Pain facilitates tactile processing
in human somatosensory cortices

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Abstract

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, the present 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.
Introduction

Touch and pain are intimately related modalities. According to every-day-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 stimuli (Chen et al. 2002; Coghill et al. 1994; Gelnar et al. 1999; Ploner et al. 2000). Although interactions between both modalities have been characterized on the behavioral level (Apkarian et al. 1994; Bolanowski et al. 2000; Hansson and Lundeberg 1999; Hollins et al. 1996; Melzack and Wall 1965), the modulatory effects of pain on cortical processing of touch and vice versa are largely unknown. A few studies showed that pain inhibits tactile processing in S1 (Rossi et al. 1998; Tommerdahl et al. 1996; Tran et al. 2003) whereas another study did not show this inhibitory effect (Dowman 1999). However, in most of these studies non-selective nociceptive and tonic painful stimuli were applied (Rossi et al. 1998; Tommerdahl et al. 1996; Tran et al. 2003) which has possibly resulted in confounding of intermodal interaction effects between touch and pain and intramodal tactile interaction effects. In addition, considering the perceptual differences between tonic and phasic pain (Rainville et al. 1992; Chen and Treede 1985), the cortical effects of tonic painful stimulation most probably differ from these 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.

Materials and Methods

Subjects

Eight healthy male subjects with a mean age of 31 years (range, 23-45 years) 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. An interval of 500 ms between conditioning and test stimuli were chosen in order 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 seconds. Stimulus intensity was 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 Tm:YAG-laser (Carl Baasel Lasertechnik, Starnberg, Germany) with a wavelength of 2000 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
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Vertical electrooculograms were used to reject epochs contaminated with blink artifacts.

Data analysis

An epoch comprising 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 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 more than 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 (50-150 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 analysis of variance 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-evoked 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 x 6 x 6 mm. This approach is a time-domain variant of the frequency-based 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, http://www.fil.ion.ucl.ac.uk/spm). Individual maps were spatially normalized to Talairach space using parameters derived from normalization of individual T1-weighted magnetic resonance images (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 which 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 1000 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 pinprick-like sensations.

_Somatosensory evoked fields_

Tactile test stimuli evoked the well-known sequence of somatosensory evoked fields (SEF) 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 SEF are shown in Figures 1 and 2, respectively. Time courses of global field power (Fig 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 about 15 ms and peaking at about 35 ms originate from anterior parts of the postcentral gyrus corresponding to cytoarchitectonical area 3b of S1. The later response peaking at about 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 (Fig 1A and 2A) show that painful conditioning stimuli yield an enhancement of the later responses to tactile test stimuli peaking at about 70 and 120 ms whereas early responses peaking at about 35 ms remain unchanged. Locations and time courses of activations (Fig. 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. Fig 3 summarizes these effects of painful and tactile conditioning stimuli. Friedman’s analysis of variance confirms a significant effect of condition on activation amplitudes (p < 0.001). Subsequent post-hoc 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**

Fig. 4 compares the effects of painful conditioning stimuli applied to the hand contralateral and ipsilateral to the test stimuli (upper panel) and the effects of auditory and ipsilateral painful conditioning stimuli (lower panel). 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 to 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 the present study, we investigated the effects of brief painful stimuli on tactile processing in human somatosensory cortices. By using magnetoencephalography and selective nociceptive cutaneous laser stimulation our results demonstrate 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 predominantly 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 Lundeberg 1999). 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 which differ perceptually from that of phasic pain (Rainville et al. 1992; Chen and Treede 1985) and may thus reflect neural mechanisms distinct from the effects of the brief painful stimuli observed in our study. Only few previous studies investigated the effects of phasic pain on tactile processing. In a recent MEG study, brief painful
conditioning stimuli have been shown to yield a decrease of S1 responses to tactile test stimuli which already involved very early S1 responses at about 30 ms (Tran et al. 2003). However, in this study painful conditioning stimuli as well as nonpainful test stimuli were electrical stimuli which both 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 (Wikström et al. 1996; Mauguiere et al. 1997) studies showing a decrease already 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. 1996). The pattern of the pain-evoked modulation of tactile processing observed in the present 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 the present 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 can not 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 (Posner and Petersen 1990; Corbetta and Shulman 2002) which follows salient stimuli and may be mediated by a right-lateralized fronto-parietal-cingulate network (Downar et al. 2002; Downar et al. 2003; Corbetta and Shulman 2002). This alerting function involves a change in the internal state in order to prepare for processing signals of high priority (Posner and Petersen 1990), characteristics which particularly apply to the sensation of pain which signals fundamental threat and urges the individual to prevent further harm. Detailed
characterization of the facilitation effect in additional, particularly psychophysical, studies will further specify the functional significance of the observed effect.
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References


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**Figure legends**

Fig. 1. Effect of conditioning stimuli on cortical responses to tactile test stimuli, exemplary individual results. *A*, Time courses of global field power defined as root mean square of the signals of all 122 sensors corrected to baseline. The left panel shows the helmet-shaped sensor array viewed from the top. *B*, Signals of single sensors. Locations of sensors are marked by shaded squares in the left panels showing the sensor array from the top, left and right.

Fig. 2. Effect of conditioning stimuli on cortical responses to tactile test stimuli, group results. *A*, Time courses of global field power defined as root mean square of the signals of all 122 sensors corrected to baseline. *B*, Locations and time courses of activations. Locations of activations are maxima of mean normalized power maps superposed on a normalized surface rendered structural T1 weighted magnetic resonance image. In the time course panels shaded areas depict phases of early (15-40 ms) and late (50-150 ms) responses during which mean amplitudes of activations were calculated. S1, primary somatosensory cortex; S2, secondary somatosensory cortex; cl, contralateral; il, ipsilateral.

Fig. 3. Effect of conditioning stimuli on mean amplitudes of early (15-40 ms) and late (50-150 ms) activations. Error bars represent SEM. Friedman's analysis of variance showed a significant effect of conditioning stimuli on mean amplitudes (p < 0.001). *, p < 0.05, **, p < 0.01 compared to amplitudes of activations without conditioning stimuli.

Fig. 4. Effects of contralateral and ipsilateral conditioning stimuli (upper panel) and of auditory conditioning stimuli (lower panel) on cortical responses to tactile test stimuli.
Mean time courses of global field power defined as root mean square of the signals of all 122 sensors corrected to baseline averaged for two subjects. cl, contralateral; il, ipsilateral.
Figure 1
Figure 2
Figure 3
Figure 4