Common cortical network for first and second pain

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Received 5 March 2004; revised 10 September 2004; accepted 21 September 2004

We measured, with whole-scalp magnetoencephalography, evoked fields from 10 healthy subjects to 1-ms thulium-laser stimuli that selectively activated nociceptive nerve fibers. The stimuli were delivered to the dorsum of the subject’s left hand. The earliest cortical responses peaked at 165 ± 7 ms, agreeing with the conduction velocity of Aδ-fibers. To stimulate unmyelinated C-fibers, we modified the method of Bragard et al. [Bragard, D., Chen, A.C., Plaghki, L., 1996. Direct isolation of ultra-late (C-fibre) evoked brain potentials by CO2 laser stimulation of tiny cutaneous surface areas in man. Neurosci. Lett. 209, 81–84], by decreasing the total energy of the laser beam and by restricting the size of the stimulated skin area to 0.2–0.3 mm2. The earliest cortical responses to these stimuli peaked at 811 ± 14 ms. Bilateral activation of the SII cortices was detected in all 10 subjects to Aδ and in 8 subjects to C stimuli, emphasizing the importance of the SII cortex in processing of pain. Additional activation was observed in the posterior parietal cortex (PPC), probably related to somatosensory coordination targeted to produce precise motor acts that reduce or prevent the pain; the PPC activation may have been accentuated by the required continuous evaluation of the perceived pain. In contrast to some earlier studies, we did not observe activation of the primary somatosensory cortex (SI). Additional activations to both types of stimuli were detected in the cingulate cortex (three subjects) and in the bilateral insular cortex (two subjects). These results implicate that the nociceptive inputs mediated by the Aδ- and C-fibers are processed in a common cortical network in different time windows. Reliable temporospatial characterization of cortical responses to first and second pain offers a unique tool for basic and clinical neuroscience to study the two distinctive pain fiber systems at cortical level.

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Keywords: Pain; Secondary somatosensory cortex; Posterior parietal cortex; Magnetoencephalography; MEG; C-fiber; Aδ-fiber

Introduction

Harmful stimuli applied to the skin activate peripheral nerve endings of the primary nociceptive neurons. Pain is mediated by small, thinly myelinated Aδ-fibers that conduct impulses at 5–30 m/s and by small-diameter, unmyelinated C-fibers that conduct very slowly, at 0.5–2 m/s. Following tissue injury, the Aδ-fiber-mediated “first” pain is often described as sharp and pin-prick-like, in contrast to the dull, long-lasting, and burning C-fiber-mediated “second” pain. Aδ-mediated acute pain elicits immediate avoidance reactions to harmful stimuli whereas the C-fiber system has been suggested to be involved in longer-lasting processes, such as tissue inflammation.

Functional imaging studies have revealed brain activation patterns to various noxious stimuli, such as heat (Casey et al., 1994; Coghill et al., 1994; Jones et al., 1991; Talbot et al., 1991), immersion in cold water (Casey et al., 1996a), electric stimulation (Bromm and Scharein, 1982; Inui et al., 2002; Tran et al., 2001), dental pain (Hari et al., 1983), CO2 delivered to nasal mucosa (Hari et al., 1997; Hummel et al., 1994; Huttenen et al., 1986), and CO2-laser (Bromm and Treede, 1987; Bromm et al., 1983; Kakigi et al., 1995; Valeriani et al., 2000; Watanabe et al., 1998) and thulium-laser (Kazarians et al., 1995; Ploner et al., 1999; Spiegel et al., 1996) pulses delivered to the skin. Activations have been frequently observed in the secondary somatosensory (SI) cortex, insula, anterior cingulate cortex, and the prefrontal cortex. Instead, participation of the human primary somatosensory (SI) cortex in pain processing is still under debate: About half of the studies report SI activation by painful stimuli (Bromm and Lorenz, 1998; Peyron et al., 2000; Treede et al., 1999a).

Recent intracranial recordings have confirmed bilateral activation of the SI cortices and insular cortex to painful laser stimuli delivered to the skin (Frot et al., 1999, 2001; Lenz et al., 1998; Peyron et al., 2002). Variability in opercular activations across studies appears mainly in the anterior–posterior direction, where the identified activations tend to follow the axis of the Sylvian fissure. The existence of supra-Sylvian laser-evoked potentials (LEPs) has been confirmed by both subdural and intracortical recordings (Frot et al., 1999, 2001; Garcia-Larrea et al., 2003).

The majority of functional brain imaging studies on pain have described cortical activation to Aδ-fiber-mediated pain, or to a
combination of Aδ- and C-fiber pain. However, it has been difficult to selectively stimulate the C-fiber system without significant activation of the Aδ-fibers. This C-fiber-based “second-pain system” can be activated by capsaicin that induces burning pain when applied to the skin. However, such a long-lasting stimulus does not allow studies of the temporal aspects of cortical pain processing. Therefore, other stimulation methods have been developed to enable recordings of millisecond-scale activation changes.

Cortical responses to C-fiber stimulation have been successfully recorded by using conduction blockade of Aδ-fibers (Bromm and Treede, 1987) or temperature-controlled laser heat stimuli (Magerl et al., 1999). Bragard et al. (1996) introduced a method to directly and selectively activate C-fibers: When CO₂ laser heat stimuli were delivered to a small (0.15 mm²) area of skin, ultra-late scalp potentials peaked at 810–1000 ms. In contrast, stimulation of a larger (15.5 mm²) area with high-energy pulses elicited cortical responses related to Aδ-fiber activity. Large-area stimulation may also elicit ultra-late C-fiber-related responses if the stimulus intensity is reduced. The physiological basis for such stimulus selectivity is the higher density and lower activation threshold of the C- than Aδ-fibers of the skin (Ochoa and Mair, 1969; Schmidt et al., 1994; Treede et al., 1994).

Therefore, laser stimulation delivered to a tiny skin area with low total energy is likely to activate predominantly the unmyelinated C-fibers. The first reports about cortical activation patterns to selective C-fiber stimulation have appeared recently (Kakigi et al., 2003; Opsommer et al., 2001a; Tran et al., 2002). Tran et al. (2002) also convincingly illustrated the prolongation of C-fiber response latency as a function of distance from the stimulus site to the brain, thereby demonstrating that the longer latencies to small- than large-area stimuli reflect conduction delays in the periphery, rather than processing in some additional neural circuits in the brain.

So far, cortical activation patterns of Aδ- and C-fiber-mediated pain have not been compared in the same subjects. Yet, understanding the functional organization and temporal dynamics of the cortical processing of the first and second pain would have important clinical implications, as the two pain fiber types differ clearly in their function and are likely to be differentially involved in various pain disorders.

Therefore, we aimed to clarify, with whole-scalp magnetoencephalographic (MEG) recordings, the cortical network involved in pain processing. For that purpose, we compared activation patterns, temporal behavior, and recovery profiles of cortical areas responding to Aδ- and C-fiber stimuli.

Materials and methods

Laser-evoked fields (LEFs) were recorded from 10 healthy volunteers (7 males, 3 females; ages 21–37 years, mean 27 years; all right-handed). The protocol was accepted by the local Ethics Committee, and a written informed consent was obtained from all subjects.

Magnetoencephalographic recordings

During the MEG recording, the subject was sitting comfortably in a magnetically shielded room, with the head supported against the helmet-shaped sensor array of the magnetometer. Laser stimuli (1 ms in duration, 2000 nm in wavelength) were produced by a thulium-YAG stimulator (BLM 1000 Tm:YAG®, Baasel Laser-tech, Starnberg, Germany), and the laser beam was conducted to the magnetically shielded room via an optic fiber.

An assistant directed the stimuli to the lateral dorsum of the subject's left hand between the first and the second metacarpal bones; the distance of the stimulator from the skin was kept constant. To avoid skin burns, the stimulus site was slightly moved after each stimulus to a random direction within an area of about 10 cm². For both types of stimulation, the interstimulus interval varied randomly between 4.5 and 5.5 s, and blocks of 100–130 stimuli were delivered twice in each session.

To activate predominantly Aδ-fibers (and thereby to produce “first pain”), the “large-area” stimuli were applied to a skin area of 10 mm² with a mean intensity of 52 mJ/mm² (range 45–60 mJ/mm²); the intensity was individually adjusted to equal 1.5 times the subjective pain threshold. These intensities corresponded to a total energy of about 500 mJ.

To activate C-fibers, we modified the method introduced by Bragard et al. (1996) who used a thin aluminum disk, drilled with calibrated holes and interposed just above the skin surface. Our laser beam was led through a small hole in a plastic plate connected to the hand piece at the end of the optical fiber that transferred the laser beam from the stimulator. Thus, these “small-area” stimuli were restricted to an area of 0.2–0.3 mm². The intensity was individually fine-tuned to elicit a delayed but not sharp pain; on average, the intensity was 190 mJ/mm² (range 175–235 mJ/mm²) corresponding to a total energy of about 50 mJ. The interstimulus interval was also for these stimuli 4.5–5.5 s; in addition, after every block of 20 C-fiber stimuli, the recording was interrupted for 1–3 min to minimize habituation (Tran et al., 2001).

The subjects were instructed to monitor the stimuli attentively, and to rate the mean intensity of the perceived pain using a Visual Analogue Scale (VAS) from 0 (no pain at all) to 10 (worst imaginable pain) after each measurement. The subjects were also asked to verbally describe the perceived stimuli. The subjects were wearing earplugs to avoid auditory contamination from the stimulator noise, and they were instructed to avoid looking at the stimulation site and to keep the stimulated hand immobile.

For control purposes, the left median nerve was stimulated with 0.3-ms constant current pulses, delivered with bipolar electrodes at the wrists once every 4.5–5.5 s, with intensities adjusted to produce a thumb twist without discomfort.

Evoked responses were recorded with a 306-channel helmet-shaped neuromagnetometer (Vectorview™, Neuromag Ltd, Helsinki, Finland). The device contains 102 identical triple sensors, each of them comprising two orthogonal planar gradiometers and one magnetometer. The exact position of the head with respect to the sensors was found by measuring the magnetic signals produced by current fields fed into four indicator coils placed at known sites on the scalp. The locations of the coils with respect to landmarks on the head were determined with a 3-D digitizer to allow alignment of the MEG and magnetic resonance image (MRI) coordinate systems. The signals were bandpass filtered through 0.03–200 Hz and digitized at 600 Hz. The 2000-ms analysis period of evoked responses included a prestimulus baseline of 200 ms; about 100 epochs were averaged for each condition. Responses coinciding with amplitudes exceeding 150 μV in the simultaneously recorded vertical electro-oculogram (EOG) were automatically rejected from the analysis.
The magnetic resonance images of the subjects were acquired with a 1.5-T Siemens Magnetom™ system. The individual brains segmented from the MR images were registered to the European Computerized Human Brain Database (ECHBD) atlas brain (Roland et al., 2001) using linear registration (Woods et al., 1998), followed by calculation of an elastic deformation field (Schormann et al., 1996). The elastic transformation allowed accurate averaging of the subjects’ individual MR images and the individual source locations in a common coordinate system; as an end result, the average source locations were visualized on top of the average MR images that reflect the anatomical variance of the subjects.

Data analysis

The source modeling (for a review, see Hamalainen et al., 1993) was based on signals recorded by 204 gradiometers. To identify sources of the measured evoked responses, deflections exceeding the noise level (about 5 fT/cm) were first visually searched to select the time windows and cortical areas of interest for further analysis. During these time periods, equivalent current dipoles (ECDs), best describing local source currents at the response peaks, were found one by one by a least-squares search using a subset of channels (usually 16–18) over the response area. These calculations resulted in the three-dimensional location, orientation, and strength of the ECD in a spherical conductor. Goodness-of-fit ($g$) of the model was also calculated to quantify how much of the measured signal variance was accounted for by the dipole solution; only ECDs with $g \geq 85\%$ at selected periods of time in the subset of channels were used for the further analysis.

After identifying the single dipoles, the analysis was extended to the whole signal duration and all channels were taken into account in computing the time-varying multidipole model. The validity of the multidipole model was evaluated by comparing the measured signals with responses predicted by the model. Whenever signals of any brain region were left inadequately explained by the model, the data were re-evaluated for more accurate estimation of the generator areas. To quantify how well the multidipole model accounted for the measured data, the $g$-values were calculated across all channels and over the entire time period, and compared between different models with the same number of dipoles to find the best possible solution. This approach, explained in detail by Hamalainen et al. (1993), has been successfully used in several previous studies of the somatosensory cortical network.

Statistical significance of the results was tested with Student’s paired two-tailed $t$ test.

Results

All subjects rated both types of stimuli as clearly painful; the reported mean ± SEM values on the VAS scale were 5 ± 1 for large-area (“A”) stimuli and 4 ± 1 for small-area (“C”) stimuli. Large-area stimuli were described as producing sharp pain, followed by a milder pain and/or warm sensation, whereas the small-area stimuli were described as producing burning and more long-lasting pain.

Fig. 1 illustrates laser-evoked fields of Subject 1. To the large-area stimuli, the earliest responses peak over the contra- and ipsilateral temporoparietal areas at 158 and 160 ms, respectively; additional deflections of opposite polarity peak at 226 and 244 ms. Over the contralateral superior parietal cortex, another response peaks at 158 ms.

To small-area stimuli, aimed to stimulate predominantly the C-fibers, the response distribution is strikingly similar although the latencies are much longer. The earliest responses peak bilaterally over the temporoparietal areas at 806 and 820 ms; over the right hemisphere, another response of opposite polarity is observed at 898 ms. A weak response peaks over the contralateral superior parietal area at 818 ms. Fig. 1 (bottom) also shows the corresponding source locations for Subject 1. The temporoparietal responses at 158 and 160 ms (to large-area “A”) stimuli) and at 806 and 820 ms (to small-area “C”) stimuli) were adequately modeled by dipoles located in the upper lips of the Sylvian fissures of both hemispheres, agreeing with activation of the secondary somatosensory (SII) cortex. The source locations of the somatosensory evoked fields (SEFs) to electric left median nerve (MN) stimuli are shown for comparison, and the 80- and 91-ms MN responses originated within 5 mm from the LEFs at SII.

As the parietal operculum of monkeys, and most likely also of humans, contains multiple somatosensory representations (Krubitzer et al., 1995), it is difficult to definitely assess whether the observed activity originated from the SII “proper” or from some other area in the parietal operculum. However, these bilateral signals arising in the upper lip of the Sylvian fissure have been referred to as SII activity in several prior MEG and ECG studies, and we follow this nomenclature.

Later temporoparietal responses (at 226 and 244 ms) originated bilaterally in the depths of the Sylvian fissures, 12–20 mm anterior to the corresponding SII responses, thereby agreeing with activation of the anterior insula. The contralateral 898-ms response to small-area stimuli also originated in the anterior insula. The contralateral parietal responses peaking at 158 and 818 ms were explained by activation of the posterior parietal cortex, close to the superior end of the postcentral fissure (Fig. 1, bottom right), clearly posterior, medial, and superior to the source of the 20-ms response to MN stimuli generated in 3b of SI hand area (Allison et al., 1989; Hari and Forss, 1999). The locations and orientations of the PPC dipoles did not differ between large- and small-area stimuli.

Cortical activation patterns

Fig. 2 shows grand average responses across all eight subjects from contra- and ipsilateral SII and from contralateral PPC, nicely replicating the single-subject data of Fig. 1 about the temporal differentiation between the A- and C-fiber responses. Very similar behavior is seen in Fig. 3 that illustrates individual response waveforms (and the replicates for subjects S7 and S8) of the contra- and ipsilateral SII responses to both types of laser stimuli. In some subjects (S1, S2, and S6), tiny early responses are also detected.

Bilateral SII responses were observed in all 10 subjects to large-area stimuli and in 8 subjects to small-area stimuli; only the responses of these 8 subjects were used for further analysis.

The SII responses to large-area stimuli peaked at 179 ± 7 and 167 ± 7 ms in the left and right hemispheres, respectively. The corresponding SII responses to small-area stimuli peaked at 823 ± 21 and 811 ± 14 ms in the left and right hemispheres, respectively. Activation of the right PPC area was also observed at two distinct latencies to large- and small-area stimuli, at 183 ± 22 and at 833 ± 22 ms.
The estimated conduction velocity (CV), obtained by dividing the recorded latency with the distance from the hand to the contralateral sensorimotor cortex, was about 6 m/s for the earliest cortical response to large-area stimulation, thereby agreeing with activation of small myelinated A\textsubscript{y}-fibers. The subjects’ descriptions of the stimuli as causing sharp, well-localized pain are in line with A\textsubscript{y}-fiber stimulation.

Similarly, the calculated CV of about 1 m/s to small-area stimuli agrees with the known conduction velocity of the nonmyelinated C-fibers and is in line with earlier studies (Bragard et al., 1996; Opsommer et al., 2001b; Tran et al., 2002). This interpretation of C-fiber stimulation is further supported by the subjects’ description of the stimuli as causing slow and burning pain. To further confirm the estimated peripheral conduction velocity of the C-fibers, responses were recorded from two subjects to small-area laser stimulation of the distal and proximal skin areas (dorsum of the left hand and the left shoulder).

Fig. 4 illustrates laser-evoked fields at the contralateral SII cortex to small-area stimuli applied to hand (distal) and shoulder (proximal) in Subject 1. To the proximal stimuli, the major responses (after the tiny A\textsubscript{y} responses) peak at 360 ms, whereas the distal stimuli elicit the strongest responses at 820 ms. The corresponding values for the other subject (S7) were 280 and 830 ms. The calculated peripheral conduction velocity is thus 1.0–1.2 m/s, strongly supporting activation of C-fibers.

**Source locations**

Fig. 5 (left) shows the mean (±SEM) source locations of SII responses to A\textsubscript{y}, C, and MN stimuli superimposed on the coronal slice of the average of the elastically transformed MR images of all subjects; the right side of the figure schematically shows the source locations. The SII responses elicited by the three different stimuli originated very close to each other in the upper lip of the Sylvian fissure. The mean source locations of the SII responses to A\textsubscript{y}, C,
and MN stimuli are shown, in head coordinates and in Talairach space, in Table 1.

In none of the subjects did the location of the SII responses differ significantly between Aδ- and C-fiber stimuli. SII responses to both pain stimuli were generated within 5 mm from the SII responses to MN stimuli in both hemispheres. The locations of the contralateral SII sources did not significantly differ between the three stimulus types, whereas the responses in the ipsilateral hemisphere were on average 5 mm more anterior to C-fiber than MN stimuli \((P < 0.02)\). Table 2 summarizes the mean ± SEM strengths of the source waveforms.

Fig. 6 (top) illustrates the source locations of the contralateral parietal responses to Aδ- and C-fiber stimuli superimposed on the average of elastically transformed MRIs of all subjects. The source of the 20-ms response to left-sided MN stimuli is shown for comparison. The images indicate that the responses to pain stimuli are generated in the posterior parietal cortex, near the superior end of the postcentral fissure. The mean Talairach coordinates \((x, y, z)\) were 24, −40, 53 for Aδ stimuli and 19, −41, 49 for C stimuli; the corresponding values were 40, −25, 44 for the MN (SI) response.

Fig. 6 (bottom) compares schematically the PPC source locations. The sources to Aδ- and C-fiber stimuli do not differ, but are clearly posterior (1.5 cm, \(P < 0.04\) for Aδ; 1.6 cm for C), medial (1.4 cm, \(P < 0.03\) for Aδ; 2 cm, \(P < 0.001\) for C), and superior (1.3 cm, \(P < 0.04\) for Aδ; 1 cm for C) to the source of the 20-ms MN response that was here used as the marker of the SI cortex.

Additional activations were observed in several other cortical areas, but these were inconsistent across subjects; strong insular responses were detected in two subjects, mesial responses (generated in different regions of the cingulate cortex) in three subjects, and prefrontal responses in one subject. Activation of the inferior temporoparietal regions was observed in two subjects.

**Response strengths and effect of stimulus repetition**

Fig. 7 illustrates the mean (±SEM) strengths of responses at contra- and ipsilateral SII and at contralateral PPC. The SII responses were on average 76% stronger to Aδ- than C-fiber
stimuli in the contralateral hemisphere and 52% stronger in the ipsilateral hemisphere. The PPC responses did not differ between Aβ- and C-fiber stimuli, being 40–73% of the strength of the contralateral \( P < 0.04 \) for Aβ stimuli and 36–55% of the ipsilateral SII responses \( P < 0.01 \) for Aβ, \( P < 0.04 \) for C).

Table 2 shows the mean \( (\pm \text{SEM}) \) source strengths to Aβ and C stimuli. The amplitudes of the C-fiber responses dropped during repetition by 10–38% \( (P < 0.01 \) in ipsilateral SII), in agreement with online observations, made during data collection, about the decrease of C-fiber responses after the first 20–40 stimuli.

**Discussion**

Previous studies have repeatedly indicated that both Aβ- and C-fibers are activated by laser heat stimuli applied to the skin, and that the predominant activation of the Aβ- or C-fibers depends on pulse intensity and on the size of the stimulated skin area (Bragard et al., 1996; Opsommer et al., 2001a; Treede et al., 1994). In the present study, reliable and distinct cortical responses were obtained, with latencies corresponding to conduction velocities of Aβ- and C-fibers. The distinction between the two fiber systems was very clear although the responses often contained tiny deflections also to the other fiber type, indicating that absolute selectivity was not achieved. The subjects’ qualitative descriptions of the perceived pain further supported the distinction between Aβ- and C-fiber activations. Our C-fiber stimulation, relying on a small hole at the end of the hand piece of the stimulator cable, instead of an aluminum plate containing holes placed on the skin (Bragard et al., 1996), provides a flexible method to apply C-fiber stimuli to different sites of the body.

In most earlier studies, the subjects have described C-fiber stimulation to elicit sensations of warmth or tactile-like sensations (e.g., Bragard et al., 1996; Cuccu et al., 2003; Opsommer et al., 2001a), rather than pain. In contrast, our subjects reported clearly painful sensation to C-fiber stimuli during recordings. However, with intensities below the individual pain thresholds, our subjects also described the stimuli as warmth. This finding is in line with earlier observations that C warmth receptors have a slightly lower threshold than C nociceptors, and much lower density in the skin (Cuccu et al., 2003; Green and Cruz, 1998; LaMotte and Campbell, 1978; Tillman et al., 1995).

The observed cortical activation patterns indicate that distinct nociceptive Aβ- and C-fiber systems mediate noxious input within different time windows to a common cortical network that includes at least the bilateral SII cortices and the posterior parietal cortex. In contrast to a recent MEG study (Ploner et al., 2002), our data did not indicate participation of the primary somatosensory cortex (SI) in processing of the painful laser stimuli. Variable additional activation of anterior insula, mesial cortex, prefrontal cortex, and inferior temporoparietal cortex was observed only in some of the subjects.

**Role of SII cortex in pain processing**

Previous brain imaging studies have shown that various painful stimuli activate the SII cortex (Davis et al., 1995, 1998; Hari et al., 1983, 1997; Howland et al., 1995; Huttunen et al., 1986; Kakigi et al., 1995; Peyron et al., 2000; Ploner et al., 1999, 2002; Talbot et

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**Table 1**

<table>
<thead>
<tr>
<th>SIIc coordinates</th>
<th>Aβ</th>
<th>C</th>
<th>MN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>43, 14, 58</td>
<td>45, 16, 61</td>
<td>48, 12, 58</td>
</tr>
<tr>
<td>Talairach</td>
<td>43, –17, 20</td>
<td>46, –16, 23</td>
<td>48, –19, 19</td>
</tr>
<tr>
<td>SIIi coordinates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>–46, 7, 58</td>
<td>–45, 12, 60</td>
<td>–48, 4, 64</td>
</tr>
<tr>
<td>Talairach</td>
<td>–48, –18, 18</td>
<td>–47, –14, 20</td>
<td>–51, –21, 23</td>
</tr>
</tbody>
</table>

The head coordinate system is as in Fig. 4.

**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>SIIc</th>
<th>SIIi</th>
<th>PPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ</td>
<td>37.4 ± 10</td>
<td>40.8 ± 9</td>
<td>14.8 ± 4</td>
</tr>
<tr>
<td>Aβ Rep</td>
<td>37.8 ± 8</td>
<td>37.5 ± 6</td>
<td>13 ± 3</td>
</tr>
<tr>
<td>C</td>
<td>20.8 ± 4</td>
<td>27.4 ± 5</td>
<td>15.2 ± 4</td>
</tr>
<tr>
<td>C Rep</td>
<td>18.3 ± 3</td>
<td>17 ± 2</td>
<td>9.4 ± 3</td>
</tr>
</tbody>
</table>

Rep = repeated measurement; SIIc = contralateral SII; SIIi = ipsilateral SII.
In 15 epileptic patients, studied with implanted depth electrodes, the sources of both laser-evoked potentials (LEPs) and somatosensory-evoked potentials (SEPs) were in the pre- and post-Rolandic upper bank of the Sylvian fissure, with no significant differences between noxious and non-noxious stimuli (Frot et al., 1999, 2001), thereby confirming findings of the earlier imaging studies.

The very first source analysis of C-fiber responses showed ultralate potentials peaking at about 930 and 1150 ms after stimulation of hand, with a scalp distribution suggesting activation of bilateral SII cortices and the anterior cingulate gyrus (Opsommer et al., 2001a). Accordingly, a recent MEG study, with intracutaneous electric stimuli applied to upper limb, showed ultra-late responses around 750 ms in the SII cortices; additional weak activation was reported in 4 out of 15 subjects in the posterior SI cortex (Tran et al., 2001).

The present results add to the information obtained in previous studies. First, the strong and consistent activation of the SII areas emphasizes the importance of the SII cortex in pain processing. Second, the similar source locations of the SII responses to Aδ and C stimuli suggest that the same, or heavily overlapping, neuronal populations in the SII region respond to peripheral noxious stimulation, regardless of the mediating fiber type.

**Activation of PPC vs. SI cortex**

In contrast to recent brain imaging studies indicating activation of the superior and posterior parts of the SI cortex to painful stimuli (Gelnar et al., 1999; Inui et al., 2002, 2003; Kanda et al., 2000; Ploner et al., 2000; Tran et al., 2001), our results did not show activation in the SI cortex, neither to Aδ- nor to C-fiber stimulation. The role of SI in pain processing has been under extensive debate. Nociceptive projections exist from thalamus to SI (Apkarian and Shi, 1994), and specific nociceptive neurons have been identified in SI (Kenshalo and Isensee, 1983); yet, a meta-
analysis of 25 PET and fMRI studies showed that SI activation to painful stimuli had been observed in only about half of the studies (Peyron et al., 2000). Several factors have been brought up to explain this discrepancy. As activation to noxious stimuli has been mainly detected in SI area 1, in the posterior crown of the central fissure (Gelnar et al., 1999; Ploner et al., 2000), the mainly radial current direction could explain weak or lacking SI activity in many MEG recordings. However, SI activation has been lacking also in EEG, functional MRI, and positron emission tomography studies that should not be affected by such functional anatomy (Derbyshire et al., 1994, 1997; Jones et al., 1991; Valeriani et al., 2000; Xu et al., 1997).

It has been suggested that significant SI activation would require sufficient spatial and temporal summation of the stimuli (Treede et al., 1999a). Accordingly, the above meta-analysis (Peyron et al., 2000) studies suggested that the intrinsic stimulus size and the repetitive application of the stimulus over different body sites are crucial factors for SI activation. Very different stimulation techniques in various studies may also have brought discrepancy to the results, and some of the detected SI signals may have reflected tactile components of the stimulus.

Direct intracranial recordings in monkeys have shown only variable and weak activation of SI cortex to noxious stimulation, possibly because the sparsely and widely distributed nociceptive neurons are intermixed with more numerous neurons that respond to innocuous tactile stimuli (Kenshalo and Isensee, 1983; Kenshalo et al., 1988).

In one patient, subdural responses from peri-Rolandic cortex to CO₂ laser stimuli showed a negative deflection with a distribution similar to, but slightly wider than, that of P25 to electric stimuli (Kanda et al., 2000). In four patients with subdural electrodes implanted for the surgical treatment of intractable epilepsy, LEPs peaked at about 150 ms, with the maximum located 2–3 and 1–2 cm medial (dorsal) to the finger somatosensory areas 3b and 1, respectively, as determined from the SEPs to vibratory stimuli and from P25 to electric stimuli (Ohara et al., 2004). The LEP peak was distributed more diffusely through the pre- and postcentral areas than the vibratory SEP and P25 peaks, and in contrast to these responses, the LEP peak did not show polarity reversal in the recording area. Such a surface-negative peak without polarity reversal could be generated either by a radial current source or by a tangential current source with the positive pole outside the recording grid. Therefore, the authors suggested a deep generator in the central sulcus (area 3a) or in the postcentral sulcus (areas 2, 5, or 7). They concluded that for a tangential source in areas 2, 5, or 7, the posterior pole might have been posterior to the recorded area. Alternatively, for two independent sources—one in the primary motor cortex and the other in the areas 1 and/or 2—the positive pole could have been located more anteriorly (Ohara et al., 2004).

In the present study, we found consistent activation of the bottom of the postcentral fissure both to Aδ- and C-fiber stimulation. The activation was highly significantly posterior and medial to hand 3b area of the SI cortex; this difference was evident both in the comparison of relative source locations and in the accurate averaging of individual brains and source locations after elastic transformation. Area 2 of the human SI comprises mainly the postcentral gyrus and a short segment of the anterior wall of the postcentral fissure (Geyer et al., 2000; Grefkes et al., 2001), whereas the deeper part of the anterior wall and the bottom of the postcentral fissure presumably comprise Brodmann’s area BA 5, and the posterior wall of the postcentral sulcus likely comprises BA 7. As the mean 20-mm distance of our posterior source from the SI cortex clearly exceeds the about 10-mm distance between cytoarchitectonic areas 3b and 1 in SI (Allison et al., 1989; Burton et al., 1997), we feel confident to claim that our posterior source is located outside of SI, most likely in BA 5/7.

Several lines of evidence support activation of BA 5/7 to painful stimuli. The homologous area in monkey cortex contains nociceptive neurons that have highly complex properties, responding best to multimodal stimuli, whereas they do not encode stimulus location and intensity with high fidelity (Dong et al., 1989, 1994). Activation of human BA 5/7 has been previously linked to pain perception in an fMRI study (Apkarian et al., 1999) that, during a thermal pain task, revealed close connection of the anterior parietal areas to stimulus parameters, whereas the more posterior parts, especially BA 5/7, were best related to temporal properties of pain perception. Signals from BA 5/7 have also been linked to increased spatial attention towards painful stimuli (Davis et al., 2002; Witting et al., 2001).

BA 5/7 is anatomically connected to other nociceptive brain areas, such as ACC, insula, prefrontal cortex, and thalamus (Friedman and Murray, 1986; Friedman et al., 1986), as well as to the premotor and primary motor cortices (Leichnetz, 1986). As PPC is a multisensory, integrative higher-order processing area that converges information from different sensory modalities and from spatial coordinates of inner and outer space, activation of PPC to painful stimuli could be related to the sensorimotor coordination that is needed to precisely define the hand location (the site of the painful stimuli) with respect to both other parts of the body and the outer space, thereby facilitating purposeful motor acts that would be needed to reduce or prevent the pain.

Taken together, the information obtained from the brain imaging studies and intracranial recordings suggests that both the most posterior parts of the SI cortex and the PPC (BA 5/7, at the bottom and the posterior wall of the postcentral fissure) are activated by painful stimuli. Our present findings, showing consistent activation in the cortex of the postcentral sulcus, indicate that both Aδ- and C-fiber-mediated pain activate area 5/7.
Although the precise roles of the posterior SI and PPC areas in pain processing are not fully uncovered, the stimulus type, its localization component, and the possible task may determine the relative strengths of activation in these areas. In our subjects, the request to continuously evaluate the pain intensity on the VAS scale may have accentuated the PPC activation. Nonetheless, activation of the PPC most likely occurs during any natural painful stimuli, as the immediate evaluation of the perceived pain is of crucial importance for purposeful avoidance reactions.

Activation of other brain areas

In several prior brain imaging studies of acute pain, activation of ACC has been almost invariably reported, and insular activation has been observed in intracranial recordings (Garcia-Larrea et al., 2003). The inconsistent activation of these regions in the present study may be partly explained by technical reasons; the opposite currents in the mesial walls of the interhemispheric fissure may cancel each other if they are equally strong and temporarily overlapping. In parietal operculum, activation generated in the SII region is typically strong and long-lasting and may therefore hamper detection of separate insular signals, especially if they are simultaneous and share similar current orientations with the SII responses.

First vs. second pain

A recent MEG study by Ploner et al. (2002) showed activation of SI, SII, and ACC areas after painful thulium laser stimuli that presumably activated both Aδ- and C-fibers. Ratios of activation strengths indicated strong SI activation during the early (100–250 ms) time window, SII activation during both early and late (500–1500 ms) periods, and ACC activation during the late time window. Therefore, it was concluded that the first (Aδ-) pain is particularly related to SI activity whereas the second pain is closely related to ACC activation; SII activity was associated with both first and second pain. Our present results with separate stimulation of Aδ- and C-fibers showed no signs of functional division between SII and PPC areas activated by first and second pain, but rather an activation of a common cortical network within different time windows.

Nociceptive fibers and chronic pain

Prior studies have indicated the usefulness of LEPs in assessment of lesions along the Aδ-fiber nociceptive pathways (Bromm and Treede, 1991; Crucu et al., 1999, 2001; Kakigi et al., 1991, 1992; Treede et al., 2003). In chronic neuropathic pain, LEPs to Aδ-fiber stimulation were decreased, in contrast to increased responses in patients with fibromyalgia (Casey et al., 1996a; Garcia-Larrea et al., 2002; Granot et al., 2001; Wu et al., 1999). The possible role of C-fibers in chronic pain has remained more obscure. LEP amplitudes to Aδ-fiber stimuli were not significantly correlated with VAS score in postherpetic neuralgia (PHN), and therefore more active contribution of C-afferents in PHN was suggested (Truini et al., 2003). Microneurographic recordings from single C-fibers of peroneal nerve, in patients suffering from chronic pain of lower extremities, have revealed several changes in the conductive properties of the C-fibers, implicating active contribution of C-fibers to chronic pain (Orstavik et al., 2003). Further, in four patients with central pain and with hyperalgesia to laser stimulation, ‘ultra-late’ responses with latency >800 ms were detected to stimulation of the painful skin area (Garcia-Larrea et al., 2002). These findings implicate the high clinical relevance of C-fiber assessment in the study of chronic pain. So far, reliable distinction of responses to Aδ- and C-fiber-mediated warmth have been successful in trigeminal skin regions of healthy subjects and of some patient groups (Crucu et al., 2003). The present results demonstrate that cortical responses to Aδ- and C-fiber-mediated pain arising in the distal hand area can be reliably recorded so that the first and second-pain systems can be directly compared. This distinction opens new possibilities to clinical applications, ranging from understanding the pathophysiological changes in chronic pain to evaluation of the effectiveness of therapeutic interventions.

Acknowledgments

This study was financially supported by the Academy of Finland. We thank Ms. M. Illman for skillful technical assistance.

References


