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FUNCTIONAL ROLE OF INDUCED GAMMA OSCILLATORY RESPONSES IN PROCESSING NOXIOUS AND INNOCUOUS SENSORY EVENTS IN HUMANS

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Abstract

Gamma time–frequency responses (TFRs) induced by painful laser in the contralateral primary somatosensory (SI) cortex have been shown to correlate with perceived pain-intensity in human. Given the functional roles of gamma TFRs in the cortical spaces, it remains unclear whether such a relationship is sustained for other brain regions where the laser-evoked potentials (LEPs) are presented. In this study, we delivered the painful laser pluses at random pain-intensity levels (i.e. strong, medium and weak) in a single train to the dorsal hand of six patients with uncontrolled epilepsy. The laser stimulus produced a painful pinprick sensation by activating nociceptors located in the superficial layers of the skin. For each patient, arrays of >64 subdural electrodes were implanted directly covering the contralateral SI, parasyllian (PS) and medial frontal (MF) cortices to study the stimulus related gamma (TFRs) in the neocortex. In addition, using the same stimulation paradigm, the modality specificity of gamma TFRs was further examined by applying innocuous vibrotactile stimuli to the same regions of the dorsal hand in a separated group of five patients. Our results showed that gamma TFRs are not modality specific, but the largest gamma TFRs were consistently found within the SI region and noxious laser elicited significantly stronger gamma TFRs than innocuous nonpainful vibratory stimuli. Furthermore, stronger pain induced stronger gamma TFRs in the cortices of SI ($r = 0.4$, $p < 0.001$) and PS ($r = 0.29$, $p = 0.005$). Given that potentially harmful noxious stimulus would automatically capture greater attention than the innocuous ones, our results support the hypothesis that the degree of SI and PS gamma TFRs is associated with an attentional drive provoked by painful stimuli.

Keywords

gamma oscillation; attention; somatosensory; local field potential (LFP); electrocorticographic (ECoG)

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INTRODUCTION

Over multiple brain regions in humans, stimulus-induced oscillatory responses in the gamma (>40 Hz) band have been associated with the internal top-down and bottom-up dynamical mechanisms of selective attention, associative learning, valence integration and visual perception in the cerebral processing (Tallon-Baudry and Bertrand, 1999; Oya et al., 2002; Debener et al., 2003; Fries, 2005; Tallon-Baudry et al., 2005). More recently, the induced frequency responses in the gamma band over the human primary somatosensory cortex (SI) are found to be enhanced by attention and vary with perceived pain-intensity (Gross et al., 2007; Hauck et al., 2007; Tiemann et al., 2010; Schulz et al., 2012). However, multiple brain regions are involved in the pain processing (e.g. SI, parasyllvian (PS) and medial frontal (MF)), and thus it remains unclear whether this relationship is still sustained for other brain regions where painful laser-evoked potentials (LEPs) are observed (Vogt et al., 1996; Rainville et al., 1997; Coghill et al., 1999; Ploner et al., 1999; Peyron et al., 2000; Frot et al., 2001, 2008; Ohara et al., 2004b, 2006; Apkarian et al., 2005). For instance, the MF region (e.g. anterior cingulate cortex (ACC)) has been shown to be an important structure in pain processing, having a central role for encoding the affective component of sensory events and responding selectively to painful thermal and mechanical stimuli (Talbot et al., 1991; Rainville et al., 1997; Hutchison et al., 1999; Price, 2000; Vogt, 2005; Liu et al., 2011a, b). Therefore, it is likely that the MF region exhibits similar pain-intensity-related responses in the gamma frequency band as those found in the SI region.

Studying the cerebral oscillatory mechanisms of pain processing can help to better understand the role of different brain regions in pain. Evidences from earlier electrophysiological studies have suggested that nociceptive processing in the brain is in the orders of milliseconds (Frot et al., 2001; Ohara et al., 2004a,b; Ohara et al., 2006; Kobayashi et al., 2009; Weiss et al., 2009; Liu et al., 2011a). Therefore, to obtain the pain-related neuronal responses with high temporal and spatial resolutions, the electrocorticographic (ECoG) approach was used to obtain local field potentials (LFPs) directly from the surfaces of the SI, PS and MF areas in the brain to test the hypothesis that the pain-induced gamma band oscillatory responses can be found not only in the SI but also can be found in the PS and MF areas, where laser-evoked potentials are recorded (Lenz et al., 1998; Ohara et al., 2004a,b; Liu et al., 2011a). In addition, we further examined the specificity of the observed gamma band oscillatory responses by comparing the oscillatory activities induced by innocuous vibratory stimuli. The vibratory stimuli can activate distinct group of peripheral sensory receptors under the skin, and therefore can serve as a nonpainful control stimulus in this study.

EXPERIMENTAL PROCEDURES

Subjects and electrode implantation

Ten patients with medically uncontrollable epilepsy (five male and five female, age 15–52 yr at the time of study) were recruited for the present study (Table 1). Part of the dataset (Subjects 1, 3 and 5) in this study was previously reported in separate studies (Ohara et al., 2004a,b). All patients in this study had epileptic seizures whose foci could not be agreeably localized by noninvasive scalp electroencephalography (EEG) approach. Subdural grid and

strip electrodes ($n > 64$) were surgically implanted over frontal, temporal and parietal regions to aid the seizure localization under a clinical protocol. Implantation sites were chosen solely for clinical purposes. Neuropsychological assessment of the patients before the surgery confirmed normal cognitive functioning. All patients gave written informed consent prior to the studies and the study protocol was reviewed and is approved annually by the Institutional Review Board at the Johns Hopkins University School of Medicine.

The positions of electrodes were determined by intraoperative observations and photographs, and preoperative radiological studies including superimposition of 3D postoperative computed tomography (CT) on 3D preoperative 1.5T MRI. When imaging data were available (i.e. preoperative MRI and postoperative CT), the Freesurfer software (<http://freesurfer.net/>) was used to yield a 3D brain surface and localize the electrode positions for visualization purposes (Dale et al., 1999). In brief, the 3D brain surface was firstly reconstructed using preoperative MRI and using spatial information (i.e. Cartesian coordinates (x, y, z)) of the electrode positions provided by postoperative CT images, the electrodes were marked with different colors by regions and superimposed onto the reconstructed 3D brain surface.

LFP recordings

Multi-channel ECoG recordings were obtained by implanting arrays of subdural grid or strip electrodes directly on the surface of the brain. These electrodes were made of platinum and embedded in medical-grade silastic, 3 mm in diameter with 2.3 mm of exposed surface, spaced 10 mm apart in a rectangular array (Ohara et al., 2004a). In order to prevent shifting of electrodes, portions of the edges of the silastic sheet were fixed to the dura. The total number of implanted electrodes was >64 in each patient. Signals were amplified and band-pass filtered 0.1–300 Hz (laser stimulation) or 30–300 Hz, notch 120 Hz (vibrotactile stimulation) and digitally recorded with sampling rates of 1000 Hz, 1400 Hz or 2500 Hz. All recordings were recorded with a reference montage using one single electrode chosen for its relative inactivity and distance from the estimated epileptic focus. Prior to analysis, all signals were re-referenced to a common average reference after removal of channels with artifact (Crone et al., 1998; Liu et al., 2010).

Common average reference approach

In the current study, ECoG recordings were acquired using a referential montage such that each electrode was referenced to a single subdural electrode that was selected for its relative inactivity. We did not use an extra-cranial reference (i.e. ear lobe) in order to avoid contamination by muscle and/or skin potentials. However, the proximity of the subdural reference electrode to the recording array made it necessary to transform the ECoG recordings to reference-free signals prior to subsequent signal processing analyses (Lehmann, 1987; Pfurtscheller, 1992; Crone et al., 2001). Otherwise, the referential montage used for recording would produce spectral power maps that arbitrarily depend upon the location of the reference and are contaminated by activity at the reference, resulting in topographic artifacts with low spatial frequency. To convert the reference-dependent raw data into reference-free data, different methods are available including the use of common average reference, bipolar and transverse approaches (Lehmann, 1987). We chose to use the

common average reference as the best compromise between competing concerns regarding the spatial representation of ECoG power spectra. This derivation was calculated at each time sample of the ECoG signal by summing the potentials from all artifact-free channels and dividing by the number of these channels, then subtracting the result from the potential in each channel. Based on our experiences, this common average reference approach can reduce common noise in the recordings while preserving reasonable distinctions among electrode sites. Such effects were clearly indicated by the presence of different patterns of LEPs and event-related (de)synchronization ERS/ERD among adjacent electrode sites (Crone et al., 1998; Ohara et al., 2004b, 2006).

Laser/vibrotactile stimulators and paradigms

For the laser stimulation paradigm, randomly varied intensities of noxious laser stimuli were applied to the dorsal hand of six patients. Laser stimuli were generated by a Tm-YAG laser system. The laser system produces an infrared beam with wavelength 2000 nm and 1 ms in duration for every laser pulse, and covers a 6-mm diameter circular area (Neurotest, Wavelight, Starnberg, Germany). Laser stimulations were transmitted through an optic fiber and delivered to the dorsum of the left/right hand area. The laser stimulation was meant to produce a painful pinprick sensation by activating the nociceptors located in the superficial layers of the skin (Carmon et al., 1976). In a separate session prior to the study the laser output energy was adjusted in an increasing manner to obtain laser energy levels corresponding to pain-intensities of weak, mild and strong for each patient (Table 2). About 3–5 laser pulses at each energy level were delivered during this session. For the study, a total of 60 laser pulses were delivered with randomized energy outputs, 20 for each energy level (weak, mild, strong). Two to three runs of stimulations were performed with an inter-run interval of 1–2 min. At the end of each run, patients were asked to rate the pain-intensity elicited by the laser using a 0–10 scale where 0 was defined as “no painful pricking sensation” and 10 was “the maximum painful pricking sensation that she/he can imagine”. To ensure the subjects were able to rate each stimuli independently and reliably, the stimulation were delivered at random locations within a dorsal hand area and the inter-stimulus-interval ranged from 6 to 8 s at random. The timing of the laser stimulations protocol were programed using an in-house developed software (SG3) using Java computer language running in the Windows 2000R environment (Oracle Corporation, Redwood City, California, USA).

For the vibrotactile stimulation paradigm, the stimuli were generated using a computer-controlled Chubbuck mechanical, cutaneous, stimulator applied to the palmar surface of the distal phalanx of the index finger, contralateral to the implanted grid electrodes (Table 2). The nonpainful vibratory stimulus used in this study was meant to produce a nonpainful touching sensation by eliciting activities in A-beta mechanoreceptive fibers (Johnson et al., 1973). The tip of the stimulator probe was round (diameter of 3 mm) and was placed on the skin with a force of approximately 50–100 g. The slow (20 Hz) and fast (120 Hz) vibrations with duration of 100 ms and with amplitude of 100 μ m were superimposed on this baseline force (Ohara et al., 2004b). For each run, approximately 200 vibratory stimuli were applied to the index finger with an inter stimulus interval of 3 s. At least two runs were performed.

Electrode classification

The electrodes were classified into four brain regions, namely the SI cortex, PS, MF and sham regions. The group of these four brain regions included both early and late sensory related cortices (SI, PS, MF) and a control region (Control, i.e. non-sensory region). The classifications were mainly done by taking into account the following two factors: (1) 3D imaging co-registration from Freesurfer (Dale et al., 1999), Statistical Parametric Mapping (SPM2; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, United Kingdom: <http://www.fil.ion.ucl.ac.uk/spm>) and (2) positive event-related potentials (ERPs) (Ohara et al., 2004a,b). For each patient, electrode sites without the measureable ERPs and located away from SI, PS, MF regions were partly selected as the control sites for statistical comparisons. The measureable ERP refers to the peak amplitude is above the 95% percentile of the baseline level. For signals recorded under different laser intensities and vibrotactile frequencies, the somatosensory-evoked potentials (i.e. LEPs and vSEPs) were processed separately by averaging the LFPs extracted for each electrode site after artifact removal.

Analysis of time–frequency response

To study time–frequency responses (TFRs), time–frequency analysis was performed on the epochs ranging from -1.024 s to 1.024 s centered at the onset of laser or tactile stimulation. We used fast Fourier transform (FFT) to estimate the power envelop of the signal, the minimum and maximum frequencies for FFT time–frequency analysis were set in the range between 4 Hz and 150 Hz which covered the low-theta to high-gamma bands in the LFPs. The width of the FFT window was ~ 256 ms and the analysis was done by advancing this sliding window throughout the entire epoch. The power estimates $A(t, f)$ in the post-stimulus interval were referenced to the pre-stimulus power $preA(f)$ (i.e. relative change to the baseline) and were expressed in decibel (dB) unit:

$$TFR(t, f) = 10 * \log_{10} [A(t, f) / preA(f)] (\text{dB}),$$

The results of TFRs were set to have 150 linear-spaced frequency bins ranging from ~ 5 Hz to ~ 150 Hz and 400 time bins. To capture the relevant TFRs in the signals, the gamma band TFRs were computed summing over the TFR estimates for the intervals of 0–300 and 0–200 ms for laser and vibrotactile modalities.

For each subject, to find the thresholds for determining significant TFRs (i.e. upper threshold) a bootstrap resampling method was performed by randomly resampling the TFRs in the post-stimulus interval along the time and trial dimensions 200 times to construct an empirical distribution across frequency. The 95th percentile of all 200 TFR estimates was taken as the upper threshold for the TFR (Delorme and Makeig, 2004).

Phase-locking value (PLV)

In order to distinguish between phase-locked (evoked) and non–phase-locked (induced) neural responses, phase locking of stimulus-related neural activity was determined by calculating the PLVs (Tallon-Baudry et al., 1996). Signals were bandpass filtered

(Butterworth filter) in the gamma frequency band (70–110 Hz) defined from TFRs. The Hilbert transformation yielded instantaneous phase and amplitude estimates for each filtered signal with an optimum temporal resolution. (PLV, bounded between zero and one) was computed as the absolute value of the mean of complex phase Φ across N trials.

$$PLV = \left| \frac{1}{N} \sum_{i=1}^N \Phi_i \right|,$$

A value of $PLV = 1$ represents the signals among experimental trials are with the same phase, a value of $PLV = 0$ suggests the opposite (i.e. nonuniform phase relationships among trials). To establish the significant thresholds for the PLV, the data for the entire interval of interest were randomly resampled for 2000 times and each time the same PLV calculation was applied (i.e. Butterworth filtering, Hilbert transformation, averaging, and baseline correction). The 99.9 percentile of the resulting 2000 PLV values was used as the threshold for determining significant phase-locking activity in the signal. This maximum statistics takes multiple comparisons into account (Nichols and Holmes, 2002). The PLV analysis was performed for the gamma band range (70–110 Hz) in this study.

Statistical analysis

Mixed-effects linear regression models were used to account for clustering measurements made on each subject and test whether different brain regions, i.e. SI, PS, MF and Sham, and intensities of sensory stimulations were associated with different magnitudes of significant gamma TFRs. The estimates of gamma TFRs were the dependent variable and brain region, pain-intensity and vibratory frequency are the predictors in the model:

$$y_{ij} = \beta_0 + \beta_1 SI_{ij} + \beta_2 PS_{ij} + \beta_3 MF_{ij} + \beta_4 P \text{ or } F y_i + b_0 + \varepsilon_{ij}$$

where y_{ij} is the estimate of gamma TFRs for the i th subject on the j th electrode site. The predictors included brain regions (i.e. SI, PS, and MF); P and F denote the pain intensity (weak, medium and strong) and the vibratory frequency (low (20 Hz) and high (120 Hz)), receptively; ε denotes the random error. The brain region was modeled as the categorical dummy-coded variable with the control region as the reference, the pain intensity and vibratory frequency were treated as a continuous variable in the model. The β_0 , β_1 , β_2 , β_3 and β_4 in the constructed model denote fixed effects estimates and the b_0 denotes the subject random effect. The analyses were conducted separately for laser and vibrotactile stimulus modalities. The significance level was set to $p < 0.05$ and the tests were two-sided. Secondary analyses examined the correlations between the gamma TFRs and pain-intensity using Pearson's correlation test ($p < 0.05$). All the statistical analyses were performed using Minitab15 (Minitab 15.1.1.0, statistical Software, State College, PA USA) and R (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL <http://www.R-project.org>).

RESULT

Laser energy levels and pain intensity

Fig. 1A shows that the laser energy levels are significantly different among laser stimulus groups of weak, medium and strong pain ($p < 0.001$, One-way ANOVA). The averaged laser energy levels are 406.7 ± 39.3 , 573.3 ± 54.7 and 746.7 ± 65.3 mJ for weak, medium and strong pain-intensity groups. In addition, Fig. 1B shows that the laser pain ratings are also significantly different between these stimulus groups ($p < 0.001$, One-way ANOVA).

Electrode classifications

The anatomical brain regions and the selections of the grid/strip electrodes were performed based on both the anatomical landmarks and ECoG approaches described in the ‘Electrode Classification’ section in ‘Material and Methods’. As described, four brain regions were determined, the Fig. 2A shows the 3D re-construction brains marked with the selected electrodes in each of the four brain regions. The electrode sites used for control were most commonly located close to the corners of the implanted grid. Fig. 2B shows the mean LEP for different brain regions and pain-intensities.

The latency ranges of the N2 and P2 LEP components were 145 ± 11 ms and 215 ± 21 ms and were consistent with our earlier studies (Ohara et al., 2004a,b). The amplitudes of the evoked N2 and P2 components were found to be the largest within the SI region. In addition, other than the control group, the amplitudes of the LEPs are positively correlated with the stimulus intensity ($p < 0.05$, Pearson’s test; see also (Ohara et al., 2004a). Fig. 2C demonstrates the mean vSEP obtained for different vibrotactile frequencies and brain regions. The early evoked components of vSEP include a positive peak (P50) at about 45–50 ms and followed by a distinct negative wave (N70) at about 70–100 ms, which are consistent with previous studies of humans (Hamalainen et al., 1990; Ohara et al., 2004b). The numbers of selected electrode in each brain region were summarized in Table 3.

Laser-induced gamma TFRs

The TFR analysis showed significant gamma TFRs shortly after the application of the laser stimulations. For the laser modality, the peak of the gamma TFRs was at around 200–220 ms into the post stimulation interval (Fig. 3A).

Consistent with previous laser studies, the evoked TFRs were also observed in the lower frequency band in all pain-related brain regions (Ohara et al., 2006; Tiemann et al., 2010; Chien et al., 2014). The results from the mixed effects linear models showed that brain region and pain-intensity significantly associated with the gamma TFRs. The gamma TFRs were significantly greater in SI region ($p < 0.01$) while the gamma TFRs in the PS and MF regions were not significantly different from the control. The pain-intensity was significantly associated with the gamma TFRs ($p < 0.001$). Fig. 3B shows the PLV estimates for each brain region for the gamma TFRs. This analysis showed a complete absence of significant phase-locking activities after the stimuli ($p < 0.05$), and thus the observed gamma TFRs were not evoked (i.e. with fixed a response latency) but induced (i.e. jitter in response latency) responses (Tallon-Baudry and Bertrand, 1999).

Vibrotactile-induced gamma TFRs

For the vibrotactile modality, the peak of the gamma TFRs was approximately 50 ms after the vibrotactile stimulation (Fig. 4A).

The overall results from the mixed effects linear models showed that the gamma TFRs were significantly different among brain regions ($p = 0.0086$). Similar to that in the laser stimulus modality the electrode sites within the SI region had the largest gamma TFRs ($p < 0.05$) and no significant difference was found among PS, MF and Sham regions. Consistent with the laser stimulation modality, Fig. 4B demonstrates the lack of phase locking relationship in the gamma frequency band upon receiving the vibrotactile stimulations.

Gamma TFRs and laser intensity

The relationships between laser-induced gamma and pain-intensity were subsequently examined for different brain regions using Pearson's correlation analysis. Fig. 5A shows the 95% confidence intervals (C.I.) of the mean for the estimated gamma TFRs grouped by the brain region (outer group) and pain-intensity (inner group).

The Pearson's correlation analysis showed that the laser-induced gamma TFRs were significantly correlated with the pain-intensity for the SI, PS regions but not for the MF and control regions ($p < 0.001$ and $p < 0.05$, $r = 0.4$ and 0.29 for SI and PS; $p = 0.053$ and $p = 0.062$, MF and control). The significance level was corrected for multiple comparisons by the total number of regions.

Gamma TFRs between noxious and innocuous vibrotactile stimulus modalities

Between stimulus modalities, the noxious laser used in this study elicited significantly stronger degrees of gamma responses in all brain regions than that induced by innocuous nonpainful vibratory stimuli ($p < 0.05$; paired t -test). The induced gamma TFRs produced by higher frequencies of vibrotactile stimulation were compatible to those induced by laser at the weak pain-intensity level.

DISCUSSION

The present study used an invasive ECoG approach to demonstrate a significant correlation of perceived nociceptive stimulus intensity with induced gamma (70–110 Hz) TFRs over the contralateral sensory regions of SI and PS in a group of six patients with uncontrolled epilepsy. In addition, using the same stimulation paradigm, the specificity of these gamma TFRs was further established by applying an innocuous vibrotactile stimulus to the same brain regions in a separated group of five patients (one overlap with painful laser). We found that the gamma band oscillatory TFRs were not modality specific, and in both modalities the largest induced gamma band oscillatory TFRs were consistently found within the SI region. However, the noxious laser elicited significantly stronger gamma band oscillatory TFRs than that induced by innocuous nonpainful vibratory stimuli. In addition, stronger pain-intensity induced stronger gamma band TFRs in the cortices of SI and PS but not in the MF.

Gamma TFRs and Pain-intensity in SI and PS

The correlations between TFRs in the gamma frequency band of SI and PS and pain-intensity observed in this study are in line with earlier laser studies in combination with EEG and Magnetoencephalography (MEG) such that gamma band TFRs in the SI cortex are directly reflecting the perceived pain-intensity in humans (Tiitinen et al., 1993; Gross et al., 2007; Hauck et al., 2007; Schulz et al., 2012; Zhang et al., 2012). Distinct spinothalamocortical pathways have previously been shown to relay the nociceptive information to the sensory cortex, and thus the neuronal responses recorded in the SI region may associate with the activities of the related wide-dynamic-range (WDR) neurons in SI and thalamic sensory neurons (Apkarian and Shi, 1994; Kenshalo et al., 1980, 1988). The cortical SI nociceptive neurons are known to detect small increases in skin temperature imposed by thermal stimulation (Kenshalo et al., 1980, 1988; Kenshalo and Isensee, 1983). The thalamic sensory nucleus (i.e. ventralis posterior (VP) in nonhuman primates or ventralis caudalis (Vc) in humans (see (Hirai and Jones, 1989; Lenz and Dougherty, 1998)) is also known to respond to noxious stimuli (Casey, 1966; Chung et al., 1986; Kenshalo et al., 1980; Kobayashi et al., 2009) and furthermore, the greater firing rates are associated with both stronger noxious heat intensity and higher innocuous vibratory frequency (Lenz et al., 1993; Weiss et al., 2009). Reduced activation in the thalamus is correlated with reduced pain perception (Bantick et al., 2002). In addition, one recent MEG study of brain resting-state shows that the phase of the alpha oscillation in the thalamus couples with cortical gamma amplitude in healthy humans (Roux et al., 2013). Therefore, the stronger TFRs in the gamma band induced by noxious laser in the SI and PS regions may be partly originated from the sensory regions of the thalamus via attention related thalamo-cortical networks (Guillery et al., 1998; Schmid et al., 2012; Harris, 2013; Kim et al., 2015a). Nevertheless, it is important to note that the contribution of SI to specific nociceptive processing, although certain, may be functionally very small, as indicated by the small proportion of direct spinothalamic afferents to SI in primates (Gingold et al., 1991; Dum et al., 2009; Kenshalo et al., 1980). Postcentral lesion in humans has resulted in a dissociation between different aspects of pain perception with a loss of sensory-discriminative capabilities while sparing pain affect (Schnitzler and Ploner, 2000; Duncan and Albanese, 2003). It should be noted that SI is anatomically close to the primary motor cortex (MI) and the current study protocol cannot exclude a possible contribution of MI potentials to SI (Frot et al., 2013).

Gamma TFRs and stimulus modality

The current results were obtained by applying two stimulus modalities separately using the same stimulation paradigm, and hence our results provided that gamma TFRs are not modality specific. Indeed, using visual and auditory stimuli, the neuronal responses in the gamma band frequency have been reported in studies of relevant sensory cortices when performing a wide range of cognitive tasks in both humans and animals (Pantev et al., 1991; Cohen and Maunsell, 2011; Ray and Maunsell, 2011; Steinmann et al., 2014; Kim et al., 2015b). A common finding of these visual stimulus related studies is that gamma oscillations are modulated by stimulus properties more than oscillations at other frequencies. For example, the amplitude of gamma oscillations increases with stimulus contrast and is modulated by stimulus orientation (Friedman-Hill et al., 2000; Frien et al., 2000; Siegel and Konig, 2003; Henrie and Shapley, 2005).

In the current study, significant gamma oscillatory TFRs were found in both stimulus modalities and the magnitudes of the gamma oscillatory TFRs were higher in the noxious painful laser condition and lower in innocuous stimulus condition. Since oscillatory gamma TFRs have an important role in neuronal interaction and synaptic activity, it could provide a mechanism for understanding neuronal processing in both local and global brain networks involved in cognitive tasks. The difference in the gamma oscillatory TFRs between stimulus modalities may be added to the current role of cortical gamma in the nociceptive processing such that gamma TFRs might reflect the attention gained by the stimulus from the related neuron assemblies (Gross et al., 2007; Hauck et al., 2007; Jensen et al., 2007; Zhang et al., 2012).

Little correlation between gamma TFRs and pain-intensity in MF region

The structures within the human MF region have a role in the networks of integrating sensory, executive, attentional, emotional, and motivational upon pain processing in the brain (Davis et al., 1997; Derbyshire et al., 1998; Ploner et al., 2002; Vogt et al., 1996). In the present study, similar gamma oscillatory TFRs were observed over the control and MF regions upon receiving noxious and innocuous stimuli with little correlation with pain-intensity. One possible explanation for this finding may be due to the stimulation paradigm used in this study. Activation of MF region is known to associate with stimulus-driven or bottom-up attention (Carter et al., 2000; Bishop et al., 2004). In the current protocol we delivered the stimulations in a single train to the contralateral dorsal hand area with relatively fixed inter-stimulus intervals, and thus less uncertainty and emotional perturbations were imposed to the patients during the study (Bush et al., 2000; Sawamoto et al., 2000). In contrast, we have been able to observe significant MF activations and interactions between MF and other sensory cortices in our previous acute pain studies (Liu et al., 2011a–c).

Absent Phase-locking responses in the gamma band (70–110 Hz)

LFPs reflect current flow in the extracellular space resulting from synchronous dendritic and somatic activity within a relatively confined space proximal to the recording site (Bressler and Kelso, 2001; Lopes da, 2013). The recorded signals represent the sum of neuronal activity which can be classified into induced (non-phase-locked) and evoked (phase-locked) responses that have short latencies after stimulus onset (Tallon-Baudry et al., 1996). Our PLV analysis separated phase and amplitude components of the LFP, thus permitting independent examinations of the relationship between them. In our recordings, we found no evidence of phase-locking responses and this is consistent with previous studies using nonpainful and painful sensory stimulus in humans (Gross et al., 2007; Tiemann et al., 2010; Jia et al., 2011; Zhang et al., 2012).

In conclusion, we recorded LFPs directly from the surface of the brain in patients with uncontrolled epilepsy, and presented compelling evidence that TFRs in the gamma (70–110 Hz) band directly reflect perceived pain-intensity for the sensory cortices of SI and PS. We discussed the possible origins for observed gamma TFRs in the brain. In addition, by comparing the brain responses to an innocuous stimulus using the same stimulation paradigm we found that these gamma band TFRs were likely not nociceptive specific but

reflecting the attention gain by the stimulus from related neuron assemblies. Lastly, understanding how the brain processes sensory input is critical to the development of appropriate interventions and rehabilitation strategies for individuals with pain-related disabilities.

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Abbreviations

CT	computed tomography
ECoG	electrocorticographic
EEG	electroencephalography
ERPs	event-related potentials
FFT	fast Fourier transform
LEPs	laser-evoked potentials
LFPs	local field potentials
MEG	magnetoencephalography
MF	medial frontal
MI	motor cortex
PS	parasylvian
PLVs	phase-locking values
SI	primary somatosensory
TFRs	time–frequency responses

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Fig. 1. Laser energy, Pain rating and Pain intensity. (A) Correlation between laser energy and pain-intensity. (B) 95% confidence interval of the mean pain rating of each pain-intensity group.

Fig. 2.

3D brain image reconstruction and evoked neuronal responses. (A) 3D reconstructed brain images marked with solid circles in different colors for the selected electrode sites. Red: Primary somatosensory region (SI), Blue: Parasyllvian (PS), Medial frontal (MF) and Black: Sham. (B) Grand average for the laser-evoked potentials (LEPs) obtained under different brain regions and pain-intensities. “*” and “**” denote the evoked laser N2-P2 components. (C) Grand average for the vibrotactile-evoked potentials (vSEPs) obtained in different brain regions with different stimulus frequencies. The evoked P50 vSEP component is denoted by the arrow signs. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 3.

Laser TFRs and gamma phase locking analysis. (A) Grand averaged time–frequency responses (TFRs) plots for different brain regions and pain-intensities. *x*-axis and *y*-axis denote time (–100 to 800 ms) and frequency (0–150 Hz). The color bar on the right denotes the magnitudes of the TFRs (i.e. compared to the baseline) in decibel (dB) unit. The total numbers of selected electrodes are given in the parentheses next to the brain region. (B) Gamma phase locking values (PLVs) for the SI, PS and MF regions. Gamma PLV (black line), gamma amplitude (gray line) and significant threshold (dash line). The *x*-axis denotes time (–100 to 1000 ms) and *y*-axis on the right and left denotes the levels of gamma amplitude and PLV, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 4. Vibrotactile TFRs and gamma phase locking analysis. All conventions are as in the legend for Fig. 3.

Fig. 5. 95% confidence interval (C.I.) for the mean gamma TFRs. (A) Gamma TFRs for laser stimulation modality clustered by brain regions and pain-intensity. W: Weak pain, M: Medium pain and S: Strong pain. (B) Gamma TFRs for vibrotactile stimulation modality clustered by brain regions and stimulation frequency. L: low frequency (20 Hz), H: high frequency (120 Hz).

Table 1

Demographic and characteristics of implanted electrodes and seizure foci

Patient	Age	Sex	Side of implanted grid/strip electrodes
002	52	F	Right and Right inter hemisphere
003	19	M	Right and Right inter hemisphere
006	31	F	Left hemisphere
007	58	M	Left and Left inter hemisphere
010	21	M	Left and Left inter hemisphere
014	15	F	Left and Left inter hemisphere
004	23	F	Right and Right inter hemisphere
013	33	M	Left hemisphere
021	21	F	Left and Left inter hemisphere
022	27	M	Right and Right inter hemisphere

Table 2

Characteristics of task performed

Patient	Side of stimulation	Task	
		Laser energy levels (weak, medium, strong) and [pain-ratings]	Frequency for vibrotactile stimulation
002	Left	(400, 560, 720 mj) [1, 2, 4]	n/a
003	Left	(360, 480, 640 mj) [1, 2, 3]	20 and 120 Hz
006	Right	(400, 600, 800 mj) [1, 3, 4]	n/a
007	Right	(400, 560, 720 mj) [1, 2, 4]	n/a
010	Right	(480, 640, 800 mj) [2, 3, 4]	n/a
014	Right	(400, 600, 800 mj) [1, 3, 4]	n/a
004	Left	n/a	20 and 120 Hz
013	Right	n/a	20 and 120 Hz
021	Right	n/a	20 and 120 Hz
022	Left	n/a	20 and 120 Hz

Table 3

Number of electrode sites

Modality	Patient	Anatomical brain regions					Control	Total (n)
		Primary somatosensory cortex (SI)	Parasylyian (PS)	Medial frontal (MF)				
Laser	002	6	4	4			8	22
	003	9	9	4			8	30
	006	4	–	–			–	4
	*007	5	4	–			4	13
	010	6	8	8			8	30
Vibrotactile	014	4	6	8			11	29
	003	9	9	4			8	30
	*004	6	2	0			2	10
	*013	4	2	0			4	10
	021	6	4	9			8	27
	*022	0	4	0			4	8

* Patients without 3D reconstructed brain images.