Differential Organization of Touch and Pain in Human Primary Somatosensory Cortex

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INTRODUCTION

The primary somatosensory cortex (SI) participates in central processing of both tactile and nociceptive stimuli (for reviews see Kaas 1990; Kenshalo and Willis 1991). However, SI is not a homogeneous area but consists of four cytoarchitectonically distinct fields arranged from rostral to caudal and referred to as areas 3a, 3b, 1, and 2 (Brodmann 1909; Vogt and Vogt 1919). These areas each contain a separate body representation (Kaas et al. 1979) characterized by a distinct connectivity (Burton and Fabri 1995; Fellleman and Van Essen 1991; Jones 1984, 1986), submodality distribution (Iwamura et al. 1993; Kaas et al. 1979; Powell and Mountcastle 1959), and receptive field configuration (Hyvärinen and Poranen 1978; Iwamura et al. 1993; Kaas et al. 1979).

Cutaneous information is predominantly processed in areas 3b and 1 whereas areas 3a and 2 mainly receive information from the deep body tissues (Hyvärinen and Poranen 1978; Iwamura et al. 1993; Powell and Mountcastle 1959). The cutaneous fields areas 3b and 1 are connected with area 2, the posterior parietal cortex, and the secondary somatosensory cortex (Burton and Fabri 1995; Burton et al. 1995; Jones et al. 1978). Anatomic (Burton and Fabri 1995; Fellleman and Van Essen 1991; Jones 1986) and physiologic studies (Garraghty et al. 1990; Hyvärinen and Poranen 1978; Iwamura et al. 1993; Kaas et al. 1979; Pons et al. 1992) indicate a partially hierarchical organization of these areas with area 3b representing the first cortical stage of tactile processing (for review see Iwamura 1998).

By contrast, a recent study in humans demonstrated simultaneous activation of SI and SII to nociceptive stimuli suggesting a parallel activation pattern (Ploner et al. 1999). However, within SI, the organization of nociceptive processing has remained largely unknown. Thus it is unclear whether the complex and hierarchical organization of tactile processing subserving elaborated sensory capacities also applies to human pain processing. We therefore used whole-head magnetoencephalography (MEG) to record cortical responses to tactile and nociceptive stimuli in healthy human subjects. By directly comparing cortical responses to both stimuli in the same subjects we investigated whether nociceptive processing shares the organization of tactile processing within SI.

METHODS

Six healthy male right-handed volunteers with a mean age of 33 yr (range, 28–38 yr) participated in the experiment. All subjects were experienced in pain experiments and gave their informed consent before participation. The study was approved by the local ethics committee.

Stimulation

Tactile and nociceptive afferents of the hands were stimulated by using electrical sensory nerve and cutaneous laser stimulation, respectively. For the nociceptive stimulations data of three subjects from our previous study (Ploner et al. 1999) were included.

In separate runs, ≥40 selective nociceptive cutaneous laser stimuli (Bromm and Treede 1984) were delivered to the dorsum of each hand in the territory of the superficial branch of the radial nerve. Right and
left hand were stimulated in subsequent runs. The laser device was a Tm:YAG-laser (Baasel Lasertech) with a wavelength of 2000 nm, a pulse duration of 1 ms, and a spot diameter of 6 mm. Interstimulus intervals were randomly varied between 10 and 14 s and stimulation site was slightly changed after each stimulus to avoid tissue damage and sensitization and habituation effects. Stimulation intensity was adjusted to twofold pain threshold intensity, i.e., 600–700 mJ pulse energy. In each individual, laser stimuli elicited clearly painful "pinprick-like" but no tactile sensations.

Tactile afferents were stimulated with 0.3 ms constant voltage pulses delivered to the superficial branch of the radial nerve just proximal to the wrist. At least 150 stimuli each were alternately delivered to both sides at random interstimulus intervals between 2 and 3 s. Stimulus intensity was adjusted to twofold detection threshold intensity, i.e., 40–60 V, thus inducing clear and consistent nonpainful sensations. An electrical stimulus was chosen because its duration closely matches that of the laser stimulus. Moreover, electrical stimuli yield highly synchronized volleys and therefore evoke well-defined and well-studied cortical responses with signal-to-noise ratio superior to natural tactile stimuli. In a control experiment, we verified that locations of responses to electrical stimuli match those to natural tactile stimuli: In 3 subjects, 150 natural tactile stimuli were delivered to the dorsum of each hand with a pneumatically driven aluminum cylinder of 2 mm diam and a skin contact duration of 600 ms.

Data acquisition and analysis

Cortical activity was recorded with a Neuromag-122 whole-head neuromagnetometer (Ahonen et al. 1993) in a magnetically shielded room. The helmet-shaped sensor array contains 122 planar SQUID gradiometers which detect the largest signals just above the local cortical current sources. Signals were recorded with a 0.03 Hz high-pass filter and digitally low-pass filtered at 120 Hz. Cortical responses were averaged time-locked to stimulus application. Vertical electrooculogram was used to reject epochs contaminated with blink artifacts. Analysis of evoked responses was focused on an epoch comprising 100 ms prestimulus baseline and 300 ms after stimulation. Sources of responses were modeled as equivalent current dipoles comprising 100 ms prestimulus baseline and 300 ms after stimulation. Sources of responses were modeled as equivalent current dipoles identified during clearly dipolar field patterns. Only sources accounting for more than 85% of the local field variance (goodness of fit) and with 95% confidence limits of source localization <10 mm were accepted. Dipole location, orientation, and strength were calculated within a spherical conductor model of each subject’s head determined from the individual magnetic resonance images (MRI) acquired on a 1.5 T Siemens-Magnetom. Dipoles were introduced into a spatio-temporal source model where locations and orientations were fixed and source strengths were allowed to vary over time to provide the best fit for the recorded data (for further details concerning data acquisition and analysis see Hämäläinen et al. 1993). Resulting source strengths as a function of time were used for latency determination.

Based on fiducial point markers, MRI and MEG coordinate systems were aligned and sources were superposed on the individual MRI scans. In each individual, distances along the three axes of the Talairach coordinate system (Talairach and Tournoux 1988) were calculated between locations of tactile and nociceptive responses. In addition, source locations were calculated in standardized Talairach coordinates.

RESULTS

In all subjects, stimulation of tactile afferents elicited clear and consistent nonpainful sensations. Conversely, nociceptive stimulation evoked at least moderately painful but no tactile sensations.

In all subjects, the well-known early 20-ms and 30-ms responses to tactile stimulation were explained by a single dipole, fitted around 30 ms, in the contralateral postcentral gyrus corresponding to the hand area of SI. In 9 of 12 hemispheres (5 left and 4 right), an additional subsequently peaking source in the contralateral SI hand area located more medially was necessary to explain the recorded signals. These early SI responses were followed by activity originating from the contralateral posterior parietal cortex in three recordings, and in all recordings, from the upper banks of the Sylvian fissures, bilaterally, corresponding to SII. By contrast, nociceptive stimuli nearly simultaneously activated a single source in the contralateral postcentral gyrus (SI) and bilateral sources in the upper banks of the Sylvian fissures (SII). No nociceptive responses were recorded from the posterior parietal cortex. Latencies and mean standardized Talairach coordinates of nociceptive and tactile responses are given in Table 1.

| TABLE 1. Peak latencies and standardized Talairach coordinates of tactile and nociceptive responses |
|-----------------------------------------------|-----------------------------------------------|
| Tactile                                      | Nociceptive                                   |
| **Latencies, ms**                             | **Latencies, ms**                             |
| SI contralateral                             | 31 ± 1*                                       | 171 ± 4 |
| SI contralateral later                        | 64 ± 8                                        |       |
| SII contralateral                             | 105 ± 5                                       | 160 ± 5 |
| SII ipsilateral                              | 116 ± 3                                       | 175 ± 5 |
| **Locations**                                | **Locations**                                 |
| SI                                           | 36, −24, 52*                                  | 26, −30, 59 |
| SII left                                     | −49, −14, 20                                  | −51, −15, 19 |

Values are mean latencies ± SE and mean standardized Talairach coordinates. SI, primary somatosensory cortex; SII, secondary somatosensory cortex; *, tactile 30-ms response. Latencies of contralateral SII responses were significantly shorter than latencies of ipsilateral SII responses to tactile (two-tailed Wilcoxon signed rank test, \( P < 0.005 \)) and nociceptive stimuli (\( P < 0.05 \)). Latencies of contralateral SI and contralateral SII responses to nociceptive stimuli were not statistically different (\( P = 0.06 \)). Because SI responses in both hemispheres were symmetrical, coordinates of SI responses are given for right hemispheric responses only.
DISCUSSION

In this study, we compared cortical responses to tactile and nociceptive stimuli in human somatosensory cortices. Within SI, our results reveal a fundamental difference in the representation of both modalities: Stimulation of tactile afferents activated two sequentially peaking sources within SI, whereas nociceptive stimuli merely evoked a single SI response. Along the postcentral gyrus, this single nociceptive source was significantly more medially located than the early tactile 30-ms response and corresponded spatially to the later peaking tactile source. These results expand previous findings indicating distinct temporal activation patterns of SI and SII in nociceptive and tactile processing (Ploner et al. 1999).

Intra- and extracranial recordings in monkeys (McCarthy et al. 1991) and humans (Allison et al. 1989a; Wood et al. 1985) revealed generation of the early 20-ms and 30-ms components of somatosensory evoked potentials and fields in cytoarchiteconical area 3b. Accordingly, in this study, 30-ms SI responses...
to tactile stimuli most likely arise from area 3b in the rostral bank of the postcentral gyrus. By contrast, the more medial location of both the nociceptive and the later peaking tactile source suggests generation of these responses in cytoarchitectonical area 1. A mean mediolateral location difference to the 30-ms SI sources (coordinate center) corresponds to the hand representations of areas 1 and 3b as revealed by intracranial recordings (Allison et al. 1989a; McCarthy et al. 1991; Wood et al. 1988), and anatomic (Jones et al. 1982), metabolic labeling (Juliano and Whitsel 1985), and functional neuroimaging studies (Burton et al. 1997). In humans, this mediolateral distance between responses attributed to areas 1 and 3b amounts to 10 mm (Allison et al. 1989a; Burton et al. 1997; Wood et al. 1988) and thus agrees well with our findings.

Macrostructurally, in humans, area 1 has been shown to comprise the crown of the postcentral gyrus and the superficial parts of its rostral and caudal banks (Geyer et al. 1997, 1999; White et al. 1997). Consequently, because MEG does not detect radially oriented currents (Hämäläinen et al. 1993), recorded activity might predominantly originate from the fissural parts and less from the convexial parts of area 1. Conversely, a mainly radial orientation of convexial area 1 sources and the predominance of more consistently activated 3b

**FIG. 2.** Comparison of tactile and nociceptive responses in SI, group results. The axes of the diagrams represent the axes of the Talairach coordinate system (Talairach and Tournoux 1988), sizes of shaded circles and areas indicate individual and mean 95% confidence limits of source localization, respectively. A: location of later peaking tactile SI sources (black circles) with respect to tactile 30-ms SI sources (coordinate center). B: location of nociceptive SI sources (black dots) with respect to tactile 30-ms sources. In one recording, no nociceptive SI response could be identified. In both comparisons, the example from Fig. 1 corresponds to the most medially located responses. Inset, mean locations of later tactile peaking SI sources and nociceptive SI sources with respect to tactile 30-ms SI sources. Note that the scaling on the right applies to all diagrams including the insert. ant, anterior; post, posterior; lat, lateral; med, medial; sup, superior; inf, inferior.
sources (Allison et al. 1989a; Wood et al. 1985, 1988) may account for the partial failure to detect area 1 responses in MEG. Furthermore, in previous studies using median nerve stimuli, frequent activation of posterior parietal cortex might have complicated identification of area 1 sources (Forss et al. 1994). However, in the posterior parietal cortex, most somesthetic neurons respond to complex activations of deep receptors related to exploratory movements (for review see Hyvärinen 1982). Consequently, in this study, stimulation of a cutaneous nerve branch supplying the dorsum of the hand might have accounted for less intensive activation of the posterior parietal cortex thus facilitating detection of area 1 sources.

Generation of nociceptive SI responses in cytoarchitectonic area 1 is supported by results from experimental animal studies: Single neuron recordings in monkeys revealed location of most nociceptive SI neurons at the rostral and caudal borders of area 1 (Chudler et al. 1990; Kenshalo and Isensee 1983). In addition, positron emission tomography studies in humans directly comparing locations of SI responses to nociceptive and tactile stimuli (Coghill et al. 1994; Iadarola et al. 1998) showed a corresponding slight but insignificant mediolateral location difference between activation foci. By contrast, using intrinsic optical imaging, a recent study in monkeys showed pain-associated activations in area 3a whereas neuronal activity in areas 1 and 3b was suppressed by painful stimuli (Tommerdahl et al. 1998). However, in this study, temporal dimensions of stimulations and responses were in the range of seconds and thus differ from the brief stimuli and responses recorded in our study which probably reflect distinct neural mechanisms. Furthermore, in this (Tommerdahl et al. 1998) and the aforementioned studies (Coghill et al. 1994; Iadarola et al. 1998), as a result of different stimulus characteristics and recording techniques, responses were most likely mainly mediated by slowly conducting C fibers whereas in the present study exclusively early A-δ fiber mediated responses were analyzed.

Locations of SI activations to nociceptive and tactile stimuli did not differ systematically. However, considering the small extent of SII and the complex folding of cortex buried in the Sylvian fissure, the possibility remains that spatial resolution of MEG might be insufficient to detect a consistent macrostructurally definable location difference.

In tactile processing, anatomic and physiologic investigations have revealed a partially hierarchical organization of somatosensory cortices with area 3b representing the first cortical stage of a processing cascade comprising area 1, the posterior parietal cortex and SII (for review see Iwamura 1998). Our result of sequentially peaking sources in area 3b, area 1, the posterior parietal cortex, and SII is likely to reflect this organizational mode. By contrast, generation of nociceptive SI responses merely in area 1 is in conflict with this processing hierarchy and thus complements previous findings indicating direct thalamic access of nociceptive information to SII (Ploner et al. 1999).

Taken together, nociceptive processing apparently does not share the elaborated and hierarchical organization of tactile processing which probably evolutionarily evolved in parallel with an improvement in sensory capacities. Instead, direct projections from area 1 (Burton et al. 1995; Jones et al. 1978; Stepniewska et al. 1993) and SII to the primary motor cortex (Friedman et al. 1986) and from SII via the insula to the temporal lobe limbic structures (Friedman et al. 1986; Shi and Cassell 1998) would provide an appropriate anatomic substrate for fast and effective integration of nociceptive information into motor and memory processes. Teleologically, this organization appears reasonable as, in pain perception, effective reactions to and future avoidance of harmful stimuli are obviously more important than object identification or manipula-

FIG. 3. Comparison of tactile and nociceptive responses in SII, group results. Location of nociceptive SII sources with respect to tactile SII sources and corresponding confidence limits of source localization. In one recording, no contralateral nociceptive SII response could be identified. For further details, see Fig. 2.
tion, the more so as almost every painful stimulus is coupled with activation of tactile pathways.

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