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CROSS-FREQUENCY COUPLING IN DEEP BRAIN STRUCTURES UPON PROCESSING THE PAINFUL SENSORY INPUTS

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Abstract—Cross-frequency coupling has been shown to be functionally significant in cortical information processing, potentially serving as a mechanism for integrating functionally relevant regions in the brain. In this study, we evaluate the hypothesis that pain-related gamma oscillatory responses are coupled with low-frequency oscillations in the frontal lobe, amygdala and hippocampus, areas known to have roles in pain processing. We delivered painful laser pulses to random locations on the dorsal hand of five patients with uncontrolled epilepsy requiring depth electrode implantation for seizure monitoring. Two blocks of 40 laser stimulations were delivered to each subject and the pain-intensity was controlled at five in a 0–10 scale by adjusting the energy level of the laser pulses. Local-field-potentials (LFPs) were recorded through bilaterally implanted depth electrode contacts to study the oscillatory responses upon processing the painful laser stimulations. Our results show that painful laser stimulations enhanced low-gamma (LH, 40–70 Hz) and high-gamma (HG, 70–110 Hz) oscillatory responses in the amygdala and hippocampal regions on the right hemisphere and these gamma responses were significantly coupled with the phases of theta (4–7 Hz) and alpha (8–12 Hz) rhythms during pain processing. Given the roles of these deep brain structures in emotion, these findings suggest that the oscillatory responses in these regions may play a role in integrating the affective component of pain, which may contribute to our understanding of the mechanisms underlying the affective information processing in humans.

Key words: pain, gamma, laser, amygdala, hippocampus, cross-frequency coupling.

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Abbreviations: FFT, fast Fourier transform; HG, high-gamma; LFPs, local-field-potentials; LH, low-gamma; SI, somatosensory cortex.

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INTRODUCTION

Oscillatory activity in the gamma (>40 Hz) frequency band has been suggested as an important neuronal mechanism for integrating multiple task relevant structures over local and distant regions in the brain (Tiitinen et al., 1993; Roelfsema et al., 1997; Crone et al., 1998a; Rodriguez et al., 1999; Muller et al., 2000; Oya et al., 2002; Muller and Keil, 2004; Edwards et al., 2005; Canolty et al., 2006), and different physiological mechanisms exhibit distinct low-gamma (LG, 30–70 Hz) and high-gamma (HG, 80–110 Hz) oscillations (Castelo-Branco et al., 1998; Herculano-Houzel et al., 1999; Crone et al., 1998a, 2001; Edwards et al., 2005). More recently, gamma oscillations also have been shown to occur within a narrow phases of the slower frequency bands (e.g. theta (4–7 Hz), alpha (8–12 Hz)), and such organizational coupling behaviors have been shown to play an important role upon performing a wide range of cognitive tasks including spatial learning, memory retention, decision making, and thus serving as a mechanism for integrating functionally relevant neuronal information (Canolty et al., 2006; Tort et al., 2008, 2009; Canolty and Knight, 2010; Lisman and Jensen, 2013).

Over the primary somatosensory cortex (SI), the enhanced gamma oscillatory responses have a functional role for modulating the attentional effects in pain processing and closely reflecting the level of perceived pain-intensity in humans (Gross et al., 2007; Hauck et al., 2007; Tiemann et al., 2010; Schulz et al., 2012). However, given that pain has a strong affective dimension; it remains unknown whether such pain-related gamma band oscillatory activity and its coupling activity can also be found in the brain areas including the frontal lobe, the amygdala and hippocampus that are known to have roles in processing the affective component of pain. In addition, the affective related responses to painful inputs are likely to occur in the orders of milliseconds in the brain and given the difficulty in localizing electrical sources from scalp recordings alone, invasive electrophysiology approach is needed to study the neuronal oscillatory responses from these deep brain structures (Casey, 1999; Casey et al., 2001; Frot et al., 2001; Fries, 2005; Liu et al., 2010, 2011a). Thus, to provide further insights into the functional role for pain-related gamma oscillations in the brain regions outside the sensory territories, high-resolution local-field-potentials (LFPs) were recorded from depth electrode contacts implanted bilaterally in the frontal lobe, amygdala and hippocampal areas upon delivering the painful laser

stimulations (Thulium YAG laser stimulator) to random locations on the dorsal hand areas of patients with uncontrolled epilepsy. Laser pulses were set to produce clear painful pinprick sensations by activating the nociceptors located in the superficial layers of the skin. Two blocks of 40 laser stimulations were delivered to each subject and the pain-intensity was controlled as at five in a 0–10 scale. We aimed to evaluate the hypothesis that the pain-related gamma band oscillatory responses can be recorded, and are coupled with the phases of the low-frequency oscillations in the deep brain structures that have roles in pain processing.

EXPERIMENTAL PROCEDURES

Subjects

Five patients with uncontrolled epilepsy (two males and three females; age: 38.8 ± 6.83 year) were recruited in the present study (Table 1). Four of them were right-handed. Informed consent was obtained and the protocol was reviewed and approved annually by the Institutional Review Board at the Johns Hopkins University, School of Medicine. The electrode placement was solely based on clinical purposes. Neurological examination, including a standard sensory testing protocol (Lenz et al., 1993), disclosed no abnormality in any patient. Patients 001, 003 and 004 in the current report also participated in previous studies (Liu et al., 2010).

Electrode implantation

LFPs were recorded using customized depth electrodes (Ad-Tech Medical Instrument Corporation. Racine, WI, USA) implanted in the frontal lobe, amygdala and hippocampus bilaterally using a stereotactic technique with a Leksell frame (Liu et al., 2010). The electrode in the frontal lobe had 8 contacts and was placed 10 mm anterior and 10 mm lateral to the anterior tip of the lateral ventricle, and with the tip of the electrode around/touching the roof of the orbit, confirmed by radiographs obtained during implantation in the operating room. The contact locations along the frontal electrodes were within Brodmann areas of 9, 10, 12, 46 (Liu et al., 2011a). Each of the amygdala and hippocampus electrodes had six contacts. The distal contacts on the amygdala electrodes were centered 12.5 mm below the target in the amygdala. The target was determined as the center of the amygdala in a pre-surgical MRI coronal image capturing the maximal amygdala area. The hippocampal electrodes were centered 12.5 mm below the lower border of the body of the hippocampus in the first coronal image posterior to the head of the hippocampus (Fig. 1). The distances between contacts within the frontal and amygdala/hippocampus electrodes were 5 and 2.2 mm center to center. The postoperative C.T. merged with preoperative MRI to confirm that the implanted electrode contacts were in the white and gray matter of the frontal lobe and within the structure of the amygdala and hippocampus (OsirX, An open-source image software (Rosset et al., 2004); StealthMerge Software, Medronic, Inc. Minneapolis, MN, USA).

LFP recording

LFPs were amplified (12A5 Astro-Med Grass, Inc., West Warwick, RI, USA), filtered (0.1–300 Hz, 6 dB/oct), and digitized at sampling rates of 1000 Hz or 2500 Hz to avoid aliasing. All recordings were recorded with a reference montage using one single contact chosen for its relative inactivity and distance from the estimated epileptic focus. Prior to analysis, all signals were re-referenced to an average reference of LFP recordings to minimize the influence of the location and activity of the reference electrode (Crone et al., 1998b; Liu et al., 2010). Each time when the laser was triggered, a brief marker signal was sent simultaneously through an optical cable connected to the laser system. This marker signal was recorded using the same clinical LEP recordings system as an independent channel embedded in the data files. In all subjects, ECoG recordings used in this study were free of seizure patterns.

Laser-stimulation/stimulation paradigm

Heat 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. The diameter of the round circle shape stimulated area was ~6 mm (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. Prior to the study, the laser energy was adjusted, in a separate session, in the increasing manner until it produced painful pinprick sensation equal to five in a 0–10 pain-intensity rating scale. About 3–5 laser pulses at each energy level were delivered during this calibration session and the area of stimulation was the same as that following the experimental session.

During the experimental section, two blocks of 40 laser stimulations were delivered to each subject after

Table 1. Demographic and epileptic focus

Patient	Age (years)	Sex	Handedness	Side of stimulation	Epileptic focus
001	48	F	Right	Right	Left hippocampus/amygdala
002	42	F	Left	Left	Left hippocampus/amygdala
003	30	M	Right	Left	Left hippocampus/amygdala
004	39	M	Right	Right	Bilateral hippocampus/amygdala
005	35	F	Right	Right	Right mesial temporal

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