Cortical Responses to Aδ-Fiber Stimulation: Magnetoencephalographic Recordings in a Subject Lacking Large Myelinated Afferents

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Controversy persists over the role of the primary somatosensory cortex (SI) in processing small-fiber peripheral afferent input. We therefore examined subject I.W, who, due to sensory neuronopathy syndrome, has no large-fiber afferents below C3 level. Cortical evoked responses were recorded with a whole-scalp neuromagnetometer to high-intensity electrical stimulation of the distal right radial, median, and tibial nerves and skin over the forearm and mechanical stimulation of (neurologically intact) lip. The responses to electrical stimulation in the Aβ-denervated limbs peaked at 110–140 ms in contralateral SI and at 140–220 ms in contralateral secondary somatosensory cortex (SII), consistent with Aδ-mediated input. I.W. was able to localize pin-prick stimuli with 4 cm accuracy. Responses to laser stimuli on the radial dorsum of the hand peaked in contralateral SII cortex at 215 ms, also compatible with Aδ-mediated input. These results support the role of the SI cortex in processing the sensory discriminative aspects of Aδ-mediated input.

Keywords: electric stimulation, magnetoencephalography, neuronopathy, pain, somatosensory

Introduction

The role and involvement of different cortical areas in the processing of Aδ- and C-afferent information is still controversial. For instance, some studies show SI activation during noxious stimulations, whereas others do not (see reviews by Bromm and Lorentz 1998; Bushnell et al. 1999; Treede et al. 1999; Peyron et al. 2000; Apkarian et al. 2005). The reasons for such a discrepancy could include differences in recording methods, stimulus type, experimental paradigm, data analysis, and cognitive factors. Moreover, confound effects may arise when other fibers are stimulated simultaneously; for example, high-intensity electrical stimulation of peripheral nerves activates both Aβ-afferents and smaller fibers. To avoid such confounds, we recorded magnetoencephalographic (MEG) cortical evoked responses to electrical peripheral nerve stimulation in a subject lacking large diameter myelinated afferents. For comparative purposes, we assessed the subject's ability to localize thin-fiber stimulation and his cortical activations to laser stimuli that activate predominantly Aδ-afferents.

Here, we show that subject (I.W.), who has small-fiber afferents but is deafferented for Aβ-fibers (Cole and Sedgwick 1992), 1) has consistent SI responses, peaking at Aδ-latency to electrical nerve stimulation, 2) shows contralateral SII responses with Aδ-related latencies to laser stimulation of the skin, and 3) is able to locate, relatively well, pin-prick cutaneous stimuli.

Materials and Methods

Subject

I.W., a 56-year-old left-handed male, lives with sensory neuronopathy syndrome, a rare disorder of cell bodies of the primary sensory neurons (Sterman et al. 1980), which led to a complete loss of large myelinated afferents from C3 down. His face area is clinically unaffected (Cole and Sedgwick 1992). The deafferentation occurred after a gastric infection at the age of 19 years (Cole 1995). Since then, clinical and electrophysiological examinations have regularly been performed, and the condition has been stable. Motor nerve conduction velocity (CV) and electromyographic findings are normal. In previous studies on I.W., no peripheral sensory potentials to nonpainful electrical stimulation of the nerves in the arms and legs were recordable. Painful cutaneous electrical and laser stimulations have evoked cortical sensory potentials, with latencies consistent with conduction in Aδ-afferents (Cole and Katifi 1991; Treede and Cole 1993), but the sites of the underlying neural generators were not identified.

In daily life, I.W. denies feeling touch below the neck. In a forced-choice situation he can, however, detect tactile stimuli that activate unmyelinated low-threshold CT (C tactile) mechanoreceptors (Cole et al. 2006; Olausson, Cole, Rylander, et al. 2008). He has slightly increased detection thresholds for innocuous cool and for hot and cold pain, suggesting some (subclinical) involvement of Aδ- and C-afferents in his neuronopathy (Olausson, Cole, Rylander, et al. 2008).

The study was performed according to the Declaration of Helsinki. The Ethics Committee of the University of Gothenburg approved the stimulation procedures and subject participation, and the Ethics Committee of Helsinki and Uusimaa Hospital District approved the stimulation and MEG procedures. I.W. gave informed consent to all tests.

MEG Recordings

MEG signals were measured at the Brain Research Unit, Low Temperature Laboratory (Helsinki University of Technology, Finland) with a 306-channel neuromagnetometer (Vectorview; Neuromag Oy, Helsinki, Finland), which houses 102 identical triple-sensor elements in a helmet-shaped array. Each sensor element provides 3 independent measures of the magnetic field from 2 planar gradiometers and 1 magnetometer, respectively. For a review on basic principles of the MEG recordings, analysis, and applications, see, for example, Hari (2004).

During MEG recordings, I.W. was sitting in a magnetically shielded room with the head supported against the helmet-shaped neuromagnetometer. The exact position of the head, with respect to the sensors, was found by measuring magnetic signals produced by currents led into 4 indicator coils placed at known sites on the scalp.

The locations of the coils with respect to landmarks on the head were determined by a 3D digitizer (Isotrak 3S10002; Polhemus Navigation Sciences, Colchester, VT) to allow alignment of the MEG and magnetic resonance imaging (MRI) coordinate systems. I.W. was asked to keep the head immobile, the eyes open, and the gaze directed to a fixation point, as well as to avoid blinking.

MEG signals were recorded with a 0.03–172-Hz bandpass, digitized at 600 Hz, and averaged time-locked to the stimuli. For evoked responses, the duration of the analysis epochs was 1000 ms, including a prestimulus period of 200 ms.

Vertical and horizontal electro-oculograms (EOGs) were recorded simultaneously, and epochs with EOG amplitudes exceeding 300 μV peak-to-peak were rejected from the analysis and online averaging. The anatomical MRIs were acquired on a 1.5-T Intera scanner (Philips, Eindhoven, The Netherlands) using a T_1-weighted protocol.

Electrical, Mechanical, and Laser Stimulation

Electric constant-current pulses were delivered using bipolar surface electrodes, with 0.2–0.5 ms pulse durations, 8.5–32 mA current intensities, and 1.0–1.5 s interstimulus intervals. In all recordings, 2 sets of responses were acquired to establish replicability. At higher intensities, the stimulation typically evoked a slightly pricking, sharp sensation, with some muscle twitch. Only the right side of the body was electrically stimulated, and a total of 200–300 epochs were averaged for each condition.

The right radial nerve was stimulated in the middle of the forearm, the median nerve at the wrist, and the tibial nerve at the lateral malleolus (see Table 1). We also stimulated the dorsal skin of the midforearm (Table 1).

Mechanical stimulation, consisting of light taps with a soft fiber-optic device that enabled precise timing of the stimulation (Jousmäki et al. 2007), was applied to the hairy skin below the right lower lip. Approximately 100 single responses were averaged.

Laser stimuli, 1-ms pulses, 2000 nm wavelength, (thulium-YAG stimulator; BLM 1000 Tm: YAG; Baasel Laser-tech, Starnberg, Germany) were applied to an area of 10 mm^2, with an intensity corresponding to a total energy of about 500 mJ. In 2 separate sessions, one of the experimenters directed the stimuli to the radial dorsum of I.W.'s left and right hand, respectively, between the first and second metacarpal bones. To avoid skin damage, the stimulus site was moved randomly within an area of about 10 cm^2. The interstimulus interval was 5–7 s, and 40 evoked responses were averaged in each session. The intensity and beam diameter of the laser stimulus were adjusted to activate predominantly Aδ-afferents (Forss et al. 2005) and thereby produce sharp "first pain" in healthy volunteers. I.W. was instructed to rate the mean intensity of the perceived pain using a visual analogue scale (VAS) from 0 (no pain) to 10 (worst imaginable pain) and also to describe verbally the perceived stimuli after each measurement. He was told not to look at the stimulation site and to keep the stimulated hand immobile.

Perceptual Localization

Mechanical stimulation was applied with a calibrated monofilament (North Coast Medical, San Jose, CA) with stimulation force of 260 mN on the ventral side of the right forearm or right lower leg. Forty-eight stimuli were applied (24 on the forearm and 24 on the lower leg in a pseudorandom order). In 32 stimulations, the skin was indented once (single stimulation), and in 16 stimulations, 3 indentations were made in a row (triple stimulation). Each indentation lasted for about 0.5 s and I.W. perceived them as "sharp but not really painful." The experimenter marked the site of each stimulus with yellow ink, and I.W. wore yellow goggles, so each indentation site was invisible to him. Following each stimulation, I.W. pointed with the left index finger to where he perceived the indentation, and the distance to the yellow marking (mislocalization) was measured. I.W. had his eyes closed during stimulation but was watching when he pointed to the place of indentation.

Data Analysis

Source Modeling

The averaged somatosensory evoked fields (SEFs) were digitally low-pass filtered at 140 Hz, and a notch filter was applied at 50 Hz. Amplitude measurements were performed with the baseline set from –200 to –10 ms. For laser evoked fields (LEFs), the signal space separation (MaxFilter) method (Taulu et al. 2004) was used before offline averaging to remove slow drifts in the recorded data.

The sources of the SEFs and LEFs were modeled with equivalent current dipoles in a spherical volume conductor (Hämäläinen et al. 1993). The origin of the conductor was fitted to the intracranial space on the basis of the subject's own MRI. The 3D locations and orientations of the sources were found one at a time with a least squares search, and only sources with a goodness of fit higher than 80% were accepted.

Results

Perceptual Localization

Localization errors did not differ between single and triple stimulations, or between arm or leg stimulation, and so these data were pooled. The localization error was 44 ± 52 mm (mean and standard deviation, $n = 47$). I.W. did not perceive one of the stimulations on the thigh; when forced to guess, he mislocalized the stimulus to the arm. For 4 stimulations (3 on the arm), he pointed directly to the target.

Cortical Activation

I.W. reported a clear prickly sensation with the strongest electrical stimuli (32 mA/0.2 ms to 27 mA/0.5 ms) and sharp, prickly but nonpainful sensation for laser stimuli (although classified 4–5 of 10 on a VAS scale, i.e. moderately painful), and these stimuli led to clear evoked responses. In contrast, weaker electrical stimuli (17–22 mA/0.2ms) were not perceived and no cortical evoked responses were identified.

Figure 1 shows the spatial distribution of the SEFs to electric stimulation of the right radial nerve. The first clear response on channel A, over the left (contralateral) central area, peaked about 115 ms after the stimulus onset. The inserts illustrate that the SEFs at this location were reproducible to electric stimulation of the radial nerve, median nerve, and forearm skin, starting at 80–110 ms and peaking at 115–140 ms. Slightly later responses were seen in the left (contralateral) temporal area, with onsets at 90–125 ms and peaks at 125–195 ms.

Table 1 summarizes the estimated CVs obtained by dividing the distance from the stimulated site to the contralateral cortex separately by the onset latency and the peak latency. Whilst this procedure gives lower-bound estimates for the CVs, the obtained values of 6–16 m/s are consistent with conduction in Aδ-afferents.

For mechanical stimulation of the right lower lip, the response over the contralateral central area started at 40 ms

Table 1
Onset/peak latencies and corresponding CVs for electric stimulation conditions[a]

	Distance (cm)	Onset (ms)	CV$_1$ (m/s)	Peak (ms)	CV$_2$ (m/s)
RADIAL	74	80	9.3	115	6.4
MEDIAN	93	100	9.3	125	7.4
FOREARM	79	85	9.3	115	6.9
TIBIAL	176	110	16.0	140	12.6

[a]RADIAL, radial nerve; MEDIAN, median nerve; FOREARM, forearm dorsal skin; TIBIAL, tibial nerve; distance, distance from the stimulated site to the contralateral cortex; CV$_1$, CV based on onset latency; CV$_2$, CV based on peak latency.
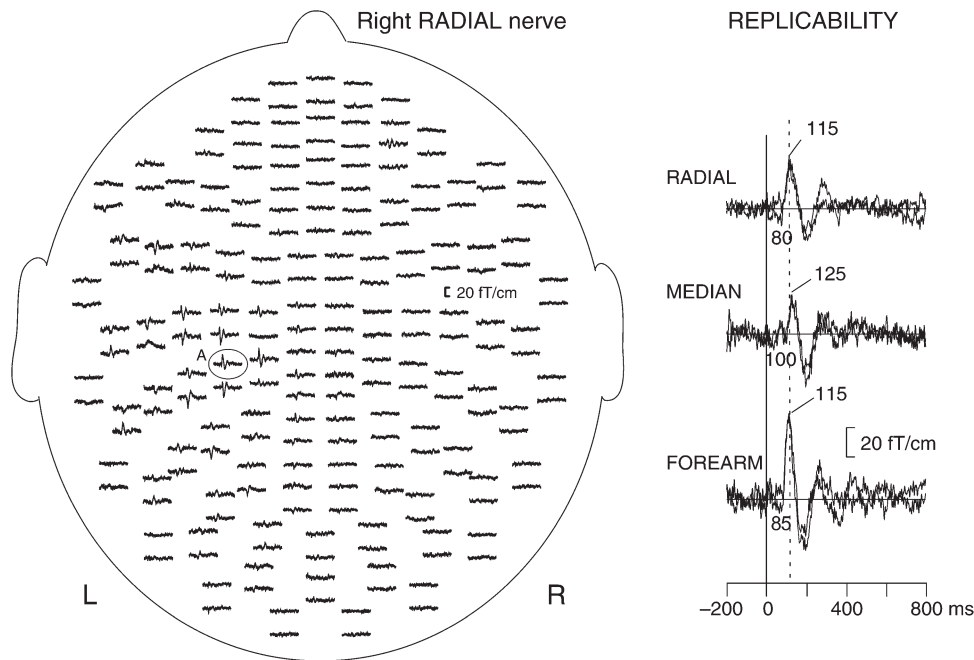
Figure 1. SEFs to electric stimulation. Left: Whole-scalp spatial distribution of the MEG signals, to right radial nerve stimulation, viewed from the top of the head. The pairs of traces represent the longitudinal and latitudinal derivatives of the magnetic field at each sensor location. Right: Replicability of responses to electric radial nerve (RADIAL), median nerve (MEDIAN), and forearm skin (FOREARM) stimulations. Latencies are indicated for the response onset (time of rise of the main deflection) and the response peak (maximum amplitude of the main deflection).

and peaked around 60 ms, and another response over the temporal area started at 125 ms and peaked at about 215 ms.

LEFs to right-hand stimulation were observed over the contralateral temporal region, with onset at about 155 ms and peak at 215 ms. A later, more variable, deflection in temporal areas peaked at about 740 ms, consistent with normally functioning C-fiber afferents (Forss et al. 2005). Responses to laser stimulation on the left hand were poorly reproducible.

Figure 2 illustrates the source locations and orientations for SEFs and LEFs, superimposed on I.W.'s MRI, as well as the corresponding source waveforms. The sources for electrically evoked signals were located in SI and SII cortices (see Table 2). In agreement with the signal latencies, the contralateral SI sources peaked to all electric stimuli within 110–140 ms and the contralateral SII sources within 120–180 ms. Both radial nerve and forearm skin stimulations elicited a second source in SI cortex, with peaks at 150 ms.

For LEFs, a contralateral SII source peaked at 215 ms. LEFs were also present in the ipsilateral temporal area, most likely related to ipsilateral SII activation. However, these responses were variable and their sources could not be reliably identified.

Mechanical stimulation of the neurologically intact right lower lip elicited contralateral SI activation, with 2 sources that peaked at about 65 and 90 ms, respectively, and bilateral SII activations with response peaks at 210–220 ms (see Fig. 3). Compared with 2 earlier studies with similar touch stimuli to lip (Jousmäki et al. 2007) and hand (Jousmäki et al. 2007; Hesse et al. 2009) applied to 10 healthy subjects (5 females, mean age 24.7 years, range 20–31 years), I.W.'s responses were delayed by about 20 and 15 ms, respectively.

The first SI sources to electric stimuli were located close to the central sulcus/gyrus (around area 3b), with an unusual orientation along the course of the sulcus when compared with Aβ stimulation–related sources. The source was 1-2 cm deeper within the sulcus for tibial than radial nerve or forearm stimulation. However, no clear cortical somatotopical organization for wrist/forearm versus leg stimulation was observed. Radial nerve and skin forearm stimulation also showed a later SI deflection, oriented perpendicularly to the wall of the central sulcus.

Rolandic sources for right lower-lip mechanical stimulation were located in the postcentral wall of the central sulcus (cytoarchitectonic area 3b), oriented perpendicular to the postcentral wall, and located 4–5 cm lateral to the first SI source in all electric stimulation conditions.

Discussion

We assessed, in a subject with a selective loss of large diameter myelinated afferents, cortical responses to high-intensity electrical and laser stimulation of small-diameter afferents; such input is in control subjects obscured by more rapidly conducting Aβ-input. Evoked MEG responses were observed in SI cortex at latencies consistent with Aδ-afferent conduction to transcutaneous electrical stimulation and in SII cortex to laser stimulation. In addition, subject I.W. was able to localize pin-prick stimuli on hairy skin with about 4 cm accuracy, implying a role for the Aδ- and C-fibers in the localization of nociceptive stimuli.

SI Activation to High-Intensity Electrical Stimuli

SI cortex shows a detailed somatotopical organization, related to its involvement in accurate tactile localization on the body surface (Penfield and Boldrey 1937; Hari et al. 1993; Schnitzler and Ploner 2000; van Westen et al. 2004). The localization capacity of the human nociceptive system might also depend on SI processing (Koltzenburg et al. 1993) although the role of the human SI cortex in pain processing is still highly
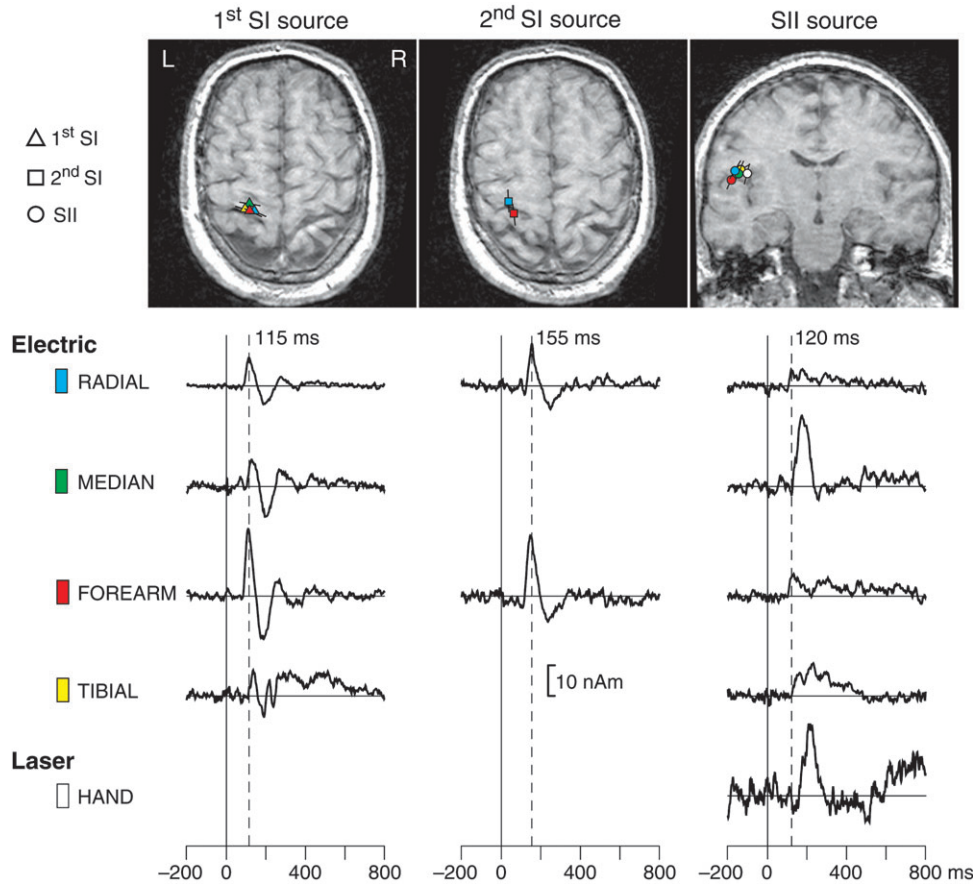
Figure 2. Multidipole models and source waveforms for electrical and laser stimulation conditions. All stimuli were applied on the right body-half. Top: SI and SII sources are superimposed on I.W.'s individual axial and coronal MRIs, respectively. Triangles, squares, and circles represent the first SI, second SI, and SII sources, respectively. Source orientations are indicated by black lines. Bottom: SI and SII source strengths as a function of time derived from the multidipole model.

Table 2
Peak latencies and source strengths for electric, mechanical, and laser stimulation conditions[a]

	Peak latency (ms)				Source strength (nAm)			
	SI_c (1)	SI_c (2)	SII_c	SII_i	SI_c (1)	SI_c (2)	SII_c	SII_i
RADIAL	115	154	120	—	9.3	13.9	5.5	—
MEDIAN	130	—	173	—	8.6	—	23.4	—
FOREARM	110	148	132	—	22.2	19.9	7.3	—
TIBIAL	135	—	160	—	8.5	—	7.7	—
LASER HAND	—	—	216	—	—	—	23.8	—
LIP	64	87	218	212	13.1	17.4	26.4	17.7

Note: (1), first SI_c source; (2), second SI_c source
[a]SI_c, contralateral (left) primary somatosensory cortex; SII_c, contralateral secondary somatosensory cortex; SII_i, ipsilateral secondary somatosensory cortex; RADIAL, radial nerve; MEDIAN, median nerve; FOREARM, forearm dorsal skin; TIBIAL, tibial nerve; LASER HAND, laser stimulation of the right hand; LIP, mechanical stimulation of right lower lip (intact innervation). All stimulations were made on the right body-half.

Figure 3. Four-dipole model and source waveforms for mechanical stimulation of the right lower lip (intact innervation). Left: SI and SII sources are superimposed on I.W.'s individual axial and coronal MRIs, respectively. Source orientations are indicated by black lines. Right: SI and SII source strengths as a function of time.

controversial (see Bushnell et al. 1999; Treede et al. 1999; Peyron et al. 2000; Apkarian et al. 2005; Forss et al. 2005), despite the evidence for nociceptive-specific and wide-range dynamic neurons in the homolog region of the monkey (Kenshalo and Isensee 1983; Kenshalo et al. 1988; Gingold et al. 1991). These discrepancies may result from differences in the applied noxious stimuli and experimental setups (e.g. electric transcutaneous and epidermal, laser, chemical, or contact-heat stimulation), as well as from different measure-
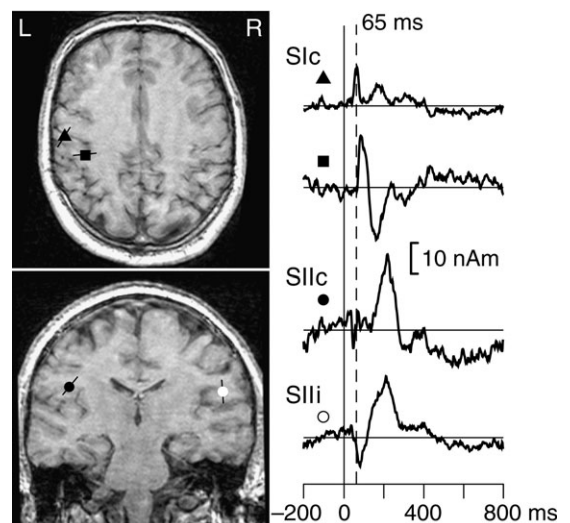
ment techniques. The meta-analysis by Peyron et al. (2000) suggests that the size of stimulated skin area and the total stimulation time are decisive factors for SI activation. Apkarian

et al. (2005) also emphasize that discrepancies in activated brain areas depend on pain modality, varying pain intensities, and individual's cognitive state. Nevertheless, activity in the human SI is reported in approximately 70% of pain studies (functional magnetic resonance imaging [fMRI], MEG, and positron emission tomography), and the authors (Apkarian et al. 2005) conclude that SI pertains to the brain network underlying perception of acute pain.

In healthy subjects, noxious electrical stimulation of skin or peripheral nerves activates both small- and large-diameter afferents, with the cortical responses reflecting an uncertain sum of touch or pain processing (e.g. Kakigi et al. 2000; Valeriani et al. 2000; Wang et al. 2003). In contrast, in I.W. we were able to elicit robust long-latency evoked responses in the contralateral SI cortex without the confound of Aβ-fiber input. Furthermore, the Aδ-mediated SI activations to upper limb stimulation were located 4–5 cm medial to the Aβ-mediated sources elicited by mechanical stimulation of the right lower lip. This result is in line with previous findings on somatotopic organization of nociceptive input (capsaicin or laser heat) to the human SI cortex (Andersson et al. 1997; Apkarian et al. 2005; Nakata et al. 2008).

It seems likely that the cortical responses to limb stimulation were mediated, to a large degree, by nociceptive Aδ-afferents. First, the latencies of the evoked responses were consistent with Aδ-mediated input. Second, cortical responses were only present at high-stimulus intensities, when perceived as sharp and pricky by the subject. Third, previous studies have shown that selective activation of Aδ-afferents subdermally resulted in SI activation with a similar latency as in our study, possibly with involvement of the cytoarchitectonic area 1 (Inui et al. 2002; Inui, Tran, et al. 2003; Inui, Wang, et al. 2003). In contrast, our results suggest involvement of area 3b in processing Aδ-mediated nociceptive information that is elicited by high-intensity electric stimulation. Whether cortical reorganization, following the deafferentation in subject I.W., would underlie the differing result cannot be assessed.

Activation of SI and Posterior Parietal Cortex with Laser Stimuli

Previous studies have shown posterior parietal cortex (PPC) or SI activations to laser stimulation (Peyron et al. 2000; Ploner et al. 2002; Forss et al. 2005; Nakata et al. 2008). Forss et al. (2005) identified and characterized the time course of PPC activation to laser-induced Aδ- and C-fiber inputs. A recent MEG study by Nakata et al. (2008) showed laser Aδ-mediated activation of both PPC and SI to stimulation of the thigh; this stimulation site enabled to disentangle the close-by located SI and PPC areas. On the other hand, Forss et al. (2005) showed, by comparing activations to innocuous electric pulses and to painful laser heat, applied to the hand, that only the PPC, and not SI, was activated by the laser stimuli.

In I.W., we observed laser stimulation–related activation in the SII cortex, whereas SI or PPC was not activated. I.W. has slightly reduced capacity for pain and temperature detection, suggesting some loss of Aδ- and C-fibers in addition to the severe loss of Aβ-fibers. Consistent with the sensitivity of the laser stimulation in detecting thin-fiber dysfunction (Treede et al. 2003), it seems possible that the absence of LEFs in SI and PPC may be influenced by I.W.'s partial loss of Aδ-fibers. However, I.W. had robust SI responses to high-intensity transcutaneous electric

stimulation (presumed to be relayed through Aδ-fibers from their stimulation intensity and propagation velocity), suggesting that the cortical responses to electrical stimuli were less sensitive than the responses to laser stimuli in reflecting I.W.'s slight thin-fiber dysfunction. On the other hand, we cannot rule out the possibility that SI/PPC responses could have appeared to laser stimuli of higher intensity.

Perceptual Localization of Pin-Prick Stimuli

Control subjects localize pin-prick stimuli on the dorsum of the hand with a precision of about 1 cm (Koltzenburg et al. 1993). Such localization capacity is not reduced following a pressure nerve block of myelinated afferents, when only C-fibers are conducting, suggesting that tactile Aβ-afferents are not involved in the localization of painful stimuli (Koltzenburg et al. 1993). The spatial precision of the Aδ and C systems is corroborated by the present observations. Since the procedure involved pointing with the hand, I.W.'s slightly worse performance could have been secondary to problems with motor control due to lack of proprioceptive input. This seems unlikely, however, since in some pointing tasks I.W. is more accurate than control subjects (Poizner H, Cole J, Adamovich S, Fookson O, Berkinblit M, unpublished data). An alternative explanation is that the observed subclinical Aδ- and C-afferents deficit (in innocuous warmth and cold pain perceptions) of I.W. may also include fibers underpinning localization of pin-prick stimulation.

Aδ and CT Systems

Previous studies of I.W. and a similarly deafferented subject G.L. have demonstrated that light tactile stimuli, which activate unmyelinated low-threshold CT afferents, can be detected in forced-choice situations (Olausson et al. 2002; Cole et al. 2006; Olausson, Cole, Rylander, et al. 2008). However, the discriminatory capacity of the unmyelinated touch CT system is poor; in such tests, both I.W. and G.L. had difficulties localizing the body quadrant stimulated (Olausson, Cole, Rylander, et al. 2008). Consistent with this poor discriminatory capacity, selective stimulation of CT afferents led to fMRI activation of somatosensory cortices (SI or SII) as well as activation (positive blood oxygen level–dependent response compared with baseline) in insular cortex (Olausson et al. 2002; Olausson, Cole, Vallbo, et al. 2008). These characteristics of the CT system are thus in sharp contrast to the spatial accuracy and somatosensory projections of the Aδ and C nociceptive systems.

Conclusion

Patients with selective degeneration of large diameter myelinated afferents offer a unique possibility to study cortical processing of afferent messages signaled by nociceptive fibers and localization accuracy of Aδ and C systems. With MEG, we showed clear somatosensory cortical responses to noxious stimulation with latencies consistent with conduction in Aδ-fibers. These results, as well I.W.'s good accuracy in locating noxious pin-prick skin indentation in contrast to his poor ability to locate CT stimulation, support a possible role for the SI cortex in the sensory discriminative aspects of pain perception.

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