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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, parasylvian (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.

Key words: gamma oscillation, attention, somatosensory, local field potential (LFP), electrocorticographic (ECoG).

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, parasylvian (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.,

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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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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.

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

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