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Nociceptive and non-nociceptive sub-regions in the human secondary somatosensory cortex: An MEG study using fMRI constraints

K. Torquati,[a,b,c,*] V. Pizzella,[a,b,c] C. Babiloni,[d,e,f] C. Del Gratta,[a,b,c] S. Della Penna,[a,b,c] A. Ferretti,[a,b,c] R. Franciotti,[a,b,c] P.M. Rossini,[e,f,g] and G.L. Romani[a,b,c]

[a]*Dipartimento di Scienze Cliniche e Bioimmagini-Università 'G. D'Annunzio', Chieti, Italy*
[b]*Instituto di Tecnologie Avanzate Biomediche-Fondazione Università 'G. D'Annunzio', Chieti, Italy*
[c]*INFM-GC Chieti, Italy*
[d]*Dip. Fisiologia Umana e Farmacologia-University "La Sapienza", Roma, Italy*
[e]*IRCCS "Centro S. Giovanni di Dio"-FBF, Brescia, Italy*
[f]*AFaR-Dip.Neurosci.Osp.Fatebenefratelli "Isola Tiberina", Roma, Italy*
[g]*Neurologia Clinica-Università Campus Biomedico, Roma, Italy*

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Previous evidence from functional magnetic resonance imaging (fMRI) has shown that a painful galvanic stimulation mainly activates a posterior sub-region in the secondary somatosensory cortex (SII), whereas a non-painful sensory stimulation mainly activates an anterior sub-region of SII [Ferretti, A., Babiloni, C., Del Gratta, C., Caulo, M., Tartaro, A., Bonomo, L., Rossini, P.M., Romani, G.L., 2003. Functional topography of the secondary somatosensory cortex for non-painful and painful stimuli: an fMRI study. Neuroimage 20 (3), 1625–1638.]. The present study, combining fMRI with magnetoencephalographic (MEG) findings, assessed the working hypothesis that the activity of such a posterior SII sub-region is characterized by an amplitude and temporal evolution in line with the bilateral functional organization of nociceptive systems. Somatosensory evoked magnetic fields (SEFs) recordings after alvanic median nerve stimulation were obtained from the same sample of subjects previously examined with fMRI [Ferretti, A., Babiloni, C., Del Gratta, C., Caulo, M., Tartaro, A., Bonomo, L., Rossini, P.M., Romani, G.L., 2003. Functional topography of the secondary somatosensory cortex for non-painful and painful stimuli: an fMRI study. Neuroimage 20 (3), 1625–1638.]. Constraints for dipole source localizations obtained from MEG recordings were applied according to fMRI activations, namely, at the posterior and the anterior SII sub-regions. It was shown that, after painful stimulation, the two posterior SII sub-regions of the contralateral and ipsilateral hemispheres were characterized by dipole sources with similar amplitudes and latencies. In contrast, the activity of anterior SII sub-regions showed statistically significant differences in amplitude and latency during both non-painful and painful stimulation conditions. In the contralateral hemisphere, the source activity was greater in amplitude and shorter in latency with respect to the ipsilateral. Finally, painful stimuli evoked a response from the posterior sub-regions peaking significantly earlier than from the anterior sub-regions. These results suggested that both ipsi and contra posterior SII sub-regions process painful stimuli in parallel, while the anterior SII sub-regions might play an integrative role in the processing of somatosensory stimuli.

Keywords: Magnetoencephalography; SEF; Secondary somatosensory area (SII); Median-nerve electrical stimulation; Pain

Introduction

Previous neurophysiological studies have shown that the contralateral primary (SI) and the bilateral secondary (SII) somatosensory cortices participate in pain processing and discrimination in healthy humans (Bromm and Lorenz, 1998; Hari et al., 1997; Kakigi, 1994; Miltner and Weiss, 1998; Treede, 2002; Treede et al., 1999). In this functional context, SI is supposed to process and encode type and intensity of sensory inputs, while SII has a multifaceted role including sensorimotor integration (Huttunen et al., 1996), integration of information from the two body halves (Hari et al., 1998), and cognitive functions, such as attention (Burton et al., 1999; Mima et al., 1998), learning (Diamond et al., 2002), memory (Diamond et al., 2002; Ridley and Ettlinger, 1976), integration, and emotional coding of nociceptive and non-nociceptive sensory inputs.

The spatial organization of the neural nociceptive and tactile functions in the human somatosensory systems is still debated. Previous positron emission tomography (PET) evidence has shown substantial overlap of the zones of SI activation in response to

* Corresponding author. I.T.A.B.-University of Chieti, via dei Vestini 33, 66013 Chieti, Italy. Fax: +39 08713556930.
E-mail address: kathya.torquati@itab.unich.it (K. Torquati).
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noxious heat and innocuous vibrotactile stimuli (Coghill et al., 1994). Conversely, a magnetoencephalographic (MEG) study has revealed possible differences in the organization of nociceptive and tactile regions in SI (Ploner et al., 2000). Compared to SI, the spatial organization of SII is more difficult to explore, due to its small extent and complex folding in the depth of the Sylvian fissure. A functional segregation of SII sub-regions devoted to the processing of noxious and tactile stimuli has been suggested. A recent MEG study (Torquati et al., 2002) has shown a complex dependence of the SII responses on the electric stimulations intensity, ranging from the sensory to a weak painful level. An interference between two different neuronal populations in SII selectively responding to non-noxious and noxious stimuli was speculated. This hypothesis has been indirectly strengthened by further MEG data modeling the responses of SI and SII after several combinations of simultaneous non-painful and painful stimuli (Torquati et al., 2003). However, the spatial resolution of MEG did not allow the discrimination of such closely located neural populations. Evidence supporting this hypothesis stems from two fMRI studies. The first one (Niddam et al., 2002) has shown that a non-painful tonic intramuscular electrical stimulation mainly activated the lateral segment of SII, while a painful tonic stimulation activated both the lateral and the medial part of SII. The second one (Ferretti et al., 2003) has demonstrated two distinct SII sub-areas of activation in the anterior–posterior direction. The posterior SII sub-regions significantly increased their activation as a function of the stimulus intensity from non-painful to painful levels. In contrast, the anterior SII sub-region activity was not significantly modulated by stimulus intensity. Based on these data, a reasonable explanation is that, in each hemisphere, SII includes at least two neuronal populations differently sensitive to painful and non-painful somatosensory stimulations. The partial divergence of the referred fMRI findings (Ferretti et al., 2003; Niddam et al., 2002) might be explained with the existence of a more medial representation for muscle nociceptive receptors and a more posterior representation for skin nociceptive receptors. Finally, Ferretti et al. (2004) studied the somatotopic organization of the SII sub-regions with median and tibial nerve electric stimulation at non-painful and painful intensity. They found that while the anterior sub-region exhibits a rough somatotopy, the posterior sub-region does not. This result further suggests that noxious and non-noxious information are integrated in SII.

The present combined fMRI and MEG study assessed the working hypothesis that the activity of such posterior SII sub-regions is characterized by amplitude and temporal evolution in line with the parallel functional organization of nociceptive systems (Ploner et al., 1999; Treede et al., 2000). Somatosensory evoked magnetic fields (SEFs) were recorded after non-painful and painful galvanic median nerve stimulations. In order to take advantage of the superior spatial resolution of fMRI, the same subjects already studied in the abovementioned fMRI study (Ferretti et al., 2003) were enrolled. In that study, the BOLD fMRI activations unveiled in SII two separate clusters of significant voxels in the antero-posterior axis, with the spatial resolution allowed by a voxel size of 4 mm × 4 mm × 3 mm (slice thickness). The ANOVA analysis across subjects on the position of the centroids of the two clusters yielded a high significance level ($P < 0.0003$) when comparing the y coordinates (anterior–posterior direction) of the two clusters, while only the pair in the left hemisphere showed a significant difference ($P < 0.01$) when comparing the x coordinates. The z coordinates did not show any significant difference. In both hemispheres, the two clusters responded differently to noxious and non-noxious stimulation. Specifically, the response of anterior sub-regions (in terms of percent signal change) did not depend on stimulus intensity, while the response of posterior sub-regions increased with stimulus intensity (i.e., was larger for painful stimuli). For clarity of the forthcoming methods section, the results of that study are summarized in Fig. 1: the anterior and posterior SII sub-areas, as observed in group data, are shown on a Talairach transformed transverse section. The curves of the BOLD response to non-painful and painful stimulation, averaged across voxels in a cluster, stimulation blocks, and subjects, show that these sub-regions are not only anatomically distinct, but also functionally distinct. These areas are also shown for every subject in that study in the second part of Fig. 1 where individual activations are superimposed on the individual non-transformed transverse sections. In the following, for the sake of brevity, these sub-regions will be termed iSIIa, iSIIp, cSIIa, and cSIIp, where the prefix "i" or "c" stands for ipsilateral or contralateral, respectively, and the suffix "a" or "p" stands for anterior or posterior, respectively.

In the present study, for each subject, the coordinates of the BOLD activations found in the SII sub-regions were used as constraints for the interpretation of the MEG data by means of a multidipole (equivalent current dipole, ECD) model.

Materials and methods

Subjects and stimulation procedure

SEFs recordings were performed in the same eight healthy volunteers (4 males, 4 females; age 19–22; right-handed) who participated in the mentioned fMRI study. The general procedures were approved by the local institutional ethics committee and conducted with the written informed consent of each subject.

Stimuli were electric rectangular pulses, 400 μs in duration, with a repetition rate of 0.3 Hz. Compared to the previous fMRI study, in which stimulus repetition rate was set to 1.9 Hz, a lower repetition rate was chosen for the present MEG study, since a short inter-stimulus interval has been found to reduce the SII neurophysiological response (Wikstrom et al., 1996). Stimuli were delivered unilaterally to the right median nerve at the wrist by means of a pair of non-magnetic AgCl electrodes.

The experimental design included the two most representative levels of the five galvanic stimulation intensities used in the fMRI experiment: a motor non-painful threshold, mainly exciting A-alpha and A-beta fibers, and a weak painful level, mainly exciting A-delta fibers (Babiloni et al., 2001). With reference to a subjective scale for pain ranging from 0 (no sensation) to 10 (pain tolerance threshold), the motor threshold corresponded to 2 (painless thumb muscle twitch) and the weak painful level corresponded to 5 (slight pain).

The stimulation current for the non-painful level reaching the motor threshold varied across subjects in the range of 3–13 mA (mean value 7.0 ± 0.3 mA), whereas the maximum stimulation current for the painful level never exceeded 40 mA.

Data acquisition

During the MEG recordings, the subjects were seated inside a magnetically shielded room and were asked to pay attention to the