

## Functional reorganization of the human primary somatosensory cortex after acute pain demonstrated by magnetoencephalography

Peter Sörös<sup>a,\*</sup>, Stefan Knecht<sup>a</sup>, Carsten Bantel<sup>b</sup>, Tanya Imai<sup>a</sup>, Rainer Wüsten<sup>b</sup>,  
Christo Pantev<sup>c</sup>, Bernd Lütkenhöner<sup>c</sup>, Hartmut Bürkle<sup>b</sup>, Henning Henningsen<sup>a</sup>

<sup>a</sup>Department of Neurology, University of Münster, Albert Schweitzer-Strasse 33, 48129 Münster, Germany

<sup>b</sup>Department of Anesthesiology, University of Münster, Albert Schweitzer-Strasse 33, 48129 Münster, Germany

<sup>c</sup>Institute of Experimental Audiology, University of Münster, Kardinal-von-Galen-Ring 10, 48129 Münster, Germany

Received 15 September 2000; received in revised form 28 November 2000; accepted 7 December 2000

### Abstract

The somatosensory system is capable of functional reorganization following peripheral denervation or training. Studies on human amputees with phantom limb pain provided evidence that these reorganizational changes are modulated through nociceptive input. In the present study we used magnetoencephalographic recordings of six healthy volunteers to assess whether acute pain by itself causes a reorganization of the primary somatosensory cortex. After the induction of an intense experimental pain at the thenar of the left hand by intradermal injection of capsaicin, the extent of the cortical hand representation and the distance between the hand representation and the localization of the lip decreased. A likely mechanism for this acute reorganization is that pain induced hyperresponsiveness of the left thenar to tactile input from neighboring body sites. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

**Keywords:** Pain; Plasticity; Somatosensory cortex; Capsaicin; Magnetoencephalography; Somatosensory evoked potentials

Cortical maps are dynamic networks which are, even in the adult brain, capable of reorganization following changes in sensory input or in behavior [3]. There is increasing evidence that reorganizational changes in the somatosensory system are, at least in part, induced and maintained by the activation of nociceptive inputs. After upper limb amputation a close correlation between phantom limb pain and the reorganization of the primary somatosensory cortex (SI) was detected [9]. There is evidence that phantom pain, rather than the loss of afferent input, causes plasticity in SI in these patients, since the amount of cortical reorganization can be reduced through the elimination of phantom pain by plexus anesthesia [1]. It is still an open question, however, whether acute pain by itself suffices to elicit functional cortical reorganization or whether this phenomenon requires chronicity of pain. We previously observed that acute pain can elicit phantom sensations in healthy subjects and suspected an underlying pain-induced hyperresponsiveness of the cortical hand representation to somatotopically adjacent input from the lip [11].

Magnetoencephalography (MEG) allows the non-invasive mapping of the human brain with a spatial resolution high enough to demonstrate the somatotopic organization of the somatosensory homunculus [14]. Somatosensory evoked magnetic fields (SEF) were recorded in six healthy male volunteers (age 26–40 years) to test the hypothesis that acute pain, elicited by the intradermal injection of capsaicin, can cause a reorganization of the human somatosensory cortex. All subjects were strongly right-handed as indicated by the Edinburgh handedness inventory [16]. None of the subjects had a regular medication or took analgesics or any other drug on the day of the measurement. All measurements were carried out in the afternoon between 16:00 and 19:00 h to minimize chronobiological influences.

The tip of the first (D1), second (D2), and fifth finger (D5) of the left hand as well as the left lower lip were stimulated by a pneumatic stimulator delivering non-painful, light superficial pressure pulses. The four stimulation sites were activated in a randomized order (interstimulus interval  $500 \pm 50$  ms, 300 stimuli per site) to minimize the effect of minor head movement during the measurements. Magnetic fields were recorded in a magnetically shielded room using a 37-channel biomagnetic system equipped with first-order axial gradiometers (Magnes I, BTi, San Diego,

\* Corresponding author. Tel.: +49-251-83-48194; fax: +49-251-83-48181.

E-mail address: soros@uni-muenster.de (P. Sörös).

CA) as described previously [9]. Data were sampled at a rate of 520.8 Hz, digitally filtered using a high pass filter of 0.1 Hz, averaged, baseline corrected and band-pass filtered with 1–30 Hz. Epochs containing an amplitude of more than 2 pT in any of the 37 channels were rejected as artifacts before averaging. To localize the neuronal sources of the magnetic field distribution the model of a single equivalent current dipole in a spherical volume conductor was applied. The dipole of the peak latency of the N50m component, equivalent to the N20m after electrical stimulation, was selected for further analysis. The Euclidean distance between the dipoles obtained for D1 and D5 served as a measure of the extent of the hand area. The center of gravity within the triangle formed by the locations derived for D1, D2, and D5 as well as the Euclidean distance between this center of gravity and the location of the lower lip were calculated.

After the first SEF measurement, capsaicin (50  $\mu$ l, concentration 0.1%) was injected intradermally into the middle of the left thenar with a 27-gauge needle. The intradermal injection of capsaicin (8-methyl-*N*-vanillyl 6-nonamide) directly activates nociceptive primary afferent C-fibers and is a widely used tool for inducing experimental pain in humans [10]. A second SEF measurement was started 5 min after injection. Before the first and after the second SEF measurement, the thresholds for light touch and pain were determined using calibrated von Frey filaments (Stoelting, Wood Dale, IL). Thresholds were tested on the following eight sites marked before the initial testing: on the four sites of pneumatic stimulation (i.e. the tip of left D1, D2, and D5 as well as the left lower lip) and on four sites of the thenar each 1 cm apart from the capsaicin injection site. A schematic illustration of the experimental paradigm is provided in Fig. 1.

Subjects were asked to assess their actual pain on a visual

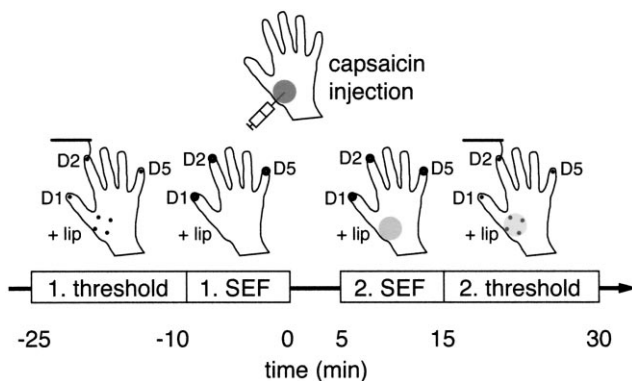


Fig. 1. Schematic illustration of the experimental paradigm. Before the first and after the second recording of somatosensory evoked magnetic fields (1, SEF; 2, SEF) the thresholds for touch and pain were determined by von Frey filaments (1, threshold; 2, threshold). The small circles at the fingers and the thenar indicate the locations of von Frey filament testing. The larger circles on the fingers indicate the sites of tactile stimulation. The grey area at the thenar represents the area of hyperalgesia around the capsaicin injection site.

analog scale between zero (no pain) and ten (most intense pain) 1 and 15 min after the injection of capsaicin. Data are presented as mean  $\pm$  SD. For comparison of the measurements before and after capsaicin injection, the non-parametric Wilcoxon test was employed. *P*-values  $<0.05$  were regarded as indicating statistical significance. All subjects gave their informed, written consent before the start of the measurements. The study protocol was approved by the Ethics Committee of the Medical Faculty, University of Münster, Germany.

The injection of capsaicin induced severe pain, being rated as  $8.5 \pm 0.7$  (mean  $\pm$  SD) on the visual analog scale (VAS) 1 min after injection, which decreased to  $3.0 \pm 1.5$  on the VAS after 15 min. The threshold for light touch did not change significantly between von Frey filament testing before and after capsaicin injection at all eight sites of testing. The threshold for pain did not change significantly at the three fingers tested and at the lower lip. In contrast, the threshold for pain decreased significantly at the four sites of the thenar after capsaicin injection ( $P < 0.001$ ), indicating the area of primary hyperalgesia.

Original MEG waveforms before and after capsaicin injection of one subject are presented in Fig. 2. The dipole moment *Q*, representing the number of activated neurons at a given point of time [12], did not change significantly between the SEF measurements before and 5 min after capsaicin injection. In all six subjects, the distances between the center of gravity of the hand representation and the localization of the lip decreased in the second SEF measurement, starting 5 min after capsaicin injection (range, 1–5 mm;  $P = 0.0277$ ;

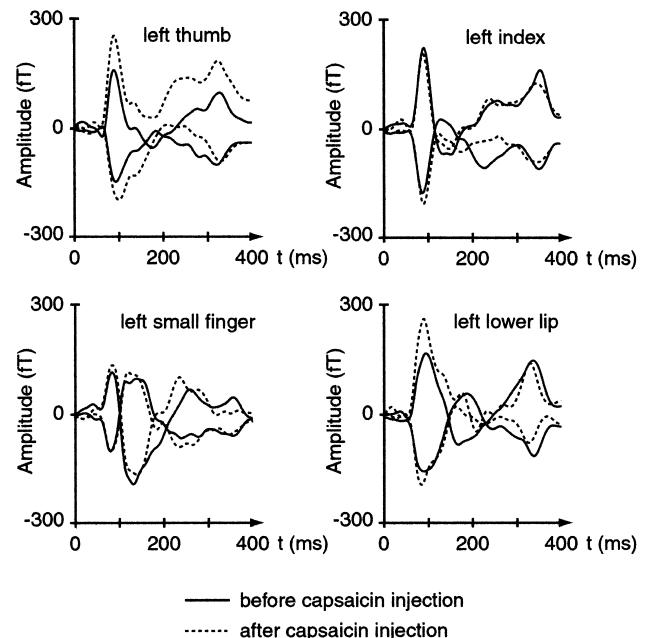


Fig. 2. Somatosensory evoked magnetic fields of a single subject during tactile stimulation at the four different sites before (filled line) and after capsaicin injection (dashed line). Only the positive and negative maxima of the 37 channels are displayed.

Fig. 3). Additionally, the distance between D1 and D5 decreased significantly in the second SEF measurement after capsaicin injection (range, 1–6 mm;  $P = 0.0464$ ; Fig. 3).

MEG is able to assess relative differences in dipole locations below 1 mm under favorable conditions, while the absolute spatial resolution is in the order of several millimeters [13]. Because of the small changes in source locations found here, the absolute shifts of individual dipoles after the injection of capsaicin cannot be determined with certainty and are not reported in this study.

The results of this study demonstrate that the strong nociceptive input evoked by the intradermal injection of capsaicin into the hand can cause a rapid functional reorganization of SI. This reorganization is characterized by a spatial shift, but not extension, of the cortical representations of the neighboring fingers and the lower lip. Previously, somatosensory reorganization has been observed after input decrease, i.e. de-afferentation or limb amputation in animals [18] and humans [6]. In addition, the increase of afferent input may also change cortical representations [7,17].

Capsaicin can also lead to a sensitization of C-fiber nociceptors at the injection site [19] and, when administered in higher concentrations than the 0.1% capsaicin solution used here, can act as a potent neurotoxin blocking C-fiber conductance [21]. Since the thresholds for touch or pain did not change significantly between the pre-capsaicin and the post-capsaicin von Frey filament testing at the sites of subsequent tactile stimulation for the SEF measurements, i.e. the fingers and the lip, the reorganizational changes seen here cannot be attributed to peripheral sensitization of nociceptors or to a conduction block of sensory nerve fibers following capsaicin injection. Rather, the effects must be attributed to a direct activation of C-fibers.

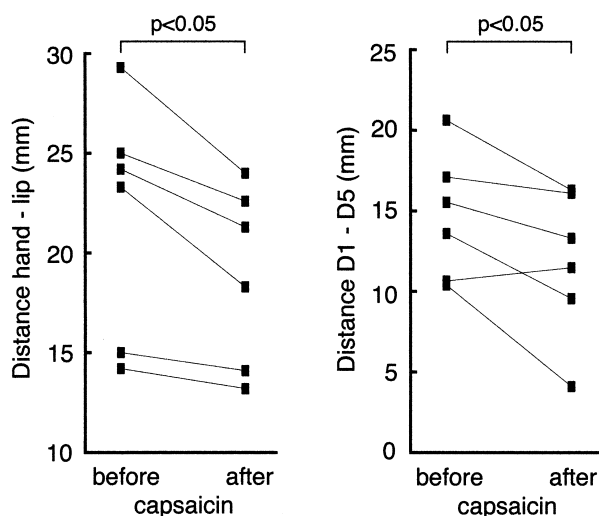


Fig. 3. Euclidean distances between the center of gravity of the representation of the left hand and the left lower lip (left panel) and between the representation of the left thumb and the left small finger (right panel) before and after capsaicin injection.

Recently, attention has been shown to change the representation of single fingers in SI [2,15]. Since the injection of capsaicin evokes a severe pain, we made no attempt to distract our subjects' attention from the painful hand during injection. We cannot exclude the possibility that the representational changes seen in our study are, at least in part, due to changes in attention. However, a major effect of attentional shifts seems unlikely since the second measurement started 5 min after capsaicin injection when the initial pain was already strongly reduced and since the pain was not located at the fingers stimulated during the SEF measurements.

In the present study we found somatosensory reorganization already 5 min after the injection of capsaicin. Animal studies demonstrated that reorganization of SI starts within minutes after peripheral nerve injury [5,8]. The mechanisms of these rapid changes of cortical representations are not entirely clear. The injection of capsaicin activates SI in humans via C-fibers [10] and can modulate intracortical inhibition in area 3b of animals [4]. A substantial overlap of dominant and latent input to area 3b was observed in monkeys [20]. Reorganizational plasticity is believed to mainly originate from the unmasking of those latent afferents [18]. Such an unmasking of overlapping tactile input by C-fiber afferents in area 3b could explain the rapid time course of the changes observed in our study. Pain could thus be a decisive factor for the activation of latent synapses.

In summary, the results of this study suggest that acute pain, evoked by the intradermal injection of capsaicin, causes rapid functional reorganization of the somatosensory cortex. This observation extends previous results on somatosensory plasticity after de-afferentation and training in animals and humans and after chronic phantom pain in human amputees. Further investigations must be directed on the time-course and on the cellular and molecular mechanisms of pain-induced plasticity. A challenging task for future research is to define the importance of somatosensory plasticity for the chronification of pain.

The authors thank Mrs Karin Berning for her help performing the MEG measurements. This study was supported by the University of Münster (IMF Sö-1-1-I/97-8, Kn-1-1-II/96-34), by the Deutsche Forschungsgemeinschaft (DFG Kn 285/4-1), and by the Benningsen-Foerder-Preis. This study was presented in part at the Fifth International Conference on Functional Mapping of the Human Brain, Düsseldorf, June 1999.

- [1] Birbaumer, N., Lutzenberger, W., Montoya, P., Larbig, W., Unertel, K., Töpfner, S., Grodd, W., Taub, E. and Flor, H., Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization, *J. Neurosci.*, 17 (1997) 5503–5508.
- [2] Buchner, H., Richrath, J., Grünholz, J., Noppeney, U., Waberski, T.D., Gobbelé, R., Willmes, K. and Treede, R.-D., Differential effects of pain and spatial attention on digit

- representation in the human primary somatosensory cortex, *NeuroReport*, 11 (2000) 1–5.
- [3] Buonomano, D.V. and Merzenich, M.M., Cortical plasticity: from synapses to maps, *Annu. Rev. Neurosci.*, 21 (1998) 149–186.
- [4] Calford, M.B. and Tweedale, R., C-fibres provide a source of masking inhibition to primary somatosensory cortex, *Proc. R. Soc. Lond. B*, 243 (1991) 269–275.
- [5] Calford, M.B. and Tweedale, R., Immediate and chronic changes in responses of somatosensory cortex in adult flying-fox after digit amputation, *Nature*, 332 (1988) 446–448.
- [6] Elbert, T., Flor, H., Birbaumer, N., Knecht, S., Hampson, S., Larbig, W. and Taub, E., Extensive reorganization of the somatosensory cortex in adult humans after nervous system injury, *NeuroReport*, 5 (1994) 2593–2597.
- [7] Elbert, T., Pantev, C., Wienbruch, C., Rockstroh, B. and Taub, E., Increased cortical representation of the fingers of the left hand in string players, *Science*, 270 (1995) 305–307.
- [8] Faggin, B.M., Nguyen, K.T. and Nicoletis, M.A., Immediate and simultaneous sensory reorganization at cortical and subcortical levels of the somatosensory system, *Proc. Natl. Acad. Sci. USA*, 94 (1997) 9428–9433.
- [9] Flor, H., Elbert, T., Knecht, S., Wienbruch, C., Pantev, C., Birbaumer, N. and Taub, E., Phantom limb pain as a perceptual correlate of cortical reorganization following arm amputation, *Nature*, 375 (1995) 482–484.
- [10] Iadarola, M.J., Berman, K.F., Zeffiro, T.A., Byas-Smith, M.G., Gracely, R.H., Max, M.B. and Bennett, G.J., Neural activation during acute capsaicin-evoked pain and allodynia assessed with PET, *Brain*, 121 (1998) 931–947.
- [11] Knecht, S., Sörös, P., Gürtler, S., Imai, T., Ringelstein, E.B. and Henningsen, H., Phantom sensations following acute pain, *Pain*, 77 (1998) 209–213.
- [12] Lü, Z.L. and Williamson, S.J., Spatial extent of coherent sensory-evoked cortical activity, *Exp. Brain Res.*, 84 (1991) 411–416.
- [13] Lütkenhöner, B. and Steinsträter, O., High-precision neuro-magnetic study of the functional organization of the human auditory cortex, *Audiol. Neurootol.*, 3 (1998) 191–213.
- [14] Nakamura, A., Yamada, T., Goto, A., Kato, T., Ito, K., Abe, Y., Kachi, T. and Kakigi, R., Somatosensory homunculus as drawn by MEG, *Neuroimage*, 7 (1998) 377–386.
- [15] Noppeney, U., Waberski, T.D., Gobbelé, R. and Buchner, H., Spatial attention modulates the cortical somatosensory representation of the digits in humans, *NeuroReport*, 10 (1999) 1–5.
- [16] Oldfield, R.C., The assessment and analysis of handedness: the Edinburgh inventory, *Neuropsychologia*, 9 (1971) 97–113.
- [17] Pascual-Leone, A. and Torres, F., Plasticity of sensorimotor cortex representation of the reading finger in Braille readers, *Brain*, 116 (1993) 39–52.
- [18] Pons, T.P., Garraghty, P.E., Ommaya, A.K., Kaas, J.H., Taub, E. and Mishkin, M., Massive cortical reorganization after sensory deafferentation in adult macaques, *Science*, 252 (1991) 1857–1860.
- [19] Schmidt, R., Schmelz, M., Forster, C., Ringkamp, M., Torebjörk, E. and Handwerker, H., Novel classes of responsive and unresponsive C nociceptors in human skin, *J. Neurosci.*, 15 (1995) 333–341.
- [20] Schroeder, C.E., Seto, S., Arezzo, J.C. and Garraghty, P.E., Electrophysiological evidence for overlapping dominant and latent inputs to somatosensory cortex in squirrel monkeys, *J. Neurophysiol.*, 74 (1995) 722–732.
- [21] Winter, J., Bevan, S. and Campbell, E.A., Capsaicin and pain mechanisms, *Br. J. Anaesth.*, 75 (1995) 157–168.