Pain Suppresses Spontaneous Brain Rhythms

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-rythm is dampened by visual stimuli, whereas alpha- and beta-oscillations over the sensorimotor cortices — termed mu-rythm — 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 Basel 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 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 x 6 x 6 mm. Further processing of tomographic power
maps was carried out using SPM99 (Wellcome Department of Cognitive
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). Among
the five strongest local power maxima individual power maps consist-
tently 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 (Salmenlin 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
ey 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 suppres-
sions of cortical oscillations. Using a time-domain variant of the
DICS method (Gross et al., 2001) pain-induced power changes
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-rhythm 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 hemi-
spheric) of suppressions. The figure illustrates the right hemi-
spheric lateralization of suppressions to right-sided painful
stimuli and the left hemispheric lateralization of suppressions
to right-sided tactile stimulation. To further clarify the lateral-
ization 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 oscilla-
tions in sensory and motor systems.
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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References
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