive vs. visual in the nociceptive–visual experiment) and Attention (attend nociceptive vs. tactile in the nociceptive–tactile experiment; attend nociceptive vs. visual in the nociceptive–visual experiment). Size effects of ANOVAs were measured with partial eta-squared (η^2_p), and α was set at .05. When significant, pairwise comparisons were performed using paired-sample

t tests, and in this case, α was set at .025 to correct multiple comparisons using the Bonferroni criterion.

Cross-modulation Frequencies

To examine the presence of cross-modulation frequencies, the signal amplitude averaged across all scalp channels at 27 and 15 Hz, corresponding to the sum and difference of the frequency of the nociceptive (6 Hz) and tactile (21 Hz) stimuli in the nociceptive–tactile experiment, and at 14.2 and 2.2 Hz, corresponding to the sum and difference of the frequency of the nociceptive (6 Hz) and visual (8.2 Hz) stimuli in the nociceptive–visual experiment was measured. To assess the significance of the responses measured at each frequency, a t test against zero was used to determine whether the magnitude of the noise-subtracted signal amplitude was significantly greater than zero.

RESULTS

Task Performance

In the nociceptive–tactile experiment, the accuracy index in the "attend nociceptive" condition was 0.86 ± 0.12, and the accuracy index in the "attend tactile" condition was 0.85 ± 0.11. This difference was not significantly different across participants, $t(15) = 0.28$, $p = .79$, $d = 0.09$. In the nociceptive–visual experiment, the accuracy index in the "attend nociceptive" condition was 0.86 ± 0.11, and the accuracy index in the "attend visual" condition was 0.99 ± 0.02. This difference was significantly different across participants, $t(11) = -4.75$, $p = .001$, $d = 2.4$, suggesting that the performance in detecting the visual target was better than the performance in detecting the nociceptive target.

Nociceptive SS-EP

In the nociceptive–tactile experiment, nociceptive stimulation elicited an increase in signal amplitude at 6 Hz in the "attend nociceptive" condition (group-level average of noise-subtracted amplitudes pooled across all scalp channels: 0.02 ± 0.03 μV) as well as in the "attend tactile" condition (0.02 ± 0.03 μV). This increase in signal amplitude was significantly different from zero ("attend nociceptive" condition: $t(15) = 3.15$; $p = .007$, $d = 1.6$; "attend tactile" condition: $t(15) = 2.35$, $p = .03$, $d = 1.2$). The scalp topography of the nociceptive SS-EP was maximal at the scalp vertex and symmetrically distributed over the two hemispheres (Figure 2). In the nociceptive–visual experiment, nociceptive stimulation elicited an increase in signal amplitude at 6 Hz in the "attend nociceptive" condition (0.03 ± 0.04 μV; difference from zero: $t(11) = 2.77$; $p = .02$, $d = 1.67$) but not in the "attend visual" condition (0.005 ± 0.02 μV; difference from zero: $t(11) = 1.12$, $p = .29$, $d = 0.68$). Such as in the nociceptive–tactile experiment, the scalp topography of the nociceptive SS-EP was maximal at the scalp vertex and symmetrically distributed over the two hemispheres (Figure 2).

Vibrotactile SS-EP

In the nociceptive–tactile experiment, vibrotactile stimulation elicited an increase in signal amplitude at 21 Hz in both the "attend nociceptive" condition (0.05 ± 0.04 μV) and the "attend tactile" condition (0.05 ± 0.04 μV). In both conditions, this increase was significantly different from zero ("attend nociceptive" condition: $t(15) = 5.61$, $p < .001$, $d = 2.89$; "attend tactile" condition: $t(15) = 5.86$, $p < .001$, $d = 3.03$). The scalp topography of the vibrotactile SS-EP was maximal over the parietal region contralateral to the stimulated side and markedly different from that of the nociceptive SS-EP (Figure 2).

Visual SS-EP

In the nociceptive–visual experiment, visual stimulation elicited a significant increase in signal power at 8.2 Hz in both the "attend nociceptive" condition (0.07 ± 0.045 μV; difference from zero: $t(11) = 5.36$, $p < .001$, $d = 3.23$) and the "attend visual" condition (0.11 ± 0.05 μV; difference from zero: $t(11) = 7.18$ $p < .001$, $d = 4.33$). The scalp topography of the visual SS-EP was maximal over occipital regions and markedly different from that of the nociceptive SS-EP (Figure 2).

Modulation of SS-EP Amplitude by Intermodal Selective Attention

The effect of selectively attending to vibrotactile input (nociceptive–tactile experiment) versus selectively attending to visual input (nociceptive–visual experiment) on the magnitude of the nociceptive SS-EPs was assessed using an ANOVA with one within-subject factor (Attention: attend nociceptive vs. attend other) and one between-subject factor (Experiment: nociceptive–tactile vs. nociceptive–visual). This revealed a significant main effect of Attention ($F(1, 26) = 7.89$, $p = .009$, $\eta^2_p = .23$), no main effect of Experiment ($F(1, 26) = 0.23$, $p = .64$, $\eta^2_p = .009$), and, most importantly, a significant interaction between the factors Attention and Experiment ($F(1, 26) = 4.46$, $p = .045$, $\eta^2_p = 0.15$). This interaction indicates that the effect of selective attention on the magnitude of nociceptive SS-EPs was significantly different between the group of participants having performed the nociceptive–tactile experiment and the group of participants having performed the nociceptive–visual experiment (Figure 5).

On average, in the nociceptive–tactile experiment, attending to the nociceptive stimulus or attending to the vibrotactile stimulus did not modulate the magnitude of the nociceptive and vibrotactile SS-EPs. Indeed, the magnitudes were highly similar across the two experimental

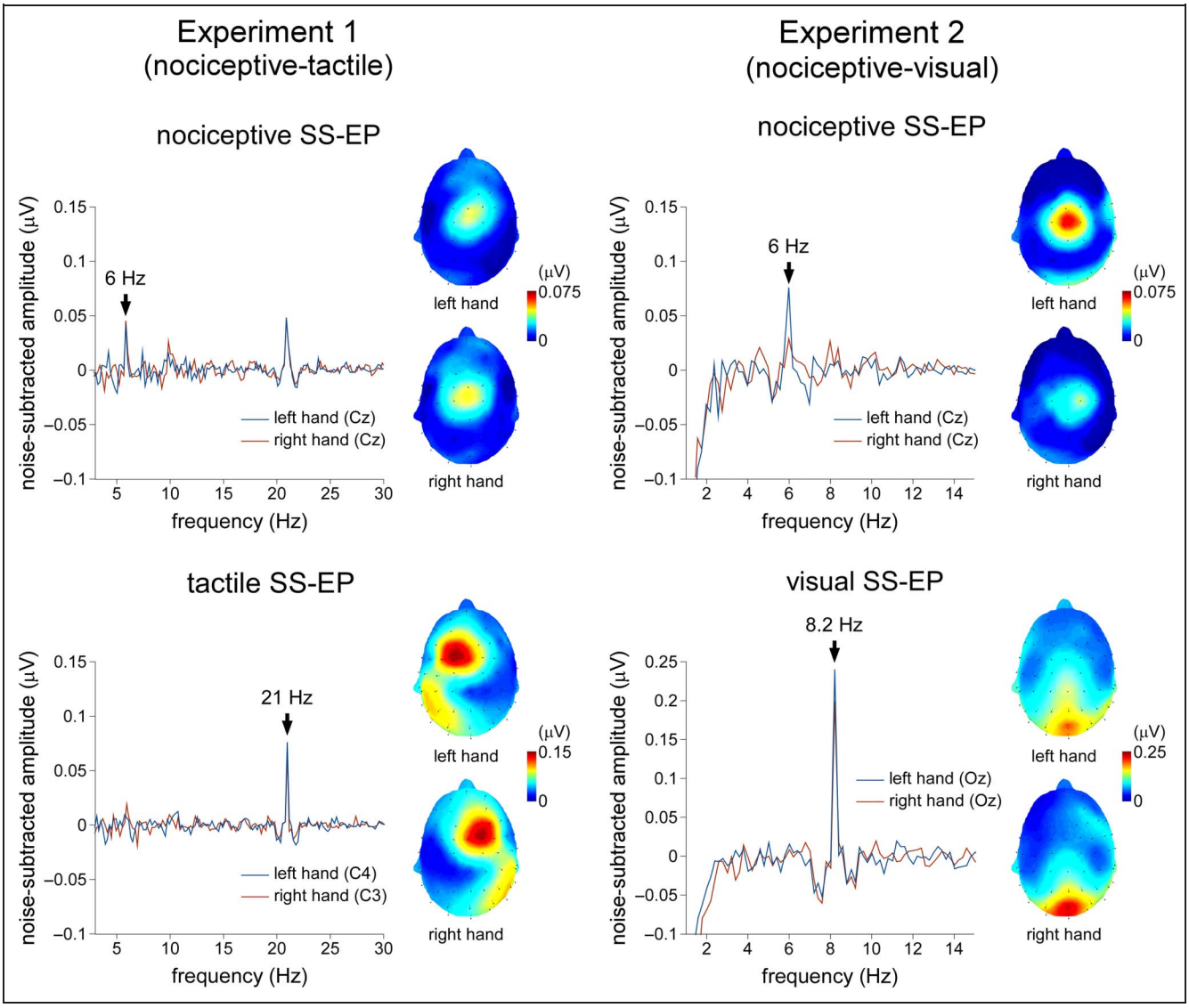

Figure 2. Experiment 1 (nociceptive–tactile). The top panel represents the noise-subtracted EEG amplitude spectrum (μV) of the nociceptive SS-EP measured at Cz (group-level average). Nociceptive stimulation elicited a significant increase in signal power at 6 Hz whose scalp topography was maximal over the scalp vertex regardless of the stimulated hand. The bottom panel represents the noise-subtracted EEG amplitude spectrum (μV) of the vibrotactile SS-EP measured at the central electrode contralateral to the stimulated hand (left hand: C4; right hand: C3; group-level average). Vibrotactile stimulation elicited a significant increase in signal power at 21 Hz, whose scalp topography was maximal over the parietal region contralateral to the stimulated hand. Experiment 2 (nociceptive–visual). The top panel represents the noise-subtracted EEG amplitude spectrum (μV) measured at Cz (group-level average). Such as in Experiment 1, nociceptive stimulation elicited a significant increase in signal power at 6 Hz whose scalp topography was maximal over the scalp vertex regardless of the stimulated hand. The bottom panel represents the noise-subtracted EEG amplitude spectrum (μV) measured at Oz (group-level average). Visual stimulation elicited a significant increase in signal power at 8.2 Hz whose scalp topography was maximal over occipital regions.

conditions (attend nociceptive vs. attend tactile; Figure 3). In the nociceptive–tactile experiment, the repeated-measures ANOVA with the factors Modality (nociceptive vs. tactile) and Attention (attend nociceptive vs. attend tactile) showed a significant main effect of Modality ($F(1, 15) = 9.39$, $p = .008$, $\eta^2_p = .39$). On average, the magnitude of the vibrotactile SS-EP was greater than the magnitude of the nociceptive SS-EP. There was no main effect of Attention ($F(1, 15) = 0.12$, $p = .74$, $\eta^2_p = .008$) and, most importantly, no significant interaction between the two factors ($F(1, 15) = 0.07$, $p = .79$, $\eta^2_p = .004$), suggesting that the magnitude of nociceptive and vibrotactile SS-EPs were not modulated by the focus of attention.

In the nociceptive–visual experiment, the repeated-measures ANOVA with the factors Modality (nociceptive vs. visual) and Attention (attend nociceptive vs. attend visual) showed also a significant main effect of Modality ($F(1, 11) = 20.6$, $p = .001$, $\eta^2_p = .65$). On average, the magnitude of the visual SS-EP was greater than the magnitude of the nociceptive SS-EP. There was no main effect of Attention ($F(1, 11) = 0.55$, $p = .48$, $\eta^2_p = .05$). However and contrasting with the nociceptive–tactile

experiment, there was a significant interaction between the factors Modality and Attention ($F(1, 11) = 22.96$, $p = .001$, $\eta^2_p = .68$). This suggests that attending to the nociceptive stimulus or attending to the visual stimulus modulated the magnitude of the nociceptive and visual SS-EPs. Post hoc pairwise comparisons showed that the amplitude of the nociceptive SS-EP was greater in the "attend nociceptive" condition as compared with the "attend visual" condition ($t(11) = 2.58$, $p = .026$, $d = 0.79$), whereas the amplitude of the visual SS-EP was greater in the "attend visual" condition as compared with the "attend nociceptive" condition ($t(11) = -2.92$, $p = .01$, $d = 0.84$). Therefore, the magnitude of the nociceptive SS-EP was greater when attending the nociceptive stimulus as compared with when attending the visual stimulus. Conversely, the magnitude of the visual SS-EP was greater when attending the visual stimulus as compared with when attending the nociceptive stimulus (Figure 4).

Cross-modulation Frequencies

In the nociceptive–tactile experiment and in the nociceptive–visual experiment, no significant increase of signal amplitude was identified at frequencies corresponding to potential cross-modulation frequencies (27 and 15 Hz in the nociceptive–tactile experiment, 14.2 and 2.2 Hz in the nociceptive–visual experiment; Figures 2 and 5).

DISCUSSION

The aim of this study was to test whether the cortical processing of nociceptive input relies on nociceptive-specific

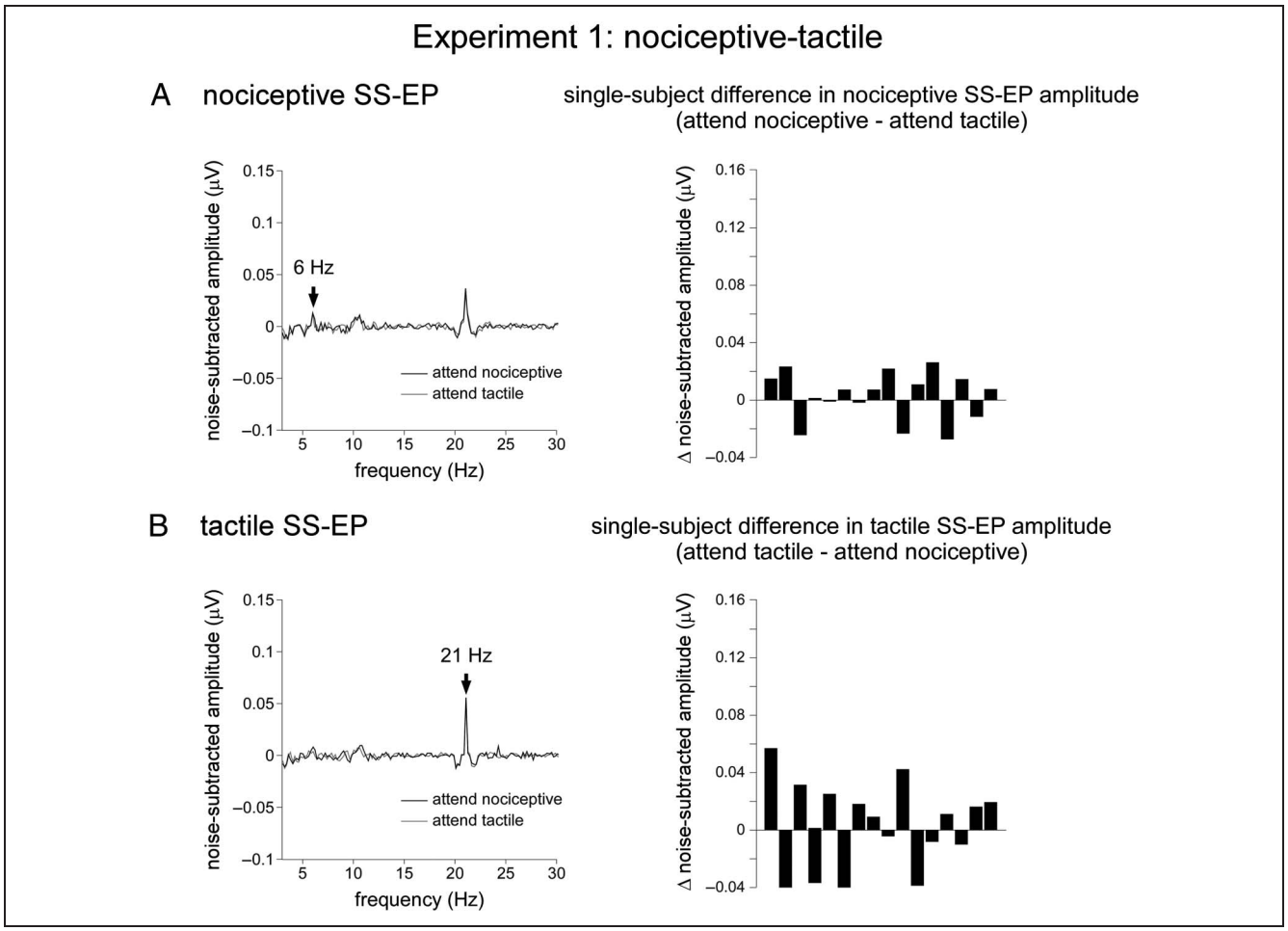

Figure 3. Effect of selective attention in the nociceptive–tactile experiment (Experiment 1). (A) The left graph represents the noise-subtracted EEG amplitude spectrum (μV) of the nociceptive SS-EP, averaged across all subjects and all scalp electrodes in the "attend nociceptive" (black waveform) and "attend tactile" (gray waveform) conditions. The right graph displays the single-subject differences between the magnitudes of the nociceptive SS-EPs obtained in the "attend nociceptive" and "attend tactile" conditions (noise-subtracted signal amplitude measured at 6 Hz). Note that its amplitude was not consistently different in the two conditions. (B) The left graph represents the noise-subtracted EEG amplitude spectrum (μV) of the tactile SS-EP, averaged across all subjects and all scalp electrodes in the "attend nociceptive" (black waveform) and "attend tactile" (gray waveform) conditions. The right graph displays the single-subject differences between the magnitudes of the vibrotactile SS-EPs obtained in the "attend tactile" and "attend nociceptive" conditions (noise-subtracted signal amplitude measured at 21 Hz). Such as for the nociceptive SS-EP, the amplitude of the vibrotactile SS-EP was not consistently different in the two conditions.

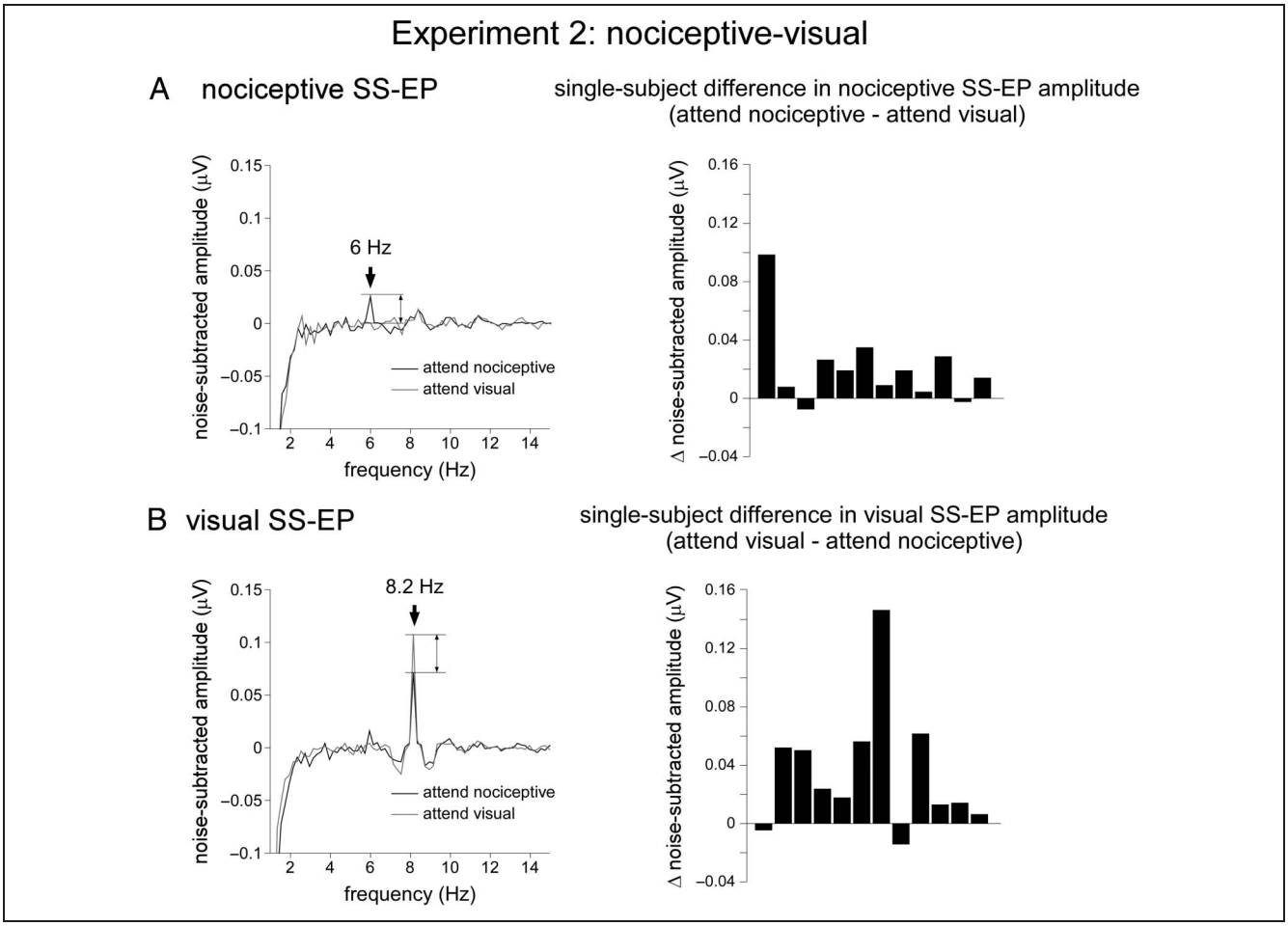

Figure 4. Effect of selective attention in the nociceptive–visual experiment (Experiment 2). (A) The left graph represents the noise-subtracted EEG amplitude spectrum (μV) of the nociceptive SS-EP, averaged across all subjects and all scalp electrodes in the "attend nociceptive" (black waveform) and "attend visual" (gray waveform) conditions. The right graph displays the single-subject differences between the magnitudes of the nociceptive SS-EPs obtained in the "attend nociceptive" and "attend visual" conditions (noise-subtracted signal amplitude measured at 6 Hz). Note that the amplitude of the nociceptive SS-EP was consistently greater in the "attend nociceptive" condition as compared with the "attend visual" condition. (B) The left graph represents the noise-subtracted EEG amplitude spectrum (μV) of the visual SS-EP, averaged across all subjects and all scalp electrodes in the "attend nociceptive" (black waveform) and "attend visual" (gray waveform) conditions. The right graph displays the single-subject differences between the magnitudes of the nociceptive SS-EPs obtained in the "attend visual" and "attend nociceptive" conditions (noise-subtracted signal amplitude measured at 8.2 Hz). Note that the amplitude of the visual SS-EP was consistently greater in the "attend visual" condition as compared with the "attend nociceptive" condition.

neuronal populations or whether it relies on nonspecific neuronal populations also involved in the processing of nonnociceptive sensory input. For this purpose, we used an experimental paradigm combining "frequency tagging" of the cortical activity elicited by different streams of sensory input with a cross-modal selective attention task to examine whether top–down attentional modulation mechanisms selectively increase the responsiveness of neuronal populations processing the attended sensory input and/or increase their phase-locking to the periodicity of the attended input (Nozaradan et al., 2011). Specifically, we hypothesized that if the cortical processing of nociceptive and nonnociceptive sensory inputs involves distinct neuronal populations, selective attention would selectively increase the magnitude of the SS-EPs elicited by the attended stream of sensory input. Conversely, if the cortical processing of the two sensory inputs involves the same neuronal populations, selective attention would indistinctly increase the magnitude of the responses elicited by the attended and unattended streams of sensory input.

Comparison of the effect of selective attention in the nociceptive–tactile and nociceptive–visual experiments revealed a significant difference in the effect of attending to vibrotactile input as compared with visual input on the magnitude of nociceptive SS-EPs. In the nociceptive–tactile experiment, we found that the magnitude of the nociceptive and tactile SS-EPs were unaffected by the focus of attention: the magnitude of the tactile and nociceptive SS-EPs were similar in both the "attend nociceptive" and the "attend tactile" conditions. This lack of differential effect of selective attention on the responses

elicited by nociceptive and nonnociceptive somatosensory input contrasted with the results obtained in the nociceptive–visual experiment, in which the magnitude of the nociceptive SS-EP was greater in the "attend nociceptive" condition as compared with the "attend visual" condition, whereas the visual SS-EP was greater in the "attend visual" condition as compared with the "attend nociceptive" condition. Taken together, these results indicate that nociceptive SS-EPs are differently affected by selectively attending to tactile or to visual input.

Consistent with the results of previous studies, the scalp topographies of nociceptive, vibrotactile, and visual SS-EPs were markedly different from one another. In both experiments, the scalp topography of nociceptive SS-EPs was maximal at the scalp vertex and symmetrically distributed over both hemispheres. The brain generators of nociceptive SS-EPs remain largely unknown. It was previously suggested that nociceptive SS-EPs could originate from a midline brain structure such as the cingulate cortex and/or bilateral activity originating from operculoinsular cortices (Colon, Nozaradan, et al., 2012; Mouraux et al., 2011). However, this should be confirmed using other techniques, such as the recording of local field potentials in patients with implanted electrodes for the presurgical evaluation of intractable epilepsy. Contrasting with the scalp topography of nociceptive SS-EPs, the scalp topography of vibrotactile SS-EPs was maximal over the parietal region contralateral to the stimulated hand, compatible with activity originating mainly from S1 (Colon, Nozaradan, et al., 2012; Mouraux et al., 2011; Giabbiconi, Trujillo-Barreto, Gruber, & Muller, 2007; Giabbiconi, Dancer, Zopf, Gruber, & Muller, 2004), whereas the scalp topography of visual SS-EPs was maximal over occipital regions compatible with activity originating mainly from visual areas (Vialatte et al., 2010; Saupe et al., 2009). These clear differences in topographical distribution indicate that the neuronal populations generating nociceptive SS-EPs reflect the activity of neuronal populations that are distinct from the neuronal populations generating nonnociceptive vibrotactile SS-EPs and visual SS-EPs. Yet, the present results show that selectively attending to nociceptive versus vibrotactile input does not differentially modulate the responses elicited by nociceptive versus vibrotactile somatosensory stimulation, whereas selectively attending to nociceptive versus visual input significantly modulates the responses elicited by nociceptive versus visual stimulation. This suggests that, although the bulk of nociceptive and nonnociceptive somatosensory SS-EPs reflect activity originating from distinct brain areas, they rely, at least in part, on the activity of shared neuronal populations. The responsiveness of these neurons would be indistinctly increased when selectively attending nociceptive input and when selectively attending vibrotactile input, but not when selectively attending visual input. Compatible with the hypothesis that the processing of nociceptive and nonnociceptive somatosensory inputs relies at least in part on the initial activation of shared neuronal populations, dynamic causal modeling of fMRI data has recently suggested that the thalamocortical projections of nociceptive and nonnociceptive somatosensory inputs to S1 and S2 are indistinguishable (Liang, Mouraux, & Iannetti, 2011).

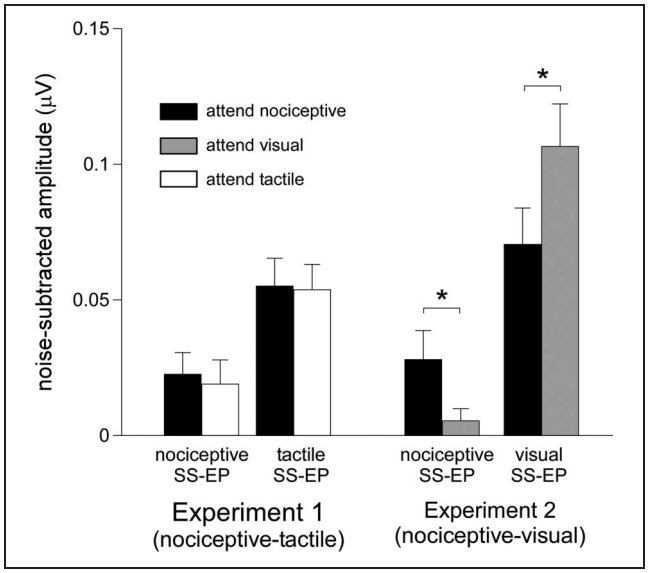

Figure 5. Group-level average (±*SD*) amplitude of the nociceptive, visual, and tactile SS-EPs obtained in the nociceptive–tactile and the nociceptive–visual experiments when attending the nociceptive, visual, or tactile stimuli. Note that the magnitude of the nociceptive SS-EP appeared to be enhanced both when attending the nociceptive stimulus and the tactile stimulus in the nociceptive–tactile experiment, whereas it was enhanced only when attending the nociceptive stimulus in the nociceptive–visual experiment. Also note that attending to the nociceptive or visual stimulus significantly modulated the amplitude of the visual SS-EP, whereas attending to the nociceptive or tactile stimulus did not modulate the amplitude of the tactile SS-EP.

Whether other experimental factors could explain the differential results obtained in the nociceptive–tactile and nociceptive–visual experiments should be considered. For example, attending to a stimulus in a given modality delivered at a particular location can enhance the ERPs elicited by sensory input of a different modality presented at this attended location (Eimer, 2001; Driver & Spence, 1998). In this study, all stimuli were delivered on the same hand (left or right), and most importantly, the distance between the location of the nociceptive and tactile stimuli and the distance between the location of the nociceptive and visual stimuli was strictly identical (Figure 1). In addition, recent studies reported strong crossmodal interaction between nociceptive and visual stimuli when the visual stimuli are delivered in the peripersonal space of the stimulated hand (De Paepe, Crombez, Spence, & Legrain, 2014). Therefore, it seems unlikely that differences in spatial location could explain the differential effect of attending to vibrotactile versus visual input on the magnitude of nociceptive SS-EPs.

A second factor that should be taken into consideration is the relatively low signal-to-noise ratio of nociceptive SS-EPs. The low amplitude of nociceptive SS-EPs as compared, for example, to vibrotactile SS-EPs could be related to the fact that the generation of nociceptive SS-EPs requires initial transduction of the thermal stimuli by heat-sensitive nociceptive afferents and that this transduction step may be an important source of intertrial variability, reducing the periodicity of the nociceptive afferent volley. Although this could have been an explanation for the lack of effect of selective attention on the magnitude of nociceptive SS-EPs in the nociceptive–tactile experiment, it could not explain the lack of effect of selective attention on the magnitude of the vibrotactile SS-EPs obtained in the same experiment nor could it explain why selective attention did significantly modulate the magnitude of nociceptive SS-EPs in the nociceptive–visual experiment. Moreover, the low amplitude of the nociceptive SS-EPs obtained in the attend visual condition could be related to the findings that attention to a given modality can result in decreased activity in cortical regions that process inputs belonging to unattended sensory modalities (Mozolic et al., 2008; Shomstein & Yantis, 2004).

A third factor that should be considered is that the visual detection task was easier to perform than the nociceptive and vibrotactile detection tasks, as suggested by the differences in task performance. Assuming that increasing task difficulty would require participants to focus more their attention toward the task-relevant stream of sensory input, one would have expected a stronger modulation by the focus of attention in the nociceptive–tactile experiment as compared with the nociceptive–visual experiment (Rauss, Pourtois, Vuilleumier, & Schwartz, 2009; Legrain, Bruyer, Guerit, & Plaghki, 2005; Berti & Schroger, 2003; Schwent, Hillyard, & Galambos, 1976). Therefore, it seems unlikely that the differences observed in the two experiments could be explained by differences in task difficulty.

Finally, cross-modulation SS-EPs could not be identified in this study, neither in the nociceptive–tactile experiment nor in the nociceptive–visual experiment. Had they been present, these cross-modulations SS-EPs would have constituted an index of the activity generated by neuronal populations onto which nociceptive and tactile inputs, or nociceptive and visual inputs, converged (Giani et al., 2012; Regan et al., 1995). Their absence could be related to the fact that participants performed a task that required to specifically focus on one of the two concurrently presented streams of sensory input. This could have interfered with the multisensory integration of the two inputs into a unified percept. Supporting this view, it has been shown that audiovisual interactions assessed using ERPs depend on whether participants attend to both sensory modalities (Talsma, Doty, & Woldorff, 2007). However, in a recent study, Giani et al. (2012) recorded SS-EPs to concomitant auditory and visual stimulation, with the aim of investigating whether the presence of cross-modulation SS-EPs is dependent on the cognitive state of the participants. In one of the experiments, the participants were engaged in a target detection task that required simultaneously attending both streams of sensory input. Even in this condition expected to promote multisensory integration, no cross-modulation SS-EPs could be observed. Another possibility that should be examined in future studies is whether nociceptive–tactile cross-modulation SS-EPs could be recorded when the intensity of the tactile stimulus is increased. Indeed, this could be expected if there are neuronal populations onto which nociceptive and nonnociceptive inputs converge if and only if their intensity is sufficient.

Conclusion

By showing that selectively attending to nociceptive or vibrotactile somatosensory input does not selectively increase the magnitude of nociceptive and vibrotactile somatosensory SS-EPs whereas selectively attending to nociceptive or visual input selectively increases the magnitude of the SS-EP elicited by the attended stream of sensory input, our results suggest that the cortical processing of nociceptive and nonnociceptive somatosensory input relies, at least partly, on shared neuronal populations whose responsiveness is indistinctly increased when selectively attending nociceptive input or vibrotactile input, but not when selectively attending visual input.

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