Successful behavior requires selection and preferred processing of relevant sensory information. The cortical representation of relevant sensory information has been related to neuronal oscillations in the gamma frequency band. Pain is of invariably high behavioral relevance and, thus, nociceptive stimuli receive preferred processing. Here, by using magnetoencephalography, we show that selective noxious stimuli induce gamma oscillations between 60 and 95 Hz in primary somatosensory cortex. Amplitudes of pain-induced gamma oscillations vary with objective stimulus intensity and subjective pain intensity. However, around pain threshold, perceived stimuli yielded stronger gamma oscillations than unperceived stimuli of equal stimulus intensity. These results show that pain induces gamma oscillations in primary somatosensory cortex that are particularly related to the subjective perception of pain. Our findings support the hypothesis that gamma oscillations are related to the internal representation of behaviorally relevant stimuli that should receive preferred processing.

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Introduction

Within the continuous flow of sensory information, a huge number of events compete for neural representation and perception. This sensory overflow requires the selection and preferential processing of relevant information in order to optimize the utilization of cerebral processing resources. Recently, induced neuronal oscillations in the gamma frequency range (about 40–100 Hz) have been suggested to represent one mechanism of the selection and preferred processing of sensory information [1–7]. These induced gamma oscillations represent event-related modulations of neuronal oscillations, are often observed in early sensory cortices and differ from evoked neuronal responses in a lack of phase locking to the sensory stimulus. Functionally, the association between induced gamma oscillations, and selection and preferred processing of sensory stimuli suggests that these responses may not only be related to the physical stimulus attributes, but also related particularly to the subjectively weighted percept of a sensory event.

Painful stimuli signal threats and are therefore of utmost behavioral relevance [8,9]. Thus, we hypothesized that painful stimuli induce gamma oscillations in somatosensory cortices. Moreover, we speculated that these pain-induced gamma oscillations may not only relate to the objective attributes of painful stimuli, but may also particularly reflect the subjective experience of pain. To address this issue, we used magnetoencephalography to record neural responses to noxious stimuli in healthy human subjects. We investigated the effects of noxious stimuli on neuronal activity in the gamma band and related these effects to objective stimulus intensity and subjectively perceived pain intensity. Our results show that pain induces gamma oscillations in the contralateral primary somatosensory cortex. Amplitudes of pain-induced gamma oscillations increase with objective stimulus intensity and subjective pain intensity. However, around pain threshold, perceived stimuli induce significantly stronger gamma oscillations than unperceived stimuli of equal stimulus intensity. These observations provide direct evidence for a close association between induced gamma oscillations and the conscious and subjective perception of behaviorally relevant sensory events.

Results

First, we aimed to identify and to characterize spatially and temporally pain-induced gamma oscillations in human somatosensory cortices. In 12 healthy male participants, 40 moderately painful cutaneous laser stimuli (intensity 600 mJ) were applied to the dorsum of the right hand. Participants were instructed to passively perceive the stimuli without any further task. The contralateral primary (S1) and bilateral secondary (S2) somatosensory cortices were localized by analyzing the well-known [10] pain-evoked (phase-locked) responses from these areas (Figure 1A). Next, we investigated possible pain-induced gamma oscillations in these areas. To this end, time-frequency representations (TFRs) were calculated for each trial and area. The analysis revealed that pain

Abbreviations: plv, phase-locking value; TFR, time-frequency representation
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induces strong and significant increases in gamma power at frequencies between 60 and 95 Hz in the contralateral S1 cortex (Figure 1B). These pain-induced gamma oscillations were observed between 100 ms and 300 ms after stimulus application coinciding with the pain-evoked response from S1 (Figure 1C). Please note that these pain-induced gamma oscillations were observed without any particular task and, thus, do not depend on the task relevance of painful stimuli, but rather on their sensory quality and their inherent behavioral relevance. No pain-induced changes in gamma power were observed in the bilateral S2 cortices. Analysis of amplitude and phase dynamics confirmed that gamma oscillations were not phase locked to stimuli, and therefore represent induced, but not evoked oscillations (Figure 2).

Second, we investigated the relationship between amplitudes of induced gamma oscillations in S1, stimulus intensity, and perceived pain intensity. To this end, randomly varied intensities of noxious laser stimuli were applied to the right hand of 13 healthy human participants. Possible stimulus intensities were 150, 300, 450, and 600 mJ, which yield sensations ranging from barely detectable to moderately painful. Forty stimuli were presented for each stimulus intensity, and subjects were asked to rate the perception of

Figure 1. Pain-Induced Gamma Oscillations in Somatosensory Cortices
(A) Group mean locations of contralateral primary (S1 cl) and bilateral secondary somatosensory (S2 cl and S2 il) cortices. Locations were obtained from analysis of evoked responses to noxious laser stimuli. Individual tomographic maps of pain-evoked power increases were calculated and averaged across subjects, resulting in a group-mean tomographic map of pain-evoked power increases with dimensionless values (see Methods for details). Talairach coordinates of activations were: −20, −37, and 57 (S1 cl), −45, −15, and 22 (S2 cl), and 50, −16, and 19 (S2 il). The additional colored voxels were not consistently found in single participants and have not been included in further analysis.
(B) Group-mean TFRs for each of the three areas. The TFRs show power as a function of time and frequency. Power is coded as z-score calculated from a 1,000-ms baseline period. Significance of activations was determined by using permutation statistics; areas below the 95% confidence level are masked by transparent gray shading. Significant oscillations following noxious stimuli (stimulus onset at 0 ms) are evident in contralateral S1 in the highgamma range at a latency of about 200 ms. Please note that the different frequency peaks do not represent harmonics, but result from interindividual variability in frequency of gamma oscillations. No significant oscillations can be seen for bilateral S2 at any time.
(C) Group-mean amplitudes of induced gamma oscillations (60–95 Hz, black lines) and evoked activity (gray lines) from contralateral S1 and bilateral S2. The left and right axes and labels correspond to evoked activity and induced gamma oscillations, respectively. Evoked activity is given in source strength and induced gamma oscillations are given in z-scores. Evoked activity and induced gamma oscillations in S1 show the same peak latency (evoked: 190 ± 10 ms; induced gamma: 192 ± 15 ms; mean ± the standard error of the mean [s.e.m]; p > 0.8, two-tailed Wilcoxon signed-rank test).

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Pain-Induced Gamma Oscillations

Author Summary

Pain is a highly subjective sensation of inherent behavioral importance and is therefore expected to receive enhanced processing in relevant brain regions. We show that painful stimuli induce high-frequency oscillations in the electrical activity of the human primary somatosensory cortex. Amplitudes of these pain-induced gamma oscillations were more closely related to the subjective perception of pain than to the objective stimulus attributes. They correlated with participants’ ratings of pain and were stronger for laser stimuli that caused pain, compared with the same stimuli when no pain was perceived. These findings indicate that gamma oscillations may represent an important mechanism for processing behaviorally relevant sensory information.
Pain-Induced Gamma Oscillations

Third, we aimed at further defining the relationship between pain-induced gamma oscillations in S1 and the subjective experience of pain. Low intensity (150 and 300 mJ) trials around pain threshold were chosen for the analysis. Per definition, some of these trials are perceived as painless, and evoked responses and induced gamma oscillations to stimuli of different intensities were analyzed. Mean amplitudes of evoked responses and induced gamma oscillations from S1 were calculated during the time window from 100 ms to 300 ms as compared to baseline amplitudes. Figure 3 shows amplitudes of evoked (phase-locked) responses and induced (non-phase-locked) gamma oscillations as a function of stimulus intensity. The results reveal that amplitudes of induced gamma oscillations and amplitudes of evoked responses from S1 increase with stimulus intensity. This increase in response amplitudes was paralleled by an increase in perceived pain intensity. These observations show that amplitudes of pain-induced gamma oscillations in S1 vary with objective stimulus intensity and subjective pain intensity.

Discussion

Our study demonstrates that painful stimuli induce gamma oscillations in the contralateral S1 cortex. These non-phase-locked gamma oscillations differ from evoked responses in a trial-by-trial jitter in latency, and occur at latencies around 200 ms and at frequencies between 60 and 95 Hz. Amplitudes of pain-induced gamma oscillations increase with both objective stimulus intensity and subjective pain intensity. However, around pain threshold, differences in the subjective perception of objectively similar stimuli were related to differences in amplitudes of induced gamma oscillations. These results show that pain-induced gamma oscillations in S1 are particularly related to the subjective perception of pain.

Here, latencies of pain-induced gamma oscillations between 100 ms and 300 ms indicate that these responses are mediated by A-delta-fibers relating to first pain sensation. Later sensations of warmth or second pain mediated by slowly conducting C-fibers occur at latencies of about 1,000 ms [11], and are unlikely to relate to cortical responses at latencies around 200 ms. Correspondingly, in the present study, “percept” and “no percept” refer to the presence and absence of A-delta-fiber–mediated first pain sensation. Moreover, our findings provide evidence for first pain–related gamma oscillations in S1, but do not preclude gamma oscillations from outside the somatosensory cortices, which were beyond the scope of our analysis.

Induced gamma oscillations have been demonstrated in tasks that require activation and further processing of object...
Figure 4. Amplitudes of Induced Gamma Oscillations and Evoked Responses to Differently Perceived Stimuli of Equal Stimulus Intensity (A) Trials rated with zero (“no percept,” black bars) were compared to trials with higher ratings (“percept,” gray bars) but the same stimulus intensity. Amplitudes of responses were calculated as relative power changes as compared to baseline. Mean rating of “percept” trials was seven, the mean number of trials per subject was 16. “Percept” and “no percept” trials were equally distributed across the recording session (ratio of the number of “percept” and “no percept” trials compared across quarters of the recording session; $p = 0.14$; Friedman’s analysis of variance). Mean amplitudes of gamma oscillations in S1 at 100–300 ms were significantly stronger for “percept” trials as compared to “no percept” trials. Amplitudes of evoked responses from S1 did not differ between conditions. The asterisk (*) indicates $p < 0.05$. (B) TFR of the difference between “percept” and “no percept” trials. Power is coded as relative power change as compared to baseline. The figure represents a subtraction of the “percept” and “no-percept” TFRs, and demonstrates “percept”-specific enhanced gamma oscillations at a maximum latency of about 200 ms. (C) Group-mean amplitude differences between “percept” and “no percept” trials. The black line shows amplitudes of induced gamma oscillations as relative power changes as compared to baseline, and the gray line shows amplitudes of evoked responses calculated as source strengths from S1. The dotted line represents the 95% confidence interval calculated from baseline. Gamma amplitudes are significantly different between “percept” and “no percept” trials, whereas amplitudes of evoked responses did not differ between trial sets.

Materials and Methods

Recordings for experiment 1. Twelve healthy male participants (mean age: 33 y, range 22–41 y) participated in the experiment. All participants gave informed consent, and the study was performed...
according to the Declaration of Helsinki with the local ethics committee’s approval.

Subjects were comfortably seated in a reclining chair. Forty nociceptive cutaneous laser stimuli were delivered to the dorsum of the right hand, and subjects were instructed to passively perceive the stimuli with closed eyes [36]. Stimulation was cutaneous laser stimuli that selectively stimulated small-diameter (nociceptive afferents with a realistic head model to estimate power in the whole brain, resulting in individual tomographic power maps with covariance matrices, neural activity during both intervals was thresholded at 0.8 of the individual personal coordinates, p = 0.15; y-coordinates, p = 0.10; z-coordinates, p = 0.84; two-tailed Wilcoxon signed-rank tests).

Third, for optimized locations of S1 and S2, time courses of activity were computed for all single trials, using the adaptive spatial filter [38,39]. Note that time courses of all activations were analyzed in source space. These time courses were subjected to a time-frequency analysis based on multi-tapers [41] using the fieldtrip toolbox (F. C. Donders Centre for Cognitive Neuroimaging: http://www.ru.nl/fcdonders/fieldtrip). A multi-taper–based analysis was chosen since this approach provides a robust and optimal way to smooth spectra in the frequency domain, and thereby enhances higher frequency oscillatory components with large-frequency jitter-like induced gamma oscillations. The analysis yields TFRs showing power as a function of time and frequency. TFRs were computed from 30 to 100 Hz in 400-ms-long windows with a spacing of 20 ms between windows. A 400-ms time window was chosen to allow a multi-taper frequency smoothing of ± 5 Hz. For each frequency, relative change to a 1,000-ms baseline was computed. Power was coded as z-scores calculated from the 1,000-ms baseline. Significance of differences between poststimulus and prestimulus activity in TFRs was determined by applying permutation statistics. To this end, the 12 prestimulus baseline (−1,000 to 0 ms) and the 1,000 ms (0 to 1,000 ms) parts of the TFRs of the 12 different subjects were randomly permuted 5,000 times. Each time, the maximum difference was computed across time and frequency. The 95th percentile of all 5,000 maximum differences was taken as threshold for the TFRs. This maximum statistics takes multiple comparisons into account [42].

Fourth, in order to distinguish between phase-locked (evoked) and non–phase-locked (induced) neural responses, phase locking of stimulus-related neural activity was determined. For each cortical area, single trial time courses were bandpass filtered (forward and reverse with a fourth-order Butterworth filter) in the gamma frequency band (60–95 Hz) defined from TFRs. The Hilbert transformation yielded instantaneous phase and amplitude estimates for each single trial with an optimum temporal resolution. Phase-locking value (plv, bounded between zero and one) was computed as the absolute value of the mean of complex phase Φ across N trials.

\[
PLV = \frac{1}{N} \sum_{i=1}^{N} \Phi_i
\]  

(1)

Evoked components show a consistent phase relationship to stimuli that is evident in a high plv. Amplitude and phase dynamics were calculated with reference to a 1,000-ms prestimulus baseline. To establish a confidence level for stimulus-induced phase locking, the time course for each region of interest was randomly permuted 5,000 times and then subjected to the same phase-locking analysis (i.e., filtering, Hilbert transformation, averaging, and baseline correction). The maximum value was used as the confidence level.

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Author contributions. AS and MP conceived and designed the experiments. LT and MP performed the experiments. JG and MP analyzed the data. JG contributed reagents/materials/analysis tools. All authors contributed to writing the paper.

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