INTRODUCTION

Touch and pain are intimately related modalities. According to everyday experience, painful stimuli and appropriate behavioral responses are associated with tactile sensations. This close association of both modalities is paralleled by a substantial overlap between the cortical representation of touch and pain. In particular, the primary (S1) and secondary (S2) somatosensory cortices are involved in processing of both modalities as revealed by functional imaging and neurophysiological studies directly comparing cortical activations to both modalities (Apkarian et al. 1994; Bolanowski et al. 2000; Hansson and Ploner, Markus, Bettina Pollok, and Alfons Schnitzler. Pain facilitates tactile processing in human somatosensory cortices. J Neurophysiol 92: 1825–1829, 2004. First published April 28, 2004; 10.1152/jn.00260.2004. Touch and pain are intimately related modalities. Despite a substantial overlap in their cortical representations interactions between both modalities are largely unknown at the cortical level. We therefore used magnetoencephalography and selective nociceptive cutaneous laser stimulation to investigate the effects of brief painful stimuli on cortical processing of touch. Using a conditioning test stimulus paradigm, our results show that painful conditioning stimuli facilitate processing of tactile test stimuli applied 500 ms later. This facilitation applies to cortical responses later than 40 ms originating from primary (S1) and secondary (S2) somatosensory cortices but not to earlier S1 responses. By contrast, tactile conditioning stimuli yield a decrease of early as well as late responses to tactile test stimuli. Control experiments show that pain-induced facilitation of tactile processing is not restricted to the site of the painful conditioning stimulus, whereas auditory conditioning does not yield a comparable facilitation. Apart from a lack of spatial specificity, the facilitating effect of pain closely resembles attentional effects on cortical processing of tactile stimuli. Thus these findings may represent a physiological correlate of an alerting function of pain as a change in the internal state to prepare for processing signals of particular relevance.

METHODS

Subjects

Eight healthy male subjects with a mean age of 31 yr (range, 23–45 yr) participated in the experiment. Informed consent was obtained from all subjects before participation. The study was approved by the local ethics committee and conducted in conformity with the declaration of Helsinki.

Procedure

The modulatory effect of phasic pain on tactile processing was studied using a conditioning test stimulus paradigm. Test stimuli were nonpainful electrical pulses activating the tactile afferents of the superficial branch of the radial nerve of the right hand. Conditioning stimuli were either nonpainful electrical stimuli or slightly painful selective nociceptive cutaneous laser stimuli. Conditioning stimuli preceded the test stimuli by 500 ms and were applied to the superficial branch of the right radial nerve or the dorsum of the right hand, respectively. An interval of 500 ms between conditioning and test stimuli were chosen to disentangle early cortical responses evoked by the conditioning stimuli from that evoked by the test stimuli. Prior to the experiment, the paradigm was explained to the subjects so that the subjects knew that only nonpainful test stimuli would occur, while conditioning stimuli would be either painful or nonpainful. Application of painful and nonpainful conditioning stimuli were blocked with the order of blocks counterbalanced between subjects. In each condition, 120 conditioning test stimulus pairs were applied.

Stimuli

Tactile test and conditioning stimuli were 120 constant voltage electrical pulses of 0.3-ms duration delivered to the superficial branch of the radial nerve of the right hand. Intervals between test stimuli were randomly varied between 4 and 6 s. Stimulus intensity was and pain and intramodal tactile interaction effects. In addition, considering the perceptual differences between tonic and phasic pain (Chen and Treede 1985; Rainville et al. 1992), the cortical effects of tonic painful stimulation most probably differ from those of phasic stimuli. Thus results from studies using tonic painful stimuli (Rossi et al. 1998; Tommerdahl et al. 1996) do not necessarily apply to the effects of phasic pain.

Given the strong association between touch and pain in somatosensory cortices, we therefore used magnetoencephalography and selective nociceptive cutaneous laser stimulation to investigate the effect of phasic painful conditioning stimuli on cortical processing of tactile test stimuli applied to the same skin site. Our results show that phasic pain facilitates tactile processing in S1 and S2, which may represent a physiological correlate of the alerting function of pain.
adjusted to twofold detection threshold intensity, i.e., 40–60 V, thus inducing clear and consistent nonpainful sensations. Characteristics of electrical conditioning and test stimuli were identical. Painful conditioning stimuli were cutaneous laser stimuli, which have been shown to selectively activate nociceptive afferents (Bromm and Treede 1984). Laser stimuli were applied to the dorsum of the right hand in the territory of the superficial branch of the radial nerve. The laser device was a Ti:YAG-laser (Carl Baasel Lasertechnik, Starnberg, Germany) with a wavelength of 2.000 nm, a pulse duration of 1 ms, and a spot diameter of 6 mm. Stimulation site was slightly changed after each stimulus. Stimulus intensity was 100 mJ above individual pain threshold, i.e., 350–400 mJ, thus consistently inducing slightly painful sensations.

**Data recordings**

Subjects were comfortably seated with eyes closed in a magnetically shielded room. Cortical activity was recorded with a Neuromag-122 whole head neuromagnetometer containing 122 planar SQUID gradiometers. Signals were digitized at 483 Hz, high-pass filtered at 1 Hz, and low-pass filtered at 120 Hz. Neuromagnetic activity was averaged time-locked to application of tactile test stimuli. Vertical electrooculograms were used to reject epochs contaminated with blink artifacts.

**Data analysis**

An epoch comparing 100 ms prestimulus baseline and 300 ms after stimulation was analyzed. Global stimulus-evoked neuromagnetic activity was calculated as root mean square of the signals of all 122 sensors corrected to baseline. Further analysis of the somatosensory-evoked fields (SEFs) was based on a spatiotemporal source model (Hämäläinen et al. 1993). Sources of evoked responses were modeled as equivalent current dipoles identified during clearly dipolar field patterns. Only sources accounting for >85% of the local field variance were accepted. Source locations, orientations, and strengths were calculated within a realistic head model (boundary-element model) of each subject’s head determined from the individual magnetic resonance images acquired on a 1.5-T Siemens-Magnetom. Time courses of activations were obtained from the spatiotemporal source model where locations and orientations of sources were kept fixed and activation strengths were allowed to vary over time to provide the best fit for the recorded data. From the resulting time courses of activations, mean amplitudes of activations were determined in an early (15–40 ms) and a late (30–150 ms) time window, and group mean time courses of activations were calculated. Statistical analysis was done with reference to Siegel and Castellan (1988). Friedman’s ANOVA and subsequent post hoc tests were used for comparison of mean amplitudes of activations.

Group mean locations of activations were calculated from covariance matrices across all sensors for the early and the late time window. From these covariance matrices, pain-activated activity was localized using a spatial filtering algorithm (Van Veen et al. 1997). The spatial filter was employed with a realistic head model to estimate power in the whole brain, resulting in individual tomographic power maps with voxel sizes of 6 × 6 × 6 mm. This approach is a time-domain variant of the frequency-based dynamic imaging of coherent sources (DICS) method, which was recently introduced to the investigation of oscillatory activity (Gross et al. 2001). Further processing of tomographic power maps was carried out using SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Individual maps were spatially normalized to Talairach space using parameters derived from normalization of individual T1-weighted MRIs (Friston et al. 1995). Mean group normalized power maps were calculated for both time windows. From these mean power maps, locations of activations, defined as local cortical power maxima exceeding 80% of the global maximum, were determined.

**Control experiments**

In two subjects, the specificity of the interaction effect was investigated. Spatial specificity was investigated by comparing the effects of painful conditioning stimuli applied to the left and right hand, i.e., contralateral and ipsilateral to the test stimulus that was always applied to the right hand. Modality specificity of the pain-induced modulation of tactile processing was verified by comparing the effects of painful conditioning stimuli with the effects of auditory conditioning stimuli. Auditory stimuli were binaural 1,000-Hz square-wave sounds of 10-ms duration. Stimulus characteristics and procedure were the same as in the other conditions.

**Results**

In all subjects, electrical stimulation of tactile afferents elicited clear and consistent nonpainful sensations, while cutaneous laser stimuli consistently evoked slightly painful pin-prick-like sensations.

**SEFs**

Tactile test stimuli evoked the well-known sequence of SEFs, with earliest responses originating from S1 and later responses originating from S1, the posterior parietal cortex and bilateral S2 (Hari and Forss 1999). Exemplary individual and group SEFs are shown in Figs. 1 and 2, respectively. Time courses of global field power (Figs. 1A and 2A) show a sequence of cortical responses peaking at 35, 59, and 127 ms in the single subject and peaking at 37, 71, and 122 ms for the whole group. Figures 1B and 2B show the spatial distribution of cortical responses. The earliest responses beginning at ~15 ms and peaking at ~35 ms originate from anterior parts of the postcentral gyrus corresponding to cytoarchitectonical area 3b of S1. The later response peaking at ~70 ms is recorded more posteriorly and medially than the earliest response and is located in the anterior and posterior walls of the postcentral sulcus corresponding to cytoarchitectonical areas 1 and 2 of S1 and to area 5 of the posterior parietal cortex. Subsequent responses are recorded bilaterally over the temporoparietal region and originate from the parietal operculum corresponding to S2. Mean Talairach coordinates of activations are −36, −32, 54 (early S1), −30, −38, 60 (late S1), −54, −14, 24 (contralateral S2), and 46, −16, 28 (ipsilateral S2).

**Effect of conditioning stimuli**

Individual and group mean time courses of global field power (Figs. 1A and 2A) show that painful conditioning stimuli yield an enhancement of the later responses to tactile test stimuli peaking at ~70 and 120 ms, whereas early responses peaking at ~35 ms remain unchanged. Locations and time courses of activations (Figs. 1B and 2B) show that this enhancement applies to the later S1 activation and the bilateral S2 activations but not to the early S1 activation. In contrast, tactile conditioning stimuli result in an attenuation of early, as well as late, activations of S1 and bilateral S2. Figure 3 summarizes these effects of painful and tactile conditioning stimuli. Friedman’s ANOVA confirms a significant effect of condition on activation amplitudes (P < 0.001). Subsequent post hoc com-
Comparisons of activations show that all later activations are significantly enhanced by painful conditioning stimuli, whereas tactile conditioning stimuli yield a significant decrease of both early and late activations.

Control experiments

Figure 4 compares the effects of painful conditioning stimuli applied to the hand contralateral and ipsilateral to the test stimuli (Fig. 4, top) and the effects of auditory and ipsilateral painful conditioning stimuli (Fig. 4, bottom). Mean time courses of global field power reveal that painful conditioning stimuli applied to the hand contralateral to the test stimulus yield an enhancement of later responses comparable with the effect of ipsilateral painful conditioning stimuli. In contrast, auditory conditioning stimuli do not yield a comparable enhancement. Thus pain-induced facilitation of tactile processing is not spatially specific and does not occur after auditory conditioning stimuli.

DISCUSSION

In this study, we investigated the effects of brief painful stimuli on tactile processing in human somatosensory cortices. Using magnetoencephalography and selective nociceptive cutaneous laser stimulation, our results show that phasic painful stimuli facilitate processing of subsequent electrical stimuli applied to tactile afferents innervating the same skin site. Time courses of activations reveal that this facilitation applies to later cortical responses originating from S1 and S2 but not to earliest S1 responses. Control experiments show that pain-induced facilitation of tactile processing is not restricted to the site of the painful conditioning stimulus and does not occur after auditory conditioning stimuli.

Previous studies investigating interactions of touch and pain focused primarily on the effect of touch on pain. The influential gate control theory (Melzack and Wall 1965) implied that activation of tactile afferents inhibits processing and perception of pain by closing a gate located in the spinal cord dorsal horn. This theory has been extensively studied and has motivated new concepts of pain therapy (Hansson and Lunde-
ANOVA showed a significant effect of conditioning stimuli on mean amplitudes of early (15–40 ms) and late (50–150 ms) activations. Error bars represent SE. Friedman’s ANOVA showed a significant effect of conditioning stimuli on mean amplitudes ($P < 0.001$). $^*P < 0.05, **P < 0.01$ compared with amplitudes of activations without conditioning stimuli.

The reverse effect of pain on touch has been less well studied. At the behavioral level, tonic pain (Apkarian et al. 1994; Bolanowski et al. 2000; Hollins et al. 1996) has been shown to decrease sensitivity to tactile stimuli on the affected limb. Correspondingly, neurophysiological recordings in humans (Rossi et al. 1998) and monkeys (Tommerdahl et al. 1996) showed a pain-evoked decrease of S1 responses to tactile stimulation. However, in these studies the effects of tonic pain were investigated that differ perceptually from that of phasic pain (Chen and Treede 1985; Rainville et al. 1992) and may thus reflect neural mechanisms distinct from the effects of the brief painful stimuli observed in our study. Only a few previous studies investigated the effects of phasic pain on tactile processing. In a recent MEG study, brief painful conditioning stimuli were shown to yield a decrease of S1 responses to tactile test stimuli that already involved very early S1 responses at ~30 ms (Tran et al. 2003). However, in this study, painful conditioning stimuli, as well as nonpainful test stimuli, were electrical stimuli, which activate tactile afferents. Thus intermodal interaction and intramodal stimulus presentation rate effects have most probably been confounded, which may account for the discrepancy between these results and our findings. Another EEG study using selective nociceptive cutaneous laser stimulation did not show a significant effect of pain on cortical processing of tactile test stimuli (Dowman 1999).

However, in this study, which did not provide spatial information on cortical activations, a near significant increase of later components of somatosensory-evoked potentials was observed, which, in principle, corresponds to the present results.

Our finding of an attenuation of both early as well as late responses due to nonpainful conditioning stimuli is in good agreement with previous EEG (Allison 1962; Greenwood and Goff 1987; Shagass and Schwartz 1964) and MEG (Mauguere et al. 1997; Wikström et al. 1996) studies, showing a decrease of the earliest cortical responses with high stimulus presentation rates. This decrease of response amplitudes with high stimulus presentation rates has been proposed to represent an intramodal sensory interaction effect on the level of the somatosensory cortices (Wikström et al. 1996a). The pattern of the pain-evoked modulation of tactile processing observed in this study indicates that this intermodal interaction effect is also located on the cortical level and does not result from interactions on the peripheral, spinal, or subcortical level. Since tactile processing in human somatosensory cortices has a predominantly serial organizational mode (Iwamura 1998), interactions on a level lower than the cortical level should have affected the earliest, as well as later, responses.

The modulatory pattern of pain on tactile processing with a facilitation of later but not the earliest stages of tactile processing closely resembles attentional effects on tactile processing in somatosensory cortices as revealed by EEG (Desmedt and Tomberg 1989; Eimer and Forster 2003; Josiassen et al. 1982; Michie et al. 1987) and MEG (Mima et al. 1998) recordings. These studies showed that focusing attention on a behaviorally relevant tactile stimulus facilitates S1 and S2 responses to tactile stimuli at latencies of 40 ms and later but do not modulate earliest S1 responses with latencies shorter than 40 ms. This attentional facilitation of tactile processing in S1 and S2 has been confirmed by functional imaging studies (Burton et al. 1999; Macaluso et al. 2002; Meyer et al. 1991; Roland 1981) and by neurophysiological studies in monkeys (Hsiao et al. 1993; Hyvarinen et al. 1980; Poranen and Hyvarinen 1982; Steinmetz et al. 2000). However, these attentional effects are spatially specific and are thus likely to reflect the orienting function of attention (Posner and Petersen 1990). In contrast, the control experiments of this study reveal that contralateral painful conditioning stimuli do also facilitate tactile processing, indicating that the present effect is not a spatially specific but a global phenomenon. Moreover, the lack of a comparable facilitation after auditory conditioning stimuli shows that the effect cannot be attributed to the cue function of the painful stimulus. Thus pain-induced facilitation of tactile processing may rather reflect the spatially unspecific alerting function of attention (Corbetta and Shulman 2002; Posner and Petersen 1990), which follows salient stimuli and may be mediated by a right-lateralized fronto-parietal-cingulate network (Corbetta and Shulman 2002; Downar et al. 2002, 2003). This alerting function involves a change in the internal state to prepare for processing signals of high priority (Posner and Petersen 1990), characteristics that particularly apply to the sensation of pain that signals fundamental threat and urges the individual to prevent further harm. Detailed characterization of the facilita-
tion effect in additional, particularly psychophysical, studies will further specify the functional significance of the observed effect.

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