

Neuromagnetic SII responses do not fully reflect pain scale

Wei-Ta Chen,^{a,b,d,e,g} Rey-Yue Yuan,^a Yang-Hsin Shih,^{b,h} Tzu-Chen Yeh,^{c,h} Daisy L. Hung,^e
Zin-An Wu,^{b,d} Low-Tone Ho,^{c,f,g,h} and Yung-Yang Lin^{b,c,d,e,f,g,*}

^aDepartment of Neurology, Taipei Medical University Hospital, and Department of Neurology, Taipei Medical University School of Medicine, Taipei, Taiwan

^bThe Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan

^cDepartment of Medical Research and Education, Taipei Veterans General Hospital, Taipei, Taiwan

^dDepartment of Neurology, National Yang-Ming University, Taipei, Taiwan

^eInstitute of Neuroscience, National Yang-Ming University, Taipei, Taiwan

^fInstitute of Physiology, National Yang-Ming University, Taipei, Taiwan

^gInstitute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan

^hSchool of Medicine, National Yang-Ming University, Taipei, Taiwan

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To elucidate the role of somatosensory cortices in coding pain magnitude, we recorded the neuromagnetic responses of ten subjects to mild, moderate, and severe pain stimulation by delivering thulium-laser pulses on the dorsum of the left hand. The stimulus intensities for producing different pain levels were determined individually, and the mean values across subjects were 255, 365, and 490 mJ for mild, moderate, and severe pain, respectively. We obtained 40 responses for each intensity condition, and analyzed the averaged cortical signals by multi-dipole modeling. All subjects showed consistent activation over the bilateral secondary somatosensory (SII) cortices for each intensity level, peaking around 150–230 ms, with 15-ms earlier on the contralateral hemisphere. The SII dipole strength was significantly larger for the moderate than for the mild pain stimulation, but lacked further increase as the pain magnitude elevated to the severe level. In contrast, the primary somatosensory cortical response was detected in only half of our subjects, and thus it seemed difficult to evaluate its role in pain intensity coding. Our results suggest that activation strength in human SII cortices reflects the magnitude of peripheral noxious inputs only up to the moderate level, and some other cerebral correlates may get involved in sensing a further increment of pain magnitude.

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Introduction

Pain perception is an essential function for humans, and the awareness of pain magnitude ensures the individual take immediate aversive behavior to avoid harm. Earlier functional imaging and electrophysiological studies on human pain processing have already shown consistent activations around the secondary somatosensory (SII) cortex (see Kakigi et al., 2005; Peyron et al., 2000 for a review). Additional responses from the primary somatosensory (SI) cortex, insula, anterior cingulate, and prefrontal cortices are otherwise inconsistently demonstrated (Kakigi et al., 2005; Peyron et al., 2000). The extent to which these pain-relevant brain responses correlate with pain intensity is not yet settled.

Cutaneous noxious laser pulses activate exclusively A δ and C nociceptive receptors without eliciting responses from A β mechanoreceptors (Bromm and Treede, 1984). The recording of laser-evoked potentials (LEP) has been therefore used as a powerful method to study cortical processing of pain information. Early studies have observed that the late LEP component correlates with subjective pain magnitude and, to a lesser degree, with the stimulus intensity (Bromm et al., 1983; Carmon et al., 1978, 1980; Kakigi et al., 1989). Recent studies were further devoted to the relationship between laser evoked responses and noxious stimulus intensities in isolated cerebral regions. For example, using subdural electrode recordings, Ohara et al. (2004) have shown that LEP over the SI, parasyllvian, and frontal cortices correlate with the intensity of noxious stimuli perceived as mild to moderate pain. Timmermann et al. (2001) demonstrated a significant positive correlation of SI and SII amplitudes with mild pain intensity (rated as less than 20 with a visual analogue scale (VAS) of 0–100), but interestingly a sharp increase in SII activation was already obtained well above pain threshold. However, it is not clear whether somatosensory

* Corresponding author. Department of Medical Research and Education, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Rd., Taipei 112, Taiwan. Fax: +886 2 28713010.

E-mail address: yylin@vghtpe.gov.tw (Y.-Y. Lin).

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cortical responses would increase further as the subject receives even stronger painful stimulation.

In the present study, we investigated how the human brain responses reflected pain magnitude using a wide range of laser stimulus intensities, starting from a mild level and increasing up to a severely painful level. By comparing the cortical activations in varying pain conditions, we evaluated the functional roles of the activated cortices in coding perceived pain magnitude. Based on the differential coding of pain intensity in SI and SII cortices as well as the S-shaped stimulus–response function in bilateral SII in response to low levels of pain stimuli (Timmermann et al., 2001), we hypothesized that the neuronal correlate of perceiving severe pain might not necessarily be reflected by the amplitude of somatosensory cortical activations.

Materials and methods

Ten healthy right-handed volunteers (2 women and 8 men; age 27–39 years, mean 32.1 ± 4.3 years) gave their informed consent and participated in this study. This research adhered to the tenets of the Declaration of Helsinki, and the experimental protocol had a prior acceptance by the institutional review board of Taipei Veterans General Hospital.

Stimulation

Cutaneous nociceptive laser stimuli were produced by a thulium-YAG stimulator (BLM 1000 Tm:YAG®, Baasel Lasertech, Starnberg, Germany). The laser beam was conducted via an optical fiber, which entered the magnetically shielded room through a small hole. An assistant held the hand piece at the end of the optical fiber and applied the stimuli upon the lateral dorsum of the subject's left hand; the distance of the lens (within the hand piece) from the skin was about 1.5 cm. The laser pulse was kept at 1 ms in duration to stimulate a spot skin area of 10 mm². After each stimulus, the hand piece was slightly moved within an area of 3–4 cm in diameter to avoid skin burns and fatigue of primary nociceptive afferents.

Pain rating

Before the recordings, the subject learned how to differentiate the first (stabbing or pinprick like) and second (warm or heat sensation) pain sensations following laser pulse stimulation (Ploner et al., 2002). We started laser pulses at 100 mJ, and increased the intensity at 50-mJ steps. The subject was instructed to rate the perceived intensity of the first stabbing-like pain on the VAS. Pain threshold (PT) was determined as the lowest intensity level (VAS = 1) that elicited clear stabbing or pinprick-like pain. We defined VAS 0 as no pain, and VAS 10 as the worst imaginable pain. To ensure reproducibility, we repeated the pain rating with three randomized stimulus intensities that had been delivered to the subject. For those subjects whose estimation was incongruent with their own earlier reports, the stimulus trials and pain rating were repeated after half an hour.

The lowest strengths of laser pulses for eliciting pain levels at VAS 2–3, VAS 5–6, and VAS 8–9 were determined individually and further applied on each subject to produce mild, moderate and severe pain, respectively.

MEG recordings

During MEG recordings, the subject sat comfortably in a magnetically shielded room with the head supported against the helmet-shaped bottom of a whole-scalp 306-channel neuromagnetometer (Vectorview™, Elekta Neuromag, Helsinki, Finland). The neuromagnetometer comprised 102 identical triple sensor elements, and each sensor element consisted of two orthogonal planar gradiometers and one magnetometer. In this study, data analysis was based on signals of the 204 planar gradiometers.

We determined the exact location of the head with respect to the MEG sensors by measuring magnetic signals produced by currents led to four head indicator coils at known sites on the scalp. The coil locations with respect to anatomical landmarks on the head were then found with a three-dimensional digitizer to allow further alignment of the MEG and magnetic resonance (MR) imaging coordinate systems. The positive *x*, *y*, and *z* axes in the head–coordinate system go towards the right preauricular point, the nasion, and the head vertex, respectively.

Each subject underwent three sessions (mild, moderate and severe pain) of laser pulse stimulation in a random order. For each session, the interstimulus interval varied between 8 and 12 s, and forty responses were averaged. All subjects gave a subjective estimate of the pain magnitude after each session. The signals were recorded with a passband of 0.1–160 Hz, digitized at 500 Hz, and stored on a disk for subsequent analysis. Epochs coinciding with signals exceeding 300 μ V in the simultaneously recorded vertical electro-oculogram were automatically rejected from being averaged.

Source modeling

In this paper, the analysis period of 500 ms included a prestimulus baseline of 100 ms. To identify the sources of the evoked responses, we visually searched those channels with signal deflections clearly exceeding the prestimulus background level and select the time windows for further analysis. Equivalent current dipoles (ECDs) that best described local source currents at the response peaks were found one by one by a least-squares

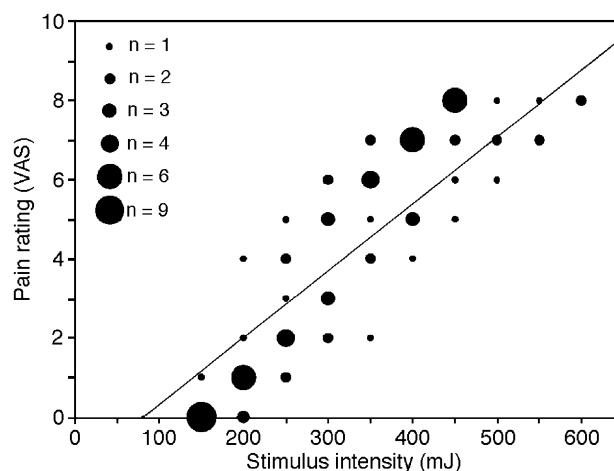
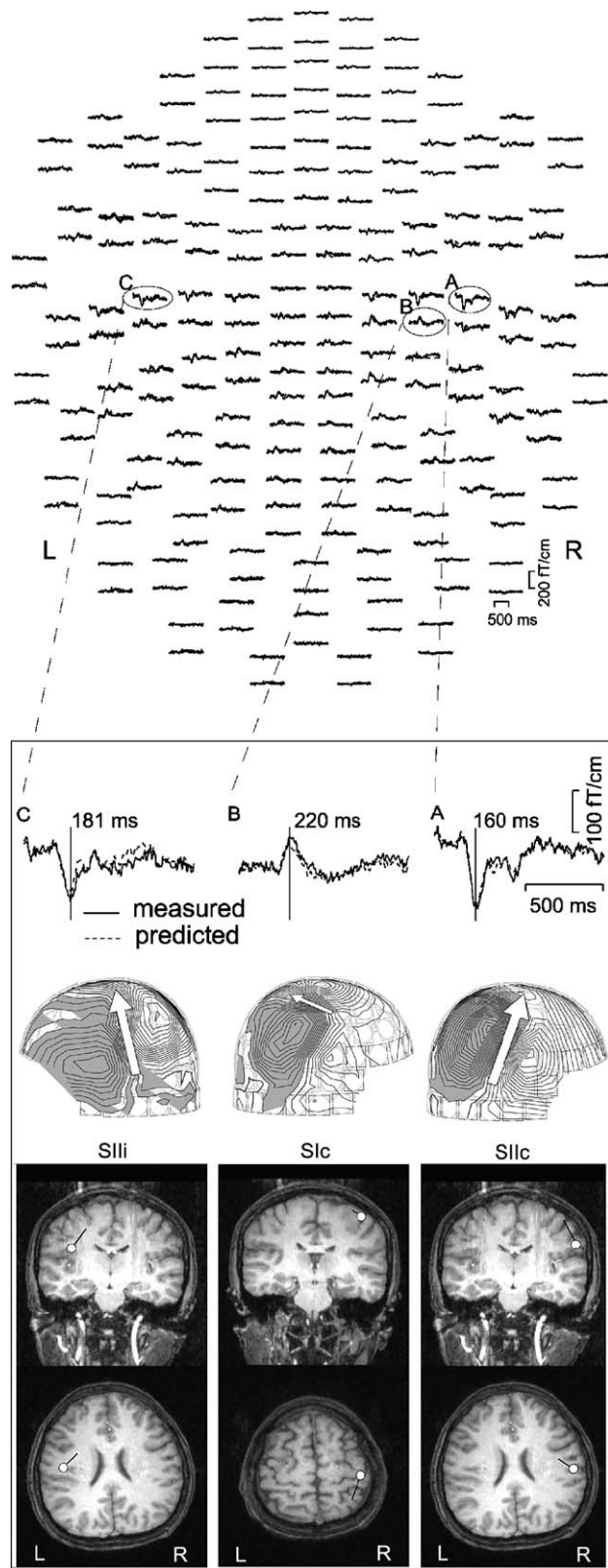


Fig. 1. The linear relationship between the subjective pain rating and the intensity level of painful laser stimulation over the left hand dorsum. The subjects reported 1 on the visual analog scale (VAS) as the pain threshold, and 10 as the worst imaginable pain.

search using a subset of channels (usually 24–30) around the maximal responses. These calculations resulted in the three dimensional location, orientation, and strength of the ECD in a spherical conductor, and then the ECD was coregistered on the



MR images of the subject's own brain, acquired with a 3-T Bruker Medspec300 scanner (Germany). The goodness-of-fit value of the dipole model was also calculated, and only ECDs explaining more than 75% of the field variance at the selected periods of time over the subset of channels were used for further analysis.

We then used a multidipole model to evaluate the validity of the identified single dipoles by comparing the measured responses with the signals predicted by the model. If the signals of some brain region were explained inadequately by the model, we reevaluated the data for a more accurate estimation of the generators. This approach, explained previously in detail (Hämäläinen et al., 1993), has been successfully applied in previous MEG studies of the somatosensory cortical network (Forss et al., 1994, 1999; Lin et al., 2003a,b; Hämäläinen et al., 1993; Hari et al., 1984, 1993; Huttunen et al., 1996).

Statistical analysis

In this study, $P < 0.05$ was taken as the significance threshold. We used Spearman's correlation to test the association between subjective pain magnitudes (VAS scores) and the corresponding pulse intensities (mJ). In terms of ECD latencies and amplitudes in individual stimulus intensities, the paired two-tailed t test was used to assess the differences between contralateral SI and SII activations, as well as the differences between bilateral SII responses.

To see the relative activation between different pain-magnitude conditions, for each subject, we normalized the amplitudes of each ECD across different stimulus intensity levels by setting the maximum amplitude value as 100%. To further evaluate the pain intensity effects, the ECD latencies and relative amplitudes were separately submitted to a one-way analysis of variance (ANOVA) with pain magnitude types (VAS 2–3, VAS 5–6, VAS 8–9) as within-subject factors. Bonferroni test was used for the subsequent post hoc tests.

Results

Correlation between stimulus intensity and pain magnitude

All subjects identified the stabbing-like pain to laser pulse stimulation. No tactile sensation was reported. Fig. 1 shows the linear correlation between the subjective pain magnitude and the applied stimulus intensity ($R^2 = 0.91$, $P < 0.001$). The mean ($\pm$ SEM) PT was 205 ± 9 mJ (range 150–250 mJ). The intensities for producing mild (VAS = 2–3; intensity range 200–300 mJ) and

Fig. 2. The spatial distribution of laser-evoked magnetic responses of Subject 1 to noxious laser pulse stimulation upon the dorsum of the left hand. The 204 recording channels are flattened and viewed from top, with the nose pointing upward. Each response doublet represents signals recorded by the two orthogonal planar gradiometers. The insert shows the enlarged signals (upper panel) from bilateral centroparietal regions, the corresponding magnetic dipole patterns (middle panel), and source locations (white dots) on MR imaging slices (lower panel). The shadowed isocontour area indicates magnetic flux emerging from the head, and each arrow indicates the orientation of the corresponding equivalent current dipole. SIc, contralateral primary somatosensory cortex; SIIc, contralateral secondary somatosensory cortex; SIIi, ipsilateral secondary somatosensory cortex; L, left; R, right.

Source waveforms of somatosensory responses for

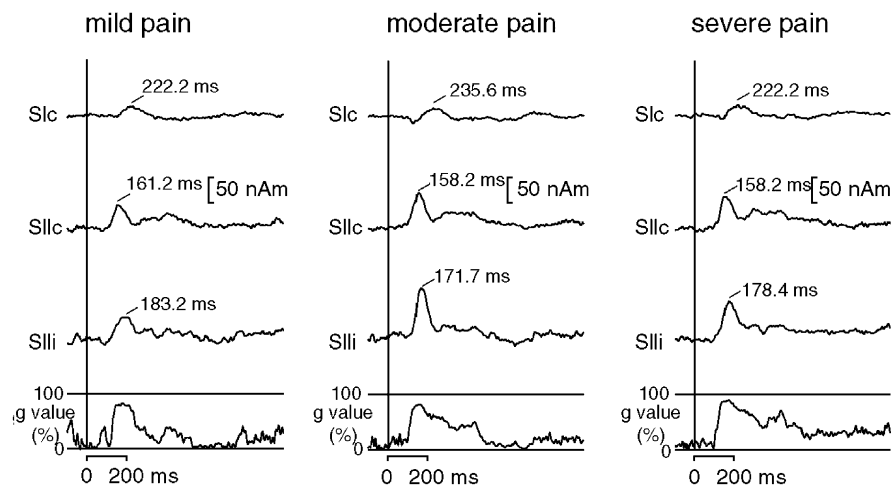


Fig. 3. Amplitudes and waveforms of the neuromagnetic responses in Subject 1 for varying levels of noxious stimuli rated as mild (VAS 2–3), moderate (VAS 5–6) and severe (VAS 8–9). Note the SIic activation is the earliest, followed by SIli and SIc.

moderate pain (VAS 5–6; intensity range 300–450 mJ) were 255 ± 12 mJ and 365 ± 19 mJ, respectively ($P < 0.001$). Pain magnitude was considered severe (VAS = 8) as the stimulus intensity reached 490 ± 20 mJ (range 450–600 mJ) ($P < 0.001$ compared with either mild or moderate pain intensities). Laser stimulation around this intensity range still remains safe (Spiegel et al., 2000). The mild, moderate, and severe pain levels correspond to 1.2 PT, 1.8 ± 0.1 PT, and 2.4 ± 0.1 PT, respectively.

Cortical responses to laser pain stimuli

Fig. 2 shows the laser-evoked neuromagnetic responses of Subject 1 to severe pain stimuli on the left hand. The post-stimulus deflections were seen over the contralateral and ipsilateral temporoparietal regions, and clear magnetic dipole patterns at individual main peaks were identified on the magnetic field maps viewed from the right (for inserts A and B) or the left (for insert C). The predicted signals (dashed lines) by the 3 ECDs closely resembled the measured responses (solid lines), suggesting a satisfactory multi-dipole solution. Superimposed on the subject's own MR images, the anterior–posterior ECD peaking at 220 ms (corresponding to insert B) was located on the contralateral SI cortex. The vertical-oriented ECDs peaking at 160 and 181 ms, corresponding to inserts A and C, respectively, were localized on the upper bank of the Sylvian fissure in both hemispheres, in line with the SII locations in several previous

studies (Forss et al., 2005; Frot et al., 1999; Hari et al., 1983; Kakigi et al., 1995, 2005; Kanda et al., 2000; Ploner et al., 1999; Raji et al., 2003).

Activations in the bilateral insular cortices, medial temporal areas and cingulate cortex were inconsistently found in one or two subjects, mainly in the responses to severe pain. Our multiple-dipole model thus included only the ECDs of the bilateral SII and contralateral SI (SIc) responses for further analysis.

Somatosensory cortical activations with respect to varying stimulus intensities

Fig. 3 shows the dipole waveforms and strengths of the laser-evoked responses to different pain intensities as a function of time in Subject 1. The amplitudes of bilateral SII ECDs were larger for the moderate pain than the mild pain conditions, but lacked a further increase for the severe pain.

Table 1 shows the mean ECD latencies and amplitudes across subjects of SI and SII responses in the three intensity levels. For each subject, we obtained clear SII activations across the three stimulus conditions, peaking around 148–226 ms contralaterally and 162–229 ms ipsilaterally. For the same pain levels, the SII responses basically were bilaterally similar in amplitudes, but the latencies were shorter for the contralateral (SIic) than the ipsilateral SII (SIli) responses ($P < 0.05$). On average across subjects, the

Table 1

The equivalent current dipole parameters [mean (SEM)] of cortical activations to laser pulse stimulations upon left hand dorsum eliciting different intensity levels of perceived pain

Pain intensity	SIli			SIic			SI		
	Latency (ms)	Amplitude (nAm)		Latency (ms)	Amplitude (nAm)		Latency (ms)	Amplitude (nAm)	
Mild (VAS 2–3)	197.1* (5.6)	38.3 (8.9)	(n = 10)	178.5 (7.6)	30.1 (5.9)	(n = 10)	201.6 (7.2)	28.8 (7.8)	(n = 4)
Moderate (VAS 5–6)	186.8* (4.4)	57.1 (12.6)	(n = 10)	172.4 (5.4)	46.0 (5.3)	(n = 10)	199.6 (9.5)	32.6 (8.4)	(n = 4)
Severe (VAS 8–9)	176.5* (3.6)	57.1 (9.7)	(n = 10)	164.3 (4.8)	46.5 (5.4)	(n = 10)	191.0 (7.4)	34.8 (9.9)	(n = 4)

SIli = ipsilateral secondary somatosensory cortex; SIic = contralateral secondary somatosensory cortex; SI = primary somatosensory cortex (contralateral); VAS = visual analogue scale.

* $P < 0.05$ for difference between SIli and SIic.

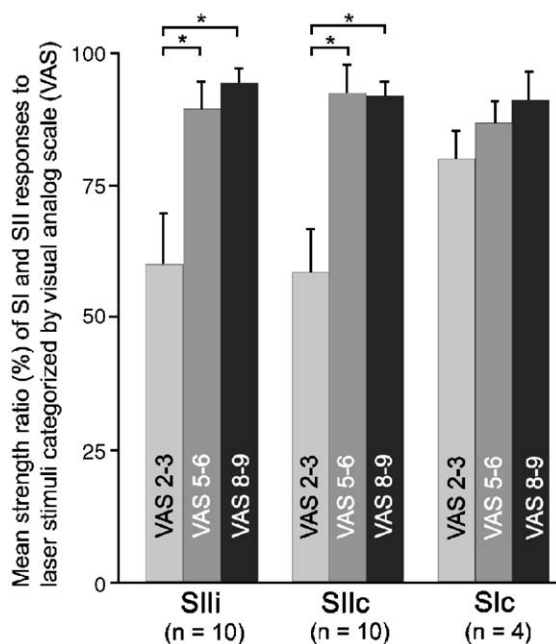


Fig. 4. Mean normalized amplitudes of SIIc, SIIi and SIIc responses to laser pulse stimuli at different pain levels. The SII activations show saturation at the moderate pain scale (VAS 5–6). The number (*n*) in parentheses indicates the number of subjects with corresponding identifiable responses.

inter-hemispheric SII latency differences tended to decrease as the pain intensity increased; 19 ms for the mild, 14 ms for the moderate, and 12 ms for the severe pain. Moreover, the SIIi latency was shorter for the severe than the mild pain condition (176.5 vs. 197.1 ms, $P = 0.005$).

As shown in Table 1, the SI responses across the three pain levels were identified in only four subjects. The number of subjects showing clear activation in the SIIc cortex increased as the reported pain magnitude elevated ($n = 4$ in mild pain, $n = 5$ in moderate pain, $n = 6$ in strong pain). Moreover, the peak latency was slightly longer for SI than SIIc, but the difference was not statistically significant.

Fig. 4 shows the relative ECD amplitudes of laser-evoked SII as well as SI responses with respect to VAS-based pain magnitudes. Both SIIi and SIIc amplitudes increased significantly as the pain intensity increased from a mild to a moderate level. However, a further increase in pain magnitude did not elicit a corresponding enhancement in SII activation.

In the four subjects with SI activation across the three pain levels, the mean ECD amplitude was slightly larger for stronger pain, but the difference was not significant.

Discussion

In this study, we identified SI activation in only about half of our subjects, in contrast to the consistent SI responses reported by Timmermann et al. (2001). The detection yield of the SI signal and its role in pain processing is currently under debate. The neuro-magnetic SI activation has been either indiscernible (Forss et al., 2005; Kakigi et al., 1995) or inconsistently elicited (Kanda et al., 2000). The anatomical variability in the extension of the postcentral gyrus may be one of the reasons for the variable yield of SI activity detection, because its crown region included in the SI

area is actually activated by noxious stimuli (Kanda et al., 2000). A recent meta-analysis also showed that the pain-activated SI responses are found in only half of PET and fMRI studies (Peyron et al., 2000), and the authors considered the intrinsic stimulus size and body sites as important factors for obtaining SI responses. Additionally, the specific nociceptive SI units in primates are relatively scarce in comparison with those responding to non-noxious inputs (Kenshalo and Willis, 1991), and the spinothalamic projections to the hand region of SI may represent less than 25% of all thalamocortical projections to this area (Gingold et al., 1991). The above observations might in part explain the relatively low signal-to-noise ratio or the inconsistency of pain-evoked SI responses.

SI is classically denoted as the major area for pain intensity coding (Kenshalo et al., 2000; Schnitzler and Ploner, 2000; Timmermann et al., 2001). However, because of the low yield of SI activation across our subjects, it seems quite difficult to evaluate its activation strength with respect to pain magnitude. Treede et al. (1999b) suggest that clear SI activation might require sufficient temporal and spatial summation of the pain stimuli, which may partly explain our findings that SI activation was elicited in slightly more subjects as the pain intensity was increased.

The consistent SII activation across subjects in our study was in line with earlier reports (Forss et al., 2005; Hari et al., 1983, 1997; Howland et al., 1995; Huttunen et al., 1986; Kakigi et al., 1995, 2005; Peyron et al., 2000, 2002; Ploner et al., 1999, 2002; Raji et al., 2003; Talbot et al., 1991; Treede et al., 1999a,b). The 12–19 ms longer latency for SIIi than SIIc agreed with earlier intracortical LEP recordings (Frot et al., 1999; Frot and Mauguière, 2003), suggesting a transcallosal connection (Swanson et al., 1978) between bilateral SII areas.

Although the pain-magnitude reported by our subjects linearly correlates with the stimulus intensity (see Fig. 1), we observed a positive correlation between SII amplitude and pain magnitude only up to a moderate pain level; thereupon, the SII activation no longer followed the perceived intensity of the pain (see Fig. 4). One subdural electrode study (Ohara et al., 2004) showed graded LEP responses in the parasyllian area to laser pain stimuli that were rated 1–4 on a 10-point pain scale. Another functional MRI study (Bornhövd et al., 2002) showed positive correlation between perfusion changes in SII/insula and laser pain intensity up to around 1.4 PT, which corresponded to our 1.8 PT for saturating the SII responses. Taken together, the above findings indicate that the SII cortices code pain intensity up to a moderate level.

Using MEG recordings, Timmermann et al. (2001) demonstrated an S-shaped function of SII activation to thulium laser stimuli of four intensity levels: 150, 300, 450 and 600 mJ. The SII activation strength acutely increased at the low stimulus intensity while growing further to a less extent at the “higher intensity”. However, their so-called “higher intensity” stimuli were rated less than 20 on a 100-point VAS pain scale, which seemed too low for a thorough investigation of pain intensity encoding. The strength of the present study was the wide range of perceived pain magnitude; the subjects were reporting VAS 8–9 for the high stimulation intensity. Our results thus further clarified the non-graded SII responses to pain stronger than the moderate degree, which seemed against the discriminative role of this area in perceiving strong noxious stimuli. Note the stimulus intensity range (150–600 mJ) was similar between Timmermann’s study and ours. The relatively low pain rating in the former study may be partly related to the larger stimulation skin area (about 30 mm² in contrast with the 10 mm² in

our present study), which reduces the sharpness of the perceived pain (Pertovaara et al., 1988). For example, as the stimulus intensity was 600 mJ, the average energy density on stimulated skin in Timmermann's study (20 mJ/mm²) was clearly smaller than that (60 mJ/mm²) in our study. Besides, the distance of the stimulator from the skin also affects the energy amount on stimulated site, but we did not know exactly whether this factor differed between both studies.

The larger stimulation area in Timmermann's study, on the other hand, might increase the above-mentioned spatiotemporal summation of pain stimulation and explains the consistent SII activation differing from the present study. Moreover, the longer recording procedures by Timmermann et al. might also cause some habituation to pain awareness and thus affect the subjective estimate on the pain scale. Additionally, the saturation strength of SII activation of our study, ranging 40–60 nAm with VAS value 5–6 (scale 0–10), is already reached with VAS values below 20 (scale 0–100) in Timmermann's study, suggesting that the perception of pain magnitude might be only weakly reflected in SII amplitudes even as pain is in the range of mild to moderate degree.

Coghill et al. (1999) used an electrically heated probe to show a stepwise increase in cerebral blood flow along with an increase in thermal pain intensity up to the grade of 16 on a 20-point numerical pain scale. To the best of our knowledge, this is the only earlier study that delivered painful stimulation with the rated magnitude close to the "severe" pain condition of our study. However, different stimulation tools, indirect measurement of neuronal activation, and limited time resolution inherent to functional neuroimaging might contribute to the discrepant findings between both studies.

It is important to note the broadening evidence of a distributed cortical network for pain intensity processing (Coghill et al., 1999; Price, 2000), although we did not obtain consistent neuromagnetic responses in other pain-related areas such as the insular cortex, anterior cingulate cortex, and posterior parietal cortex. Psychophysical studies of a split-brain patient confirm that both cerebral hemispheres can independently process pain intensity information arising from a unilateral painful stimulus as long as the stimulus intensity is sufficiently high to evoke relevant pathways and dimensions of the experience of pain (Stein et al., 1989). Similarly, subjects who have had one cerebral hemisphere surgically removed have almost no disruption of their capacity to experience and evaluate pain intensity (Knecht et al., 1996). Combining psychophysical and PET studies, Coghill et al. (1999) suggest the involvement of multiple brain areas in processing pain intensity information including the medial and lateral pain systems, and even the bilateral cerebellar regions. Their findings imply that sensory-discriminative processing of pain is not exclusively confined within the somatosensory cortex. This idea may partly explain the preservation of pain awareness after extensive cerebral cortical lesions. Therefore, the cerebral coding for severely intense pain, to which SII activation reaches a plateau, might involve multiple cortical and subcortical regions subserving the cognitive, attentional, and affective aspects of pain (Coghill et al., 1999; Garcia-Larrea et al., 1997; Price, 2000).

Conclusion

The human SII cortex is abundantly activated by moderate noxious stimuli (~2 PT), and its activation size reflects the pain

magnitude only up to the moderate level. The cerebral correlates for sensing further increments of noxious inputs may involve activation in more distributed brain regions that may be not reliably recorded with MEG.

Acknowledgments

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