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Pain Suppresses Spontaneous Brain Rhythms

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The neuronal activity of the resting human brain is dominated by spontaneous oscillatory activity of primary visual, somatosensory and motor areas. These spontaneous brain rhythms are related to the functional state of a system. A higher amplitude of oscillatory activity is thought to reflect an idling state, whereas a lower amplitude is associated with activation and higher excitability of the specific system. Here, we used magnetoencephalography to investigate the effects of pain on spontaneous brain rhythms. Our results show that a focally applied brief painful stimulus globally suppresses spontaneous oscillations in somatosensory, motor and visual areas. This global suppression contrasts with the regionally specific suppressions of other modalities and shows that pain induces a widespread change in cortical function and excitability. This global change in excitability may reflect the alerting function of pain which opens the gates for processing of and reacting to stimuli of existential relevance.

Keywords: cutaneous laser stimulation, human, magnetoencephalography, nociception, oscillations, pain, somatosensory

Introduction

From the earliest recordings of the human electroencephalogram, spontaneous oscillatory activity at frequencies around 10 Hz (alpha-band) and 20 Hz (beta-band) has been consistently observed over primary visual, somatosensory and motor areas (Berger, 1929; Gastaut, 1952; Hari and Salmelin, 1997; Niedermeyer, 1999). In each of these systems oscillations show a modality-specific reactivity. The occipital alpha-ryhthm is dampened by visual stimuli, whereas alpha- and beta-oscillations over the sensorimotor cortices — termed mu-rhythm — are attenuated by touch and limb movements (Hari and Salmelin, 1997; Pfurtscheller, 1999). This modality specificity is complemented by a spatial specificity with stimulus-induced modulations of oscillations occurring predominantly in the contralateral hemisphere (Hari and Salmelin, 1997; Pfurtscheller, 1999). Spatial distribution and reactivity suggest that oscillatory activity is related to the functional state of a system. A higher amplitude of oscillatory activity is thought to reflect an idling state of a system, whereas a lower amplitude is associated with activation of a system (Hari and Salmelin, 1997; Niedermeyer, 1999; Pfurtscheller, 1999). In addition, suppression of oscillatory activity has been related to a higher degree of excitability in the sense of a thalamocortical gate which can be opened by endogenous or exogenous events (Steriade and Llinas, 1988).

Recently, the effects of pain on spontaneous oscillations have been investigated. Neurophysiological studies revealed that phasic painful stimuli suppress oscillations over the sensorimotor cortex predominantly of the contralateral hemisphere (Mouraux *et al.*, 2003; Ohara *et al.*, 2004; Raij *et al.*, 2004) which, in principle, corresponds to the effect of tactile stimuli. However, pain is a unique experience which disrupts ongoing behavior, demands attention and urges the individual to react (Melzack and Casey, 1968; Eccleston and Crombez, 1999). Thus, pain broadly interferes with sensory, motor and cognitive processes. Correspondingly, pain may not only selectively modulate the function of the sensorimotor system but of cortical systems in general. Therefore, we used the high spatial and temporal resolution of magnetoencephalography to investigate the global effects of pain on spontaneous oscillatory activity.

Materials and Methods

Twelve healthy right-handed male subjects with a mean age of 33 years (range 22–41 years) participated in the study. 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.

Stimulation

Forty painful cutaneous laser stimuli, which evoke a highly synchronized selective activation of nociceptive afferents without concomitant activation of tactile afferents (Bromm and Treede, 1984) were delivered to the dorsum of the right hand. 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. The laser beam was led through an optical fiber from outside into the recording room. Stimulation site was slightly changed after each stimulus. Interstimulus intervals were randomly varied between 10 and 14 s. Applied stimulus intensity was 600 mJ, which evoked moderately painful sensations. The subjects passively perceived the stimuli with closed eyes. In four of the subjects, in an additional recording, the left hand was stimulated using the same parameters as in the right-hand stimulation condition.

Recordings and Analysis

During the recordings the subjects were comfortably seated with closed eyes in a magnetically shielded room. Cortical activity was continuously recorded with a Neuromag-122 whole-head neuromagnetometer. Signals were digitized at 483 Hz.

As a first step, time windows and frequency bands of pain-induced changes of cortical activity were identified. To this end, time frequency representations (TFR) were calculated using a Fourier transform approach (Delorme and Makeig, 2004). For each trial the TFR comprised an epoch from 1500 ms before to 3000 ms after stimulus application. A global grand average TFR was obtained by averaging TFRs across trials, sensors and subjects. This global grand average TFR showed prominent pain-induced suppressions of cortical activity in the alpha- (7–15 Hz) and beta- (15–25 Hz) band in a time window between 500 and 1500 ms after stimulus application. Thus, further analysis focused on these frequency bands and on this time window.

In the next step, locations of pain-induced suppressions of cortical activity were calculated. To this end cross-spectral density matrices of power changes in the time window between 500 and 1500 ms as

compared to a baseline period from −1000 to −10 ms were calculated. From these matrices pain-evoked activity was localized using a spatial filtering algorithm (Van Veen *et al.*, 1997; Gross *et al.*, 2001). The spatial filter was employed with a realistic head model to estimate power in the whole brain, and resulted in individual tomographic power maps with voxel sizes of 6 × 6 × 6 mm. 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 T_1-weighted magnetic resonance images (Friston *et al.*, 1995). Among the five strongest local power maxima individual power maps consistently showed maxima located in the bilateral central region and in the occipital cortex. Mean group normalized power maps were calculated for each of the three regions.

In a third step time courses of pain-induced power changes in the bilateral central region and in the occipital cortex were determined. Using the temporal spectral evolution (TSE) method (Salmelin and Hari, 1994), signals were band-pass filtered from 7 to 15 and from 15 to 25 Hz respectively. Filtered signals were rectified, averaged across trials and across 10 sensors over the bilateral central region and 12 sensors over the occipital cortex. The signals recorded from these sensors showed clear modulation of oscillatory activity. Results did not depend on the number of sensors. From the individual time courses group mean time courses of pain-induced power changes were calculated. For each area and frequency band 95% confidence intervals of power changes were calculated as twice the standard deviation of the 1000 ms prestimulus baseline.

For statistical comparison mean amplitudes of pain-induced power changes during the time window between 500 and 1500 ms were determined for both frequency bands. The lateralization of pain-induced modulations was analyzed by comparing mean amplitudes of right- and left-hemispheric modulations using sequentially Bonferroni-corrected two-tailed Wilcoxon signed-rank tests. Lateralization was visualized by calculating a lateralization ratio (left hemispheric/right hemispheric) of pain-induced modulations to right- and left-sided stimulation.

Control Experiment

In order to compare the effects of pain and touch on cortical activity electrical stimulation of tactile afferents was carried out in 12 healthy right-handed subjects (4 female, 8 male, mean age 32 years, range 24–44 years). Electrical stimuli were applied by using ring electrodes attached to the middle and end phalanx of the index finger of the right hand. Stimuli were rectangular constant voltage pulses of 0.3 ms duration with an interstimulus interval of 3 s. Stimulus intensity was adjusted to 2- to 3-fold detection threshold intensity evoking clear and non-painful sensations. Time courses of tactile-induced power changes in the bilateral central region and in the occipital cortex were determined using the same procedure as for the pain-induced effects. Mean amplitudes of tactile-induced power changes were calculated during a time window between 0 and 1000 ms for both frequency bands. Statistical analysis and visualization was the same as for the painful stimulation condition.

Results

First, time windows and frequency bands of pain-induced modulations of oscillatory activity were determined. Thus, global grand average time frequency representations (TFR) were calculated. Figure 1 shows that the brief painful stimuli suppress cortical oscillatory activity between 500 and 1500 ms after stimulus application. This suppression occurs in the alpha-band (7–15 Hz) and in the beta-band (15–25 Hz). [Note that the early power increase below the alpha-band reflects evoked responses which have been analyzed previously (Ploner *et al.*, 1999, 2000, 2002; Timmermann *et al.*, 2001).]

Second, we determined locations of pain-induced suppressions of cortical oscillations. Using a time-domain variant of the DICS method (Gross *et al.*, 2001) pain-induced power changes

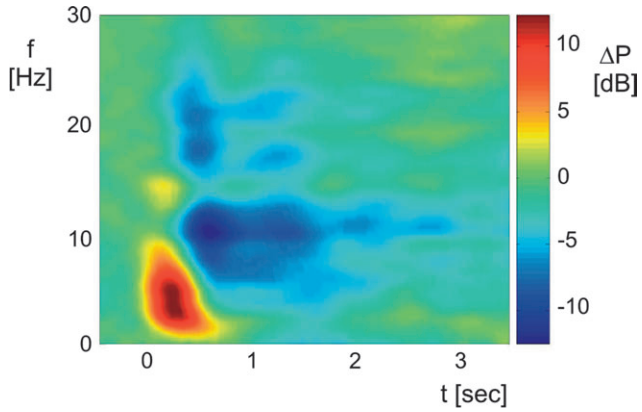

Figure 1. Time frequency representation (TFR) of pain-induced modulations of spontaneous neuronal activity averaged across sensors, trials and subjects. Power increases and decreases (ΔP) from baseline are coded in red and blue, respectively.

were localized in the previously identified time window (500–1500 ms) and frequency bands (alpha, beta) relative to a 1000 ms prestimulus baseline. Figure 2 shows the group mean locations of pain-induced power changes. Foci of suppression of spontaneous oscillatory activity were located in the bilateral sensorimotor cortices and in the occipital cortex. Within the bilateral sensorimotor cortices, suppressions in the alpha-band were located slightly more posterior than suppressions in the beta-band corresponding to location in primary somatosensory and motor cortices respectively. Thus, pain suppresses the sensorimotor mu-rhythm bilaterally as well as the occipital alpha-rhythm.

Third, time courses of pain-induced modulations were calculated for each region and frequency band (Fig. 2). Time courses show that the significant pain-induced suppression of about 2000 ms duration applies to the 10 Hz 'sensory' and 20 Hz 'motor' components of the mu-rhythm bilaterally and to the occipital alpha-rhythm. The suppression of the mu-rhythm is stronger in the right, ipsilateral hemisphere than in the left, contralateral hemisphere. This contrasts with the effect of tactile stimuli applied to the right hand. Tactile stimuli induce a short-lasting suppression of the mu-ryhthm mainly in the left, contralateral hemisphere and no comparable suppression of the occipital alpha-rhythm. Figure 3 illustrates the lateralization of suppressions of the mu-rhythm to painful and tactile stimulation by showing a lateralization ratio (left hemispheric/right hemispheric) of suppressions. The figure illustrates the right hemispheric lateralization of suppressions to right-sided painful stimuli and the left hemispheric lateralization of suppressions to right-sided tactile stimulation. To further clarify the lateralization of the pain-induced modulations we applied painful stimuli to the left hand in four of the subjects. The results show that left-sided painful stimuli also yield a right-lateralized suppression of the mu-rhythm. Thus, these findings show that pain-induced modulations of the mu-rhythm are generally lateralized to the right hemisphere and do not reflect an ipsilateral dominance.

Discussion

The present findings reveal that brief painful stimuli yield a global right-lateralized suppression of spontaneous oscillations in sensory and motor systems.

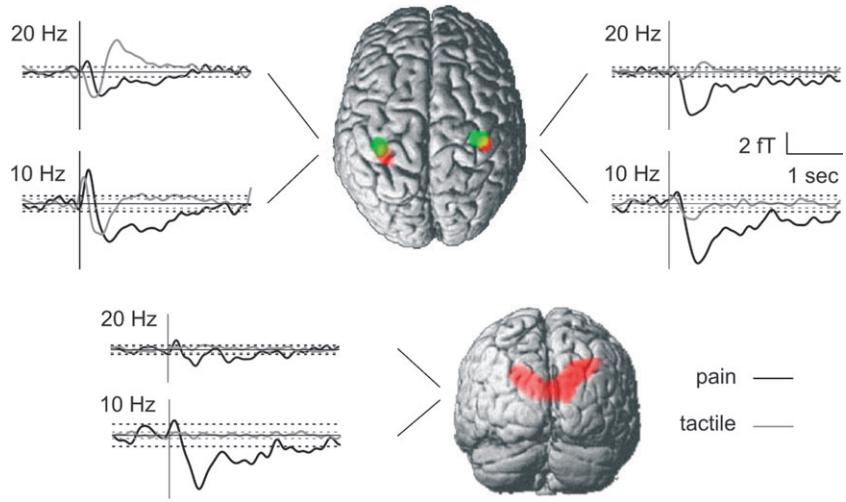

Figure 2. Group mean locations and time courses of pain-induced modulations. Locations of 20 Hz and 10 Hz suppressions are coded in green and red respectively. Time courses of pain-induced modulations (black lines) are compared to tactile-induced modulations (grey lines). The dotted lines show 95% confidence intervals of modulation for each modality, area and frequency band.

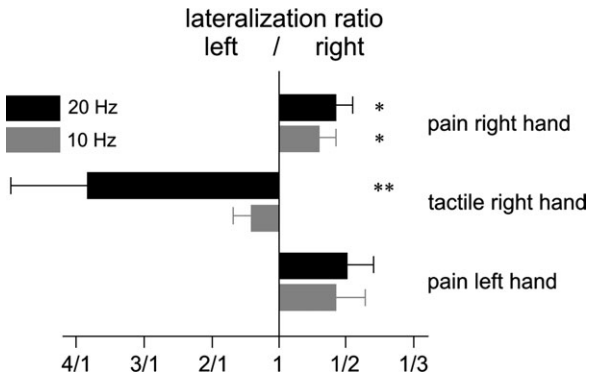

Figure 3. Lateralization ratio (left hemispheric/right hemispheric) of suppressions to painful and tactile stimuli. Note that left- and right-lateralized suppressions of the mu-rhythm correspond to bars to the left and the right side, respectively. Error bars represent SEM; $*P \leq 0.05$, $**P \leq 0.01$, sequentially Bonferroni-corrected, two-tailed Wilcoxon signed rank tests.

Our results correspond with recent neurophysiological studies which showed a pain-induced suppression of the mu-rhythm (Mouraux *et al.*, 2003; Ohara *et al.*, 2004) lateralized to the right, contralateral hemisphere (Raij *et al.*, 2004). However, these studies focused on pain-induced effects on the mu-rhythm and did not investigate global effects of pain on spontaneous brain rhythms. Other studies investigating the effects of tonic pain on spontaneous oscillatory activity also revealed pain-induced decreases in alpha-power and mostly an increase in beta-power (Backonja *et al.*, 1991; Veerasarn and Stohler, 1992; Chen and Rappelsberger, 1994; Ferracuti *et al.*, 1994; Chang *et al.*, 2002). However, the effects of tonic pain most probably comprise complex pain-coping strategies and, thus, reflect neural mechanisms distinct from the modulations induced by the brief painful stimuli of the present study.

Further, our results reveal for the first time that the effects of pain outreach the modality and topographically specific effects exerted by other sensory and motor events (Hari and Salmelin, 1997; Pfurtscheller, 1999). Considering that spontaneous oscillations are related to the functional state and the excitability of cortical areas (Pfurtscheller, 1999) our results demonstrate that pain induces a widespread change in cortical function and excitability. This global pain-induced change in cortical function and excitability may be related to the unique biological significance of pain which disrupts ongoing behaviour, demands attention and urges the individual to react (Melzack and Casey, 1968; Eccleston and Crombez, 1999). More specifically, our finding of a global change in excitability may reflect the alerting function of pain, which may be mediated by a right-lateralized cortico-subcortical network dedicated to the detection of salient events (Downar *et al.*, 2000; Corbetta and Shulman, 2002). The right-sided lateralization of this network together with a preponderance of the right hemisphere in the processing of pain (Hari *et al.*, 1997; Coghill *et al.*, 2001) and negative affect (Davidson, 1995) could well account for the right-hemispheric lateralization of the observed effects. The alerting function of pain along with a global suppression of spontaneous brain rhythms may 'open the gates' of sensory and motor systems and prepare the individual for processing of and reacting to stimuli of existential relevance. This pain-induced gating of sensory and motor information may be related to the recently described phenomenon of pain-induced facilitation of sensory (Ploner *et al.*, 2004) and motor processing (Raij *et al.*, 2004).

Notes

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