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Short-term modulation of the ipsilateral primary sensory cortex by nociceptive interference revealed by SEPs

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Abstract

We studied the modulation of the topographic arrangement of the human ipsilateral primary somatosensory cortex following interference of nociceptive stimuli by means of dipole source analysis. Multichannel somatosensory evoked potentials were obtained by electrical stimulation of digits 1 and 5 of the left hand before, during and after the application of pain to digits 2–4 of the right hand. The primary cortical response of the SEP (N20) was obtained for dipole localization of the representation of the primary sensory cortex receiving input from digits 1 to 5. The 3D-distance between these sides was calculated for further analysis. To account for possible attentional effects recordings were performed while simultaneously to this intervention subjects were asked to turn their attention to the right or left hand in a pseudorandom order. The application of pain induced an expansion of the 3D-distance between digits 1 and 5. Focusing attention to the stimulated limb or the site of the intervention did not yield to an additional effect. Our results provide further evidence for the presence of a quickly adapting interaction between primary somatosensory areas of both hemispheres following an interference of nociceptive stimulation in SEPs. This modifying process is probably mediated by interhemispheric and intercortical connections leading to hyperexcitability of the primary sensory cortex contralateral to that receiving nociceptive input. Spatial attention does not seem to have an impact on this kind of short-term intercortical plasticity.

Keywords: Intercortical plasticity; Interhemispheric connections; Source reconstruction; Somatotopy; Somatosensory evoked potentials; Receptive field; Pain

The sensory maps of the primary somatosensory cortex in primates are known to dynamically adapt to afferent input. Reorganization of this arrangement subsequent to altered sensory input was investigated by microelectrode mapping techniques in animal studies [1,18]. As a long-term effect deafferentation of the cortex in humans leads to an expansion of the somatosensory representation from adjacent cortical areas into the deafferented territories deprived from sensory input [18]. The amount of this reorganization seems to depend on phantom limb pain [9]. Short-term cortical plasticity has been observed as well and the timing of it appears to be highly dynamic. For instance, artificial denervation or even directing attention to a particular body part leads to an alteration in the dependent cortical somatosensory representation within minutes [3,4,20,22].

Several studies using different techniques, such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) stressed that the primary sensory cortex, in addition to SII and the anterior cingulum, plays also an important part in nociception [29]. SI receives painful and non-painful input from thalamic nuclei [25] and involves neurons that code spatial painful and innocuous somatosensory stimuli [7]. It has been shown that lesions within SI cause contralateral disturbances in the perception of pain [11]. Animal studies showed that the expansion of the receptive field after denervation is immediately mirrored in the primary sensory cortex contralateral to the deafferented one [6]. In humans, psychophysical studies have revealed changes in the sensory perception of one hand during artificial deafferentation of the other hand [2,31] and showed an impact on tactile spatial acuity by sensory interference of the opposite hand or neighboring digits [8,26]. These studies suggest rapidly adapting interactions between the primary sensory cortical areas of both hemispheres. A recent study using dipole source analysis in median nerve SEP demonstrated that artificial deafferentation of primary sensory cortex immediately leads to reorganizational changes in the primary sensory cortex contralateral to the deafferented one [30]. In

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this context the question arises to what extent an alteration of the nociceptive input to the primary sensory cortex in humans can lead to reorganizational changes in the primary sensory cortex contralateral to that receiving nociceptive input.

Using dipole modeling the 3D-distance between the dipoles, representing the cortical activation during an electrical stimulation of different digits, is an appropriate marker of the extension of a receptive field [23,27]. Our aim was to further investigate the issue of nociceptive perception as a factor modulating the somatotopographical map of the ipsilateral primary somatosensory cortex. Furthermore, we addressed if these mechanisms were dependent on the state of attention.

Ten healthy subjects (three females and seven men aged 25–30 years) participated in the study. None had a history of neurological or psychiatric disease. All participants were right-handed, as assessed by the Edinburgh laterality inventory [21] and gave written informed consent in accordance with the declaration of Helsinki. The study protocol was approved by the local ethics committee.

Electrical stimulation of digits 1 and 5 of the left hand was performed at a frequency of 3.1 Hz using constant current square wave pulses (0.2 ms width). Stimulation intensity was set to twice the sensory threshold. First, SEPs were recorded during a resting condition, in the absence of any manipulation to the right hand and subjects were instructed to follow their spontaneous thoughts to reduce any attention-mediated effects.

Digits 2–4 of the right hand were then dipped into ice water to obtain nociceptive stimulation. Four runs of 6 min were necessary to obtain a sufficient number of 4000 sweeps. Intensity of pain perception caused by dipping digits 2–4 into ice water was estimated by a pain score (numeric rating scale [NRS], 0–10) at the begin and end of each replication. To avoid nerve conduction block induced by excessive cooling, between the runs a break of a minimum of 5 min was kept and extended until pain sensation at the digits returned to normal (NRS $\leq$ 1). The temperature at the dorsal hand proximal to the digits 2–4 remained stable during the condition. During this intervention, two different conditions were tested:

Subjects were asked to direct their attention to the right or left hand by silently counting air puff events, occurring randomly every 3–8 s at the dorsal surface of the hand with a threshold just above sensory threshold. The sequence of conditions was changed in a pseudorandom order for each participant.

Participants lay prone on a bed in a dimly lit room and were instructed to relax with their eyes open. Evoked responses were recorded using a symmetrically arranged 96-channel montage. The 3D-electrode positions were measured using a 3D-digitizer (Zebris Medical GmbH, Isny, Germany). The band-pass of records was set from 20 Hz to 500 Hz. SEPs were sampled with 2000 points over a 50 ms pre- and 50 ms post-stimulus period. Four runs of 1000 sweeps for each condition were acquired, resulting in 4000 sweeps per condition (16,000 sweeps in total).

Signals were analyzed by BESA-Program for source localization (MEGIS Software GmbH, Munich, Germany) and digitally filtered (high pass: 20 Hz, 12 dB/Oct, zero phase Butterworth type 3). Channels showing a noise amplitude of more than twice the median noise amplitude of the data set were excluded.

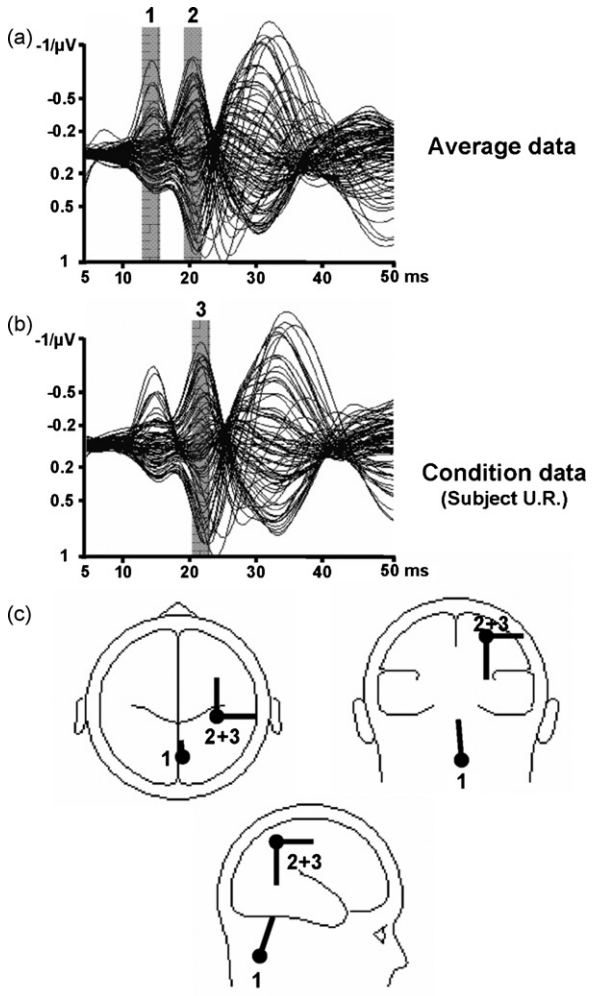

Fig. 1. Illustration of the procedure of dipole source modeling: first, all sweeps of the SEPs from each subject were collapsed, resulting in at least 16,000 averaged sweeps. In this data set a single dipole was fitted in the time window of ±1 ms (step 1, a) around the brain stem potential at typically 16 ms post-stimulus. A regional source consisting of three orthogonal dipoles at one location was then fitted in the time window of ±1 ms around the peak of the N20 potential (step 2, b). The solution computed in step 2 was applied to the individual data recorded for each condition and digit, while the brain stem source calculated in step 1 was held fixed in location and orientation (step 3, b). (c) Gives the location of the dipoles within the three-shell spherical headmodel for an exemplary subject (U.R.).

For dipole localization, a three-shell spherical head model was used. The outer sphere was fitted to the individual 3D-electrodes (least square fit). The shells of these individual spheres were set to 6 mm for the skin 0.33 $[\Omega/m]^{-1}$, 7 mm for the skull 0.0042 $[\Omega/m]^{-1}$ and a homogeneous conductivity of 0.33 $[\Omega/m]^{-1}$ within the innermost compartment. The outer sphere was fitted to the individual 3D-electrodes (least square fit) by rotating them using four anatomic landmarks: the nasion, the right and left pre-auricular points, and the inion.

Source location was performed in three steps as illustrated in Fig. 1.

(1) All averages from each subject were collapsed, resulting in at least 16,000 averaged sweeps to increase the signal to