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REVIEW/MISE AU POINT

Steady-state evoked potentials to study the processing of tactile and nociceptive somatosensory input in the human brain

Étude du traitement cortical des afférences somatosensorielles tactiles et nociceptives par enregistrement de potentiels évoqués stationnaires

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Summary The periodic presentation of a sensory stimulus induces, at certain frequencies of stimulation, a sustained electroencephalographic response of corresponding frequency, known as steady-state evoked potentials (SS-EP). In visual, auditory and vibrotactile modalities, studies have shown that SS-EP reflect mainly activity originating from early, modality-specific sensory cortices. Furthermore, it has been shown that SS-EP have several advantages over the recording of transient event-related brain potentials (ERP), such as a high signal-to-noise ratio, a shorter time to obtain reliable signals, and the capacity to frequency-tag the cortical activity elicited by concurrently presented sensory stimuli. Recently, we showed that SS-EP can be elicited by the selective activation of skin nociceptors and that nociceptive SS-EP reflect the activity of a population of neurons that is spatially distinct from the somatotopically-organized population of neurons underlying vibrotactile SS-EP. Hence, the recording of SS-EP offers a unique opportunity to study the cortical representation of nociception and touch in humans, and to explore their potential crossmodal interactions. Here, (1) we review available methods to achieve the rapid periodic stimulation of somatosensory afferents required to elicit SS-EP, (2) review previous studies that have characterized vibrotactile and nociceptive SS-EP, (3) discuss the nature of the recorded signals and their relationship with transient event-related potentials and (4) outline future perspectives and potential clinical applications of this technique.

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MOTS CLÉS
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Résumé À certaines fréquences de stimulation, l'application d'un stimulus sensoriel évoque une réponse électroencéphalographique stationnaire soutenue, de fréquence identique à la fréquence de stimulation (potentiels évoqués stationnaires ou *steady-state evoked potentials* [SS-EP]). Selon plusieurs études, ces réponses pourraient être le reflet d'un phénomène de résonance entreprenant des populations de neurones impliquées dans les étapes précoces du traitement sensoriel cortical. Les potentiels évoqués stationnaires offrent plusieurs avantages, tel qu'un rapport signal sur bruit élevé et la possibilité de marquer l'activité corticale générée par la présentation simultanée de plusieurs trains de stimulation (*frequency tagging*). Récemment, nous avons montré que des SS-EP peuvent être obtenus par l'activation sélective des nocicepteurs cutanés et que le traitement cortical des afférences somatosensorielles nociceptives et non-nociceptives fait intervenir des réseaux corticaux distincts. La technique des SS-EP constitue donc une opportunité pour étudier les processus corticaux impliqués dans la perception de douleur ainsi que la perception vibrotactile chez l'homme, de même que pour caractériser les éventuelles interactions entre ces processus. Dans cet article de revue, (1) nous décrivons les différentes méthodes permettant de stimuler rapidement et périodiquement les afférences somatosensorielles, afin d'obtenir des SS-EP ; (2) nous examinons les études antérieures par enregistrement de SS-EP vibrotactiles et nociceptifs ; (3) nous discutons la nature des signaux enregistrés et (4) nous évoquons les perspectives futures et les applications cliniques potentielles de cette technique.

Introduction

Since the first recording of electrical activity from the human brain by Hans Berger [7], a great number of investigators have used non-invasive electroencephalographic (EEG) techniques to study how the human brain processes sensory inputs. The majority of studies have relied on the recording of event-related brain potentials (ERP), i.e., changes in the ongoing electrical brain activity time-locked to a transient external event like the sudden onset of a sensory stimulus [58,61].

In 1966, Regan introduced the technique of ''steady-state evoked potentials'' (SS-EP) as an alternative approach to characterize stimulus-evoked activity in the ongoing EEG. Unlike conventional transient ERP, which Regan described as ''the response to a kick in the system'', SS-EP reflect a sustained cortical response induced by the long-lasting periodic repetition of a sensory stimulus, described by Regan [61] as ''the response to a gentle shake of the system at a fixed repetition rate''. These steady-state responses remain constant in amplitude and phase over time, and are thought to result from an entrainment or resonance of a population of neurons responding to the stimulus at the frequency of stimulation [26,48,79] or from the linear superposition of independent transient responses elicited by the fast repetition of the sensory stimulus [9,11]. Whereas transient ERP are identified in the time domain as a series of time-locked deflections following the onset of the stimulus, SS-EP are identified in the frequency domain as peaks appearing at the frequency of the repeated stimulus and/or at harmonics of that frequency [61].

An increasing number of studies have used SS-EP to explore the neural activity involved in the cortical processing of visual and auditory sensory modalities and, to a lesser extent, the somatosensory modality. These studies showed that SS-EP reflect, at least in part, activity originating from early, modality-specific sensory cortices [23,56,59,66,67,71].

Recently, we showed that it is possible to record SS-EP in response to the rapid periodic thermal activation of cutaneous nociceptors in humans [46], as well as to the rapid periodic electrical stimulation of nociceptive intra-epidermal free nerve endings [13]. We found that the scalp topography of these nociceptive SS-EP was maximal at the scalp vertex, and symmetrically distributed over both hemispheres, suggesting a radial source originating from midline brain structures (Fig. 1). Most interestingly, at stimulation frequencies greater than 3 Hz, this midline scalp topography contrasted strongly with the lateralized scalp topography of the SS-EP obtained by vibrotactile stimulation, which displayed a clear maximum over the parietal region contralateral to the stimulated side, suggesting a tangential source possibly originating from the contralateral primary somatosensory cortex (S1). Because the spatial distribution of nociceptive SS-EP was significantly different from the spatial distribution of non-nociceptive vibrotactile SS-EP, we hypothesized that nociceptive SS-EP reflect the activity of a population of neurons spatially distinct from the somatotopically-organized population of neurons underlying vibrotactile SS-EP.

As compared to methods based on the recording of transient ERP, but also as compared to other non-invasive methods to sample brain activity in humans such as functional MRI, investigating brain function using SS-EP offers several outstanding advantages. First, studies performed in other sensory modalities have shown that SS-EP exhibit a high signal-to-noise ratio [42,54,79]. Hence, nociceptive SS-EP could be used to sample neural activity that cannot be sampled reliably using other techniques. Second, because SS-EP have been shown to reflect, at least in part, neural activity originating from modality-specific sensory cortices, it is possible that nociceptive SS-EP reflect cortical activity that is at least partly specific for

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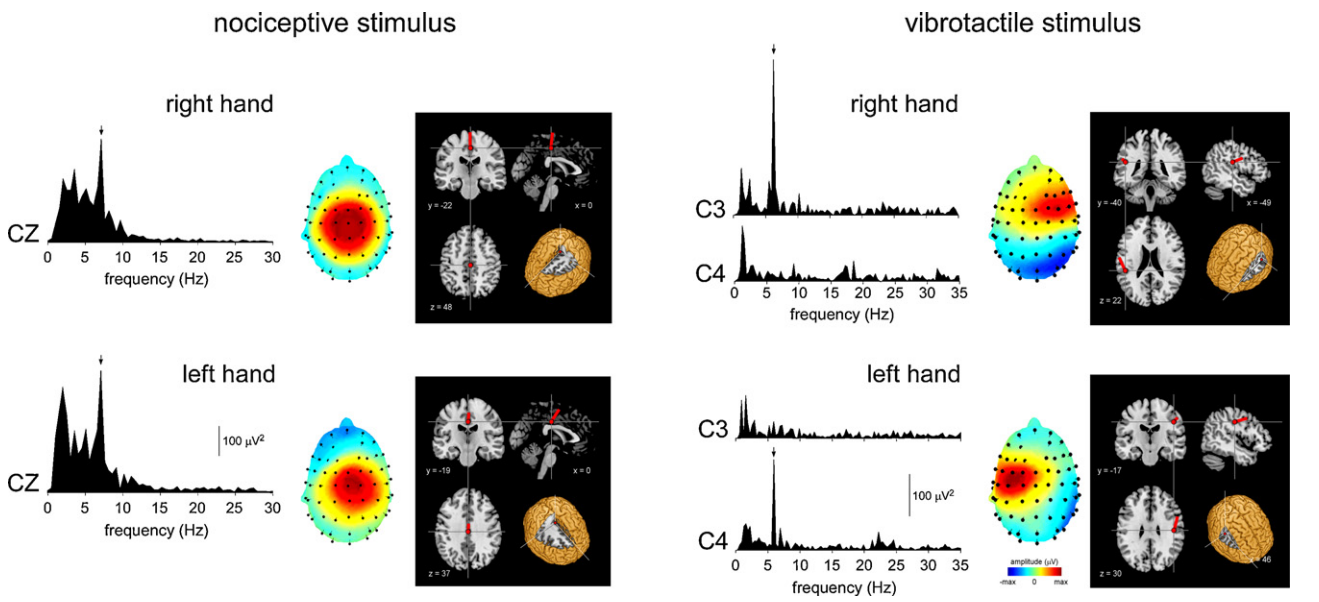

Figure 1 In this experiment, 2.3-s trains of nociceptive stimuli (7 Hz thermal CO_2 laser stimulation) were applied to the hand dorsum. The elicited responses were compared to those elicited by trains of vibro-tactile stimulation (6 Hz transcutaneous electrical stimulation of the superficial radial nerve). The left and right panels show the responses elicited by nociceptive and vibro-tactile stimulation, respectively. The left part of the panel represents the group-level average of the frequency spectrum of the EEG signals recorded at electrode Cz during the 7 Hz periodic stimulation of nociceptive fibres, and at electrodes C3 and C4 during the 6 Hz periodic stimulation of non-nociceptive fibres (noise-subtracted signal power, μv^2). Note that, for the two modalities and at all stimulus locations, the stimulus elicited a significant SS-EP at the corresponding frequency (marked by the vertical black arrows). The middle part of the panels represents the topographical distribution of the stimulus-induced increase in EEG signal power at the frequency of stimulation (group-level average). Note that, for all stimulus locations, the scalp topography of the nociceptive SS-EP was maximal at the vertex (electrode Cz), whereas the scalp topography of the vibro-tactile SS-EP was maximal over the parietal region contralateral to the stimulated side. The right part of the panels shows the location of a single equivalent dipole fitted to the group-level topographical maps of nociceptive and the vibro-tactile SS-EP elicited by stimulation of the left and right hand. Note that, nociceptive SS-EP were best modelled by a single radial dipole located near the midline, whereas non-nociceptive SS-EP were best modelled by a single tangential dipole, located in the parietal lobe contralateral to the stimulated side.
Figure adapted from Mouraux et al. (2011).

nociception and the perception of pain [46]. Third, SS-EP are not induced by the sudden onset of a stimulus, but by the sustained modulation of a long-lasting stream of sensory input. Hence, as compared to nociceptive ERP, nociceptive SS-EP are probably less imprinted by cortical activity related to stimulus-triggered attentional capture [27,36,46]. Fourth, different stimulation frequencies can be used to *tag* the different sensory inputs constituting a multimodal stimulus and, thereby, isolate the neural activity related specifically to each stream of input [43,61,74]. This frequency-tagging approach has been used successfully to characterize the neural activity involved in the multimodal integration of audiovisual stimuli, and its modulation by selective attention [16,22,23,31,49,50,64,73]. Hence, frequency-tagging of concomitant nociceptive and non-nociceptive somatosensory inputs could constitute a unique mean to characterize their respective neural representations, as well as to study how these sensory inputs integrate at cortical level.

For all these reasons, the recording of vibrotactile and nociceptive somatosensory SS-EP could constitute a promising approach to study the cortical representation of touch and nociception in humans. Importantly, exploring fully this new line of research will require optimizing current stimulation techniques to achieve the rapid, periodic, selective and controlled activation of nociceptors required to elicit SS-EP.

Here, we will review the use of SS-EP as a technique to study the neural representation of touch and nociception in humans. Specifically:

- we will describe different methods to achieve the rapid periodic stimulation of somatosensory afferents required to elicit SS-EP;
- we will discuss the nature of the recorded signals and its relationship with transient ERP;
- we will review previous studies characterizing tactile and nociceptive SS-EP;
- and we will discuss future perspectives and potential clinical applications of this technique.

Rapid periodic stimulation of somatosensory afferents

To elicit somatosensory SS-EP, studies have relied on mechanical vibrotactile stimulation of mechano-sensitive cutaneous afferents [1,5,22,23,48,52,65,66,71,72], thermal

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stimulation of heat-sensitive nociceptive afferents [46] and direct electrical stimulation of sensory nerve fibres [2,13,34,41,46,54,60].

Mechanical vibrotactile stimulation

Several studies have devised stimulation methods to periodically activate low-threshold mechanoreceptors by applying a light force onto the skin and, thereby, elicit somatosensory SS-EP related to the perception of vibrotactile sensations. For example, Nangini et al. [52] developed an inflatable membrane connected to a pneumatic controller containing magnetic valves for switching the airflow to the membrane. Other investigators have relied on piezoelectric devices [65] or solenoid vibrators (e.g. [1]). One advantage of these methods of stimulation is that different frequencies of stimulation may be expected to preferentially activate different types of low-threshold mechanoreceptors, having different frequency response characteristics. For example, relatively low frequencies of stimulation should preferentially elicit neural activity related to the activation of Meissner corpuscles, whereas higher frequencies of stimulation should preferentially elicit activity related to the activation of Pacinian corpuscles [25,29]. Most studies have used vibrotactile stimuli consisting of a greater than 100 Hz carrier frequency (i.e. frequencies at which Pacinian corpuscles are especially sensitive to vibration) periodically modulated at a frequency below 40 Hz. A disadvantage of these methods is that care must be taken to ensure that the mechanical vibration generated by the stimulator is not concomitantly transduced by sensory receptors of the ears (air and body conduction). It should be noted that, in principle, mechanical stimulation of the skin could also be used to periodically activate mechano-sensitive nociceptors and, thereby, elicit nociceptive SS-EP, for example, using the pinprick device developed by Ziegler et al. [80]. However, because of the unavoidable concomitant activation of low-threshold mechanoreceptors, the technique would not be selective for nociceptive afferents, thus limiting the interpretability of the obtained EEG responses.

Thermal stimulation of heat-sensitive somatosensory afferents

Recently, we showed that it is possible to activate periodically heat-sensitive afferents of the skin using an infrared CO_2 laser stimulator [46]. Brief (20 ms) and focal (5 mm beam diameter) laser pulses were delivered to the hand and foot dorsum at a rate of 7 Hz. To avoid skin overheating and possible sensitization or habituation of the activated nociceptors, the target of the laser stimulus was displaced immediately after each pulse, using a flat mirror set on a two-axis computer-controlled device powered by two high-speed servomotors. The displacement followed a zigzag path, such that the same spot was stimulated only once in each train. The advantage of this approach is that it is entirely selective for heat-sensitive free nerve endings of the thermo-nociceptive system. Higher frequencies of stimulation could be obtained using, for example, a device driven by galvanometers, as these have switching times as short as a few microseconds. In principle, it may also be possible to activate periodically heat-sensitive free nerve endings without displacing the stimulus, for example, using a Peltier-type contact stimulator having the capacity to both rapidly heat and cool the skin [33,68,78], or using an infrared laser stimulator able to adjust laser power output as a function of an online measurement of target skin temperature such as to account for the increasing baseline temperature [40]. One possible drawback for all approaches using thermal stimulation to elicit nociceptive SS-EP is the fact that they rely on the transduction of the thermal stimulus into a neural impulse. Hence, the elicited responses can only reflect the activation of a subpopulation of short activation latency heat-sensitive afferents, able to preserve the periodicity of the afferent input. Furthermore, variations in the heat transfer to the skin, variations in transduction and variations in nerve conduction velocities could result in variations of the temporal dynamics of the elicited afferent input, possibly blurring its periodicity, in particular, at high frequencies of stimulation [46].

Electrical stimulation of somatosensory nerve fibres

An alternative approach to elicit somatosensory SS-EP is to bypass transduction processes altogether, by depolarizing directly afferent sensory nerve fibres. A number of studies have relied on transcutaneous electrical stimulation of a nerve trunk to selectively and directly activate large diameter thickly myelinated Aβ-fibres involved in the perception of touch [2,13,34,41,46,54,60]. Similarly, we recently showed that intra-epidermal electrical stimulation to deliver very focal currents restricted to the epidermis can be used to activate nociceptive free nerve endings selectively [47] and, thereby, elicit nociceptive SS-EP [13]. Several devices have been proposed, consisting of a small surface cathode surrounded by a cylindrical anode [28,30]. Importantly, the selectivity of this technique relies on the difference in receptor depth of nociceptive and non-nociceptive somatosensory receptors [28,53] and, therefore, the technique is selective only at low intensities of stimulation [47]. An advantage of all approaches based on the direct electrical stimulation of afferent nerve fibres is that, as they bypass transduction, the periodicity of the afferent input may be better preserved and, hence, the elicited SS-EP may be more robust, in particular, at high frequencies of stimulation. Furthermore, direct electrical stimulation of sensory afferents may ensure that the elicited responses are not related to the activation of only a small subpopulation of rapidly-adapting somatosensory receptors. A drawback of this approach is that the results can be difficult to interpret if the recorded signals are contaminated by an electrical stimulation artefact, appearing at the frequency of stimulation.

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Nature of steady-state evoked potential signals and relationship with transient event-related brain potentials

How SS-EP emerge within the human EEG, and their relationship with transient ERP remains a matter of debate [11].

A first hypothesis is that SS-EP are simply the result of the linear summation of successive transient responses elicited by the fast repetition of the sensory stimulus [9,11]. In this view, SS-EP would result from the same neural activity underlying transient ERP [11]. This hypothesis has been mainly tested in the auditory modality [3,9,10,14,63], and is suggested by the observation that the auditory SS-EP elicited by stimulation at 40 Hz can be largely explained by the linear sum of middle latency auditory ERP (i.e. series of ERP waves appearing 8-80 ms after the onset of a brief auditory stimulus such as an auditory click) [20]. Building on this observation, a number of studies have attempted to demonstrate that SS-EP emerge from the linear superposition of transient responses by computing the sum of real or simulated transient responses and by examining how well they correlate with actual SS-EP. While some studies have shown evidence in favour of the superposition hypothesis [24,69], others have failed to demonstrate a significant correlation between SS-EP and transient ERP [3,14,63]. To explain such discrepant results, it has been suggested that these approaches do not account for the influence of neural adaptation and/or refractoriness [9,11]. Using approaches accounting for this influence, investigators have succeeded in finding a linear relationship between SS-EP and transient ERP, both in the auditory domain [9] and in the visual domain [11].

A second hypothesis is that SS-EP result from a stimulus-driven entrainment of a network of neurons responding to the periodically-modulated feature of the eliciting stimulus [26,79]. Therefore, at preferred frequencies of stimulation, the network — or part of the network — of neurons responding to that stimulus feature is hypothesized to resonate to the stimulus [26,79]. According to this hypothesis, SS-EP would reflect the ability of the neurons to oscillate at particular frequencies, and to synchronize their activity to an external periodic event [19,26]. Compatible with this view, it has been shown that the magnitude of the SS-EP elicited by a flickering visual stimulus in the human visual cortex is markedly greater for particular frequencies of stimulation than for adjacent frequencies of stimulation, indicating a preference of the underlying neuronal oscillators for given frequencies and their harmonics [26]. The preferred response frequencies of a given ensemble of neurons could be explained by the temporal characteristics of the axonal connexions constituting the resonating network. In other words, the resonance hypothesis proposes that SS-EP are the result of an emergent property of a network of interconnected neurons. In this view, the brain is considered as a non-linear system and, most importantly, the neural activity captured by SS-EP may differ markedly from the neural activity reflected in transient ERP [61].

In summary, whether or not SS-EP can be entirely explained by a linear superposition of successive transient ERP or whether they reflect a stimulus-driven entrainment of neurons resonating at the frequency of stimulation remains an open question, and the two hypotheses may coexist (i.e. SS-EP elicited by a given stimulus presented at a given frequency could reflect mainly the superposition of transient ERP while SS-EP elicited by another type of stimulus or presented at another frequency could reflect mainly a stimulus-driven neuronal entrainment).

Vibrotactile somatosensory steady-state evoked-potential

Using either transcutaneous electrical stimulation [2,13,34,41,46,54,60] or mechanical stimulation of low-threshold mechanoreceptors [1,5,22,23,48,52,65,66,71,72], several studies aimed at characterising the SS-EP related to the perception of vibrotactile sensations.

Using a carrier frequency to elicit a steady afferent somatosensory input (e.g. 128 Hz; [66]) modulated using a range of frequencies extending from 2 to 41 Hz [48,54,65,66,71,72], investigators have reported that vibrotactile stimulation of the hand palm elicits maximal SS-EP at periodicities around 27 Hz [48], 26 Hz [66] or 21 Hz [71,72]. When stimulating the foot sole, maximal amplitudes were observed at slightly lower modulation frequencies, around 19—25 Hz [72]. Hence, it appears that the preferred frequency to elicit somatosensory SS-EP lies in the range of 20—30 Hz. This differs from the visual modality, where greatest SS-EP amplitudes are usually found between 10 and 18 Hz for flash stimuli and at even lower frequencies for patterned stimuli [61,71]. It also differs from the auditory modality, where greater SS-EP amplitudes originating from the cortex are usually obtained using modulation frequencies in the range of 40 Hz [19]. As discussed in the preceding section, these different frequency response properties have been interpreted as resulting from differences in the temporal characteristics of the connexions constituting the responding network [26,61]. It should be noted that single-cell recordings performed in animals have shown the existence, in S1, of neurons with exquisite responsiveness to high frequency vibrations (e.g. 127 Hz; [35]), probably encoding input transduced by Pacinian afferents. Given that several recent studies (e.g. [4]) have shown that EEG is able to sample high-frequency responses (500—600 Hz) to transient somatosensory stimuli originating from S1 (referred to as high-frequency bursts), future studies could examine the feasibility of recording high-frequency vibrotactile SS-EP.

Whatever the method used to activate non-nociceptive somatosensory afferents, the scalp topography of the elicited SS-EP displays a clear maximum over the parietal region contralateral to the stimulated side, and source analysis studies have yielded results compatible with activity originating from the primary somatosensory cortex contralateral to the stimulated side [22,23,46,60,66,71]. Single-cell recordings performed in animals have shown that rapidly-adapting afferent units, which encode vibrotactile somatosensory input, have strong projections to areas 3b and area 1 of the contralateral S1 cortex [44], thus supporting the view that SS-EP elicited by vibrotactile stimulation originate mainly from these regions. It should be noted that the scalp topographies of vibrotactile SS-EP are highly similar to the scalp topographies of the early components

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of transient non-nociceptive somatosensory ERP (e.g., the N20 wave following electrical stimulation of the median nerve) [15,61]. Nevertheless, through a direct comparison of both types of responses, Nangini et al. [52] suggested that early-latency somatosensory ERP and vibrotactile SS-EP may originate from slightly distinct subregions of area 3b.

In a recent study, we found that the scalp topography of vibrotactile SS-EP differs when very low modulation frequencies are used (e.g. 3 Hz; [13]. Indeed, and contrasting with the lateralized parietal scalp topography obtained at higher stimulation frequencies, the scalp topography of the SS-EP elicited by 3-Hz stimulation was symmetrically distributed over both hemispheres, and maximal over the vertex and fronto-central regions. Furthermore, this scalp topography was similar to that of the late P2 wave of transient somatosensory ERP [45]. Such as the late P2 wave [27], the magnitude of the 3-Hz SS-EP showed a marked habituation, suggesting that both responses reflect unspecific and non-obligatory stages of sensory processing, strongly dependent on the context within which the afferent sensory input occurred and possibly related to stimulus-evoked attentional capture [13,27,36,38].

Nociceptive somatosensory steady-state evoked-potential

Using EEG, investigators have relied mostly on the recording of transient laser-evoked brain potentials (LEPs) to study nociception and pain perception in humans [12,21,76]. A large number of studies suggested that LEPs reflect, at least partially, the neural processes by which the perception of pain emerges from nociceptive input [6,77]. As a consequence, it has been hypothesized that LEPs constitute a reliable approach to study how pain is ''represented'' in the brain [75]. 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 detection and the orientation of attention toward the occurrence of a transient, salient sensory event [27,36,37] (see Ref [37] in this issue).

As previous studies have shown that SS-EP are effective to capture neural activity related to sensory processing, originating mainly from primary sensory cortices [32,57,66,71], the effective recording of nociceptive SS-EP could constitute a novel mean to characterize the cortical processing of nociceptive input in humans.

We recently showed that it is possible to record nociceptive SS-EP using rapidly-displaced laser pulses delivered to the skin at a 7-Hz periodicity [46]. Subsequently, we showed that nociceptive SS-EP can also be obtained using intra-epidermal electrical stimulation to selectively activate epidermal free nerve endings [13], this time using a range of frequencies extending from 3 to 43 Hz.

Whatever the method used to activate nociceptive afferents selectively, and whatever the location of the stimulus (hand and foot dorsum), the scalp topographies of the recorded nociceptive SS-EP were symmetrically distributed over both hemispheres, and displayed a clear maximum over midline, fronto-central regions [13,46]. Source analysis showed that the elicited responses could be satisfactorily explained by a single radial source located in anterior midline brain structures such as the anterior cingulate cortex [46]. However, given the uncertainty inherent to EEG source analyses, a contribution from bilateral symmetrical sources located within operculo-insular cortices can clearly not be excluded. Whatsoever, our findings indicate that nociceptive SS-EP reflect the activity of a cortical network that is distinct from the somatotopically organized cortical network involved in the generation of vibrotactile SS-EP [13,46], (Fig. 1). Consistent with the hypothesis that cortical activity originating from these regions contributes to the bulk of nociceptive SS-EP, but not to vibrotactile SS-EP, Dum et al. [18] showed that, unlike tactile somatosensory input, the primary target of nociceptive spino-thalamic input is not the contralateral S1, but the insular cortex, the secondary somatosensory cortex and, above all, the cingulate cortex.

Using low-energy laser stimuli to activate selectively low-threshold C-warm receptors of the skin, we also attempted to record SS-EP related to the selective activation of unmyelinated C-fibres [46]. Although participants reported the clear perception of a diffuse and long-lasting warm sensation, laser stimuli applied at a frequency of 7-Hz did not elicit an identifiable C-fibre SS-EP. This lack of measurable EEG response could be explained by the fact that the magnitude of SS-EP is not only determined by the magnitude of the underlying neural activity, but also by the constancy of its phase over the repeated stimulation cycles. Indeed, differences in the temporal properties of the C-fibre responses (response latency of C-fibre free nerve endings, variability in C-fibre nerve conduction velocity) elicited by each successive laser pulse could be expected to dampen or even abolish the periodicity of the C-fibre afferent input. Future studies should examine whether C-fibre SS-EP can be recorded using lower frequencies of stimulation.

Future perspectives: frequency tagging of somatosensory steady-state evoked potentials

Several studies have shown that different stimulation frequencies can be used to *tag* the cortical responses elicited by each of several, concurrently applied, sensory stimuli [43,61,74]. For example, simultaneously presenting an auditory stimulus modulated at frequency F1 and a visual stimulus modulated at frequency F2 elicits two distinct peaks in the EEG spectrum, at frequencies F1 and F2, respectively. This frequency-tagging approach has been used successfully to demonstrate top-down attentional modulation of visual [43,49], vibrotactile [22,23] and auditory [8,51] inputs, and to characterize the cortical activity involved in the multimodal integration of audiovisual stimuli [16,31,55,64,70,73]. Recently, in a preliminary and unpublished experiment, we have shown that distinct SS-EP can be reliably recorded following concomitant nociceptive, vibrotactile and visual stimulation and that the elicited responses, appearing as three separate peaks in the EEG frequency spectrum, have distinct scalp topographies (Fig. 2). Hence, frequency-tagging of the EEG responses to concomitant nociceptive and non-nociceptive somatosensory stimulation could constitute a unique mean to characterize their respective neural representations, as well as to study how these sensory inputs integrate at cortical level. Furthermore, the approach could be used to examine

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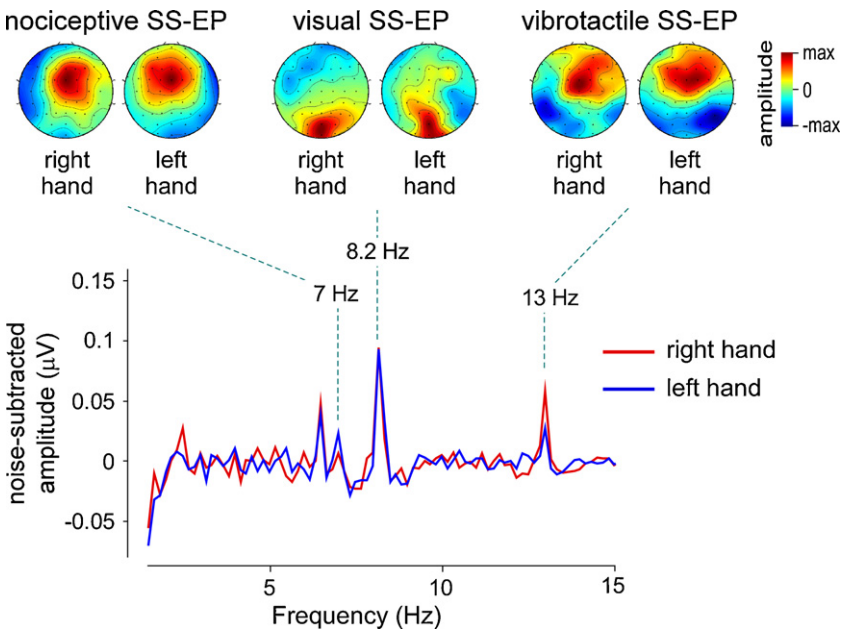

Figure 2 In this experiment, 5-s trains of nociceptive (7-Hz thermal CO_2 laser stimulation of the hand dorsum), tactile (13 Hz transcutaneous electrical stimulation of the superficial radial nerve) and visual (8.2 Hz visual stimulation using an electroluminescent diode placed above the hand dorsum) stimuli were concurrently delivered in blocks of 20 trains, to the left and right hand. The bottom panel represents the noise-subtracted EEG amplitude spectrum (μv), averaged across all subjects and all scalp electrodes, for the left (blue) and the right (red) hand. Note that all three stimuli elicited consistent and distinct SSEPs, appearing as three separate peaks in the EEG frequency spectrum at the corresponding stimulation frequencies (7, 8.2 and 13 Hz). Note also at 6.5 Hz, a peak corresponding to the subharmonic of the 13 Hz tactile SS-EP. The upper panel represents the group level average scalp topographies of nociceptive (7 Hz), tactile (13 Hz) and visual (8.2 Hz) SS-EP elicited by stimulation of the left and right hand. Note that the scalp topographies of the elicited SS-EP are distinct according to the modality. The nociceptive SS-EP (7 Hz) was maximal over the scalp vertex, whereas the tactile SS-EP (13 Hz) was maximal over the parietal region contralateral to the stimulated side and the visual SS-EP (8.2 Hz) was maximal over occipital regions. These results indicate that all three responses originate from distinct neuronal populations.

whether neural processes involved in the integration of nociceptive and non-nociceptive somatosensory stimuli can be revealed by the presence of cross-modulation frequencies in the EEG, appearing at frequencies $nF_1 \pm mF_2$, where n and m are integers and F1 and F2 are the frequencies of stimulation of two concurrent streams of sensory input. For example, concomitant nociceptive stimulation at frequency F1 = 7 Hz and non-nociceptive stimulation at frequency F2 = 9 Hz could elicit cross-modulation SS-EP appearing at F2 + F1 = 16 Hz and F2-F1 = 2 Hz, and such responses would constitute an index of the activity generated by neuronal populations onto which the different sensory inputs converge [61,62]. A small number of studies have already shown cross-modulation SS-EP induced by the integration of auditory and visual inputs [62]. Showing the presence of such cross-modulation frequencies constitutes unequivocal evidence for a non-linear process of convergence of the two sensory inputs. For example, such cross-modulation SS-EP could reflect the activity of a population of neurons whose output corresponds to the product of the two input oscillations. Admittedly, whether or not the concomitant presentation of nociceptive and non-nociceptive somatosensory stimuli elicits cross-modulation SS-EP remains to be determined, as such components have not yet been described. However, if such responses can be identified, they would open a new door to study directly the cortical mechanisms involved in multimodal perceptual integration [17,39].

Clinical applications

A small number of studies have highlighted the potential clinical usefulness of recording vibrotactile SS-EP [54,60]. One advantage over the recording of transient ERP is the high signal-to-noise ratio of the elicited responses and, hence, the short time required to obtain reliable signals. This could be potentially interesting, in particular, in circumstances where patient collaboration is poor (e.g. children, patients with cognitive impairment) or when it is crucial to obtain rapid estimates of the elicited responses (e.g. perioperative neuromonitoring of spinal cord function; [60]).

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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