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Measuring complex behaviors of local oscillatory networks in deep brain local field potentials

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HIGHLIGHTS

- The complex behaviors of the thalamic local field potentials were investigated and quantified based on power spectral and time-frequency analysis.
- Significant difference in the behaviors were found in thalamic local field potentials between neuropathic pain and dystonic tremor groups.
- The study provides a strategy for studying the brain states in a multi-dimensional behavior space and a framework to screen quantitative characteristics for biomarkers related to diseases or nucleus.

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ABSTRACT

Background: Multiple oscillations emerging from the same neuronal substrate serve to construct a local oscillatory network. The network usually exhibits complex behaviors of rhythmic, balancing and coupling between the oscillations, and the quantification of these behaviors would provide valuable insight into organization of the local network related to brain states.
New method: An integrated approach to quantify rhythmic, balancing and coupling neural behaviors based upon power spectral analysis, power ratio analysis and cross-frequency power coupling analysis was presented. Deep brain local field potentials (LFPs) were recorded from the thalamus of patients with neuropathic pain and dystonic tremor. *t*-Test was applied to assess the difference between the two patient groups.
Results: The rhythmic behavior measured by power spectral analysis showed significant power spectrum difference in the high beta band between the two patient groups. The balancing behavior measured by power ratio analysis showed significant power ratio differences at high beta band to 8–20 Hz, and 30–40 Hz to high beta band between the patient groups. The coupling behavior measured by cross-frequency power coupling analysis showed power coupling differences at (theta band, high beta band) and (45–55 Hz, 70–80 Hz) between the patient groups.
Comparison with existing method: The study provides a strategy for studying the brain states in a multi-dimensional behavior space and a framework to screen quantitative characteristics for biomarkers related to diseases or nuclei.
Conclusions: The work provides a comprehensive approach for understanding the complex behaviors of deep brain LFPs and identifying quantitative biomarkers for brain states related to diseases or nuclei.

1. Introduction

The direct recording of local field potentials (LFPs) from a subcortical nucleus using implanted deep brain electrodes provides a unique window to explore the function of these structures in

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humans. Deep brain LFPs exhibit oscillatory behaviors with multiple neural oscillations (Brittain and Brown, 2014; Brown and Williams, 2005; Oswal et al., 2013). These oscillations provide rich information regarding diseases, their symptoms or potential therapy techniques that may be applied to these diseases. These oscillations could potentially be used as relevant biomarkers. Excessive pallidal oscillatory activity in the 4–10 Hz range has been observed in patients with primary dystonia (Silberstein et al., 2003). Recently, we have demonstrated that alpha oscillations in sensory thalamus and periaqueductal gray (PAG)/periventricular gray (PVG) directly correlate to pain intensity, which could be a quantitative signature for neuropathic pain (Green et al., 2009).

The neurophysiological and neuropathological function of a nucleus involves multiple neural oscillations simultaneously, including delta, theta, alpha, beta, gamma oscillations, etc. The presence of multiple oscillations in deep brain LFPs suggests that there might exist subsystems operating at different frequencies and they could form a local oscillatory network in a given nucleus (Priori et al., 2004). Bispectral analysis has shown that there is nonlinear quadratic phase coupling between low beta oscillations and other oscillations at theta, alpha and high beta bands in subthalamic LFPs (Marceglia et al., 2006; Wang et al., 2014). The alpha-gamma cross-frequency coupling in ventral striatum LFPs differentiates between positive and negative feedback during reward processing in depression (Lega et al., 2011). These studies suggest that these oscillations could represent the behaviors of the local oscillatory network. Quantifying the local oscillatory network is likely to be important for understanding the role of multiple oscillations in brain function.

It remains poorly understood how oscillatory neural activities are generated from the local network. The interactions among these oscillations represent the behaviors of the local oscillatory network and the dynamically altered oscillatory activity may be associated with certain neurological and neuropsychiatric disorders (Rubchinsky et al., 2012; Wang, 2010; Witte et al., 2011). Previously varied methods have been applied to neural oscillation analysis (Le Van Quyen and Bragin, 2007), and the extracted neural correlates of stimuli and associated behaviors exhibit trajectories through high-dimensional brain state space (Freeman, 2011). The current study characterized these oscillatory neural activities by taking the neural population behaviors of rhythm, balancing and coupling into consideration. The rhythmic behavior is fundamental to the representation of neural oscillations, and the amplitude of such oscillations is proportionate to the degree of synchrony with which ensembles oscillate (Pfurtscheller and Lopes da Silva, 1999). The balancing behavior between neural oscillations may arise from the balance of underlying processes, for instance, the inhibitory and excitatory activities of neurons in the same nucleus (Ostojic, 2014; Poil et al., 2012; Tahvildari et al., 2012). There are several studies that describe the power ratio between EEG theta and beta band being related to attentional control and affect regulation (Barry et al., 2003; Putman et al., 2010, 2014). Moreover, the coupling behavior between oscillations may represent the integration among oscillations (Buzsaki and Wang, 2012; Canolty and Knight, 2010; Jensen and Colgin, 2007) It has been hypothesized that these rhythm, balancing and coupling behaviors should happen simultaneously within the same nucleus (Brittain and Brown, 2014; Buzsaki, 2006). The measures of these neural behaviors are usually pre-defined, e.g. for the coupling behavior between oscillations, a priori assumption is often made about the modulating and the modulated frequency bands, and there is lack of a systematic approach to identify the significant measures of these neural behaviors, especially to characterize them simultaneously. This paper aimed to achieve this by quantifying these behaviors from the neural oscillations and develop a framework to study the neural behaviors in a multi-dimensional fashion.

This study aimed to provide a power-based framework to quantify the rhythmic, balancing and coupling behaviors of the local oscillatory network with thalamic LFPs and investigate the differences of these behaviors between neuropathic pain and dystonic tremor. The rhythm of thalamic oscillations was quantified by the power at each frequency. The balancing between neural oscillations was quantified by the power ratio between frequencies. The coupling between neural oscillations was quantified by the correlation of time-variant power across frequencies. Finally, the rhythmic, balancing and coupling behaviors of thalamic LFPs were analyzed in patients with neuropathic pain and dystonic tremor.

2. Materials and methods

2.1. Patients

Thirteen patients with neuropathic pain and six patients with dystonic tremor were recruited. The pain patients (age: 47 ± 9, mean $\pm$ SD) underwent unilateral implantation of deep brain stimulation (DBS) electrode into the sensory thalamus or both sensory thalamus and PAG at the John Radcliffe Hospital, Oxford. The dystonic tremor patients (age: 36 ± 20, mean $\pm$ SD) underwent unilateral or bilateral implantation of DBS electrode into the ventral intermediate nucleus of thalamus (Vim) or both Vim and Globus Pallidus internus (GPi) at the John Radcliffe Hospital, Oxford. Approval of the local research ethics committee of Oxfordshire, UK, and informed consent for this study were obtained.

2.2. Electrode implantation

The surgical procedures of targeting and implantation of DBS electrodes (models 3387™, Medtronic®) have been previously reported (Bittar et al., 2005; Green et al., 2006; Krauss et al., 2004; Owen et al., 2006a, 2006b). The DBS target structures were localized on the fused CT/MRI images using Radionics Image Fusion™ and Stereoplan™ (Radionics, MS, USA) pre-operatively and electrode implantation was then performed under local anaesthesia. The final electrode placement and localization of each electrode contact were confirmed for all patients by post-operative stereotactic MRI or CT, with fusion to the pre-operative MRI.

2.3. Neurophysiological recordings

The LFPs were recorded from the sensory thalamus in the neuropathic pain group and the Vim in dystonic tremor group during the period of 4–6 days post-operatively via the externalized electrodes. All patients were seated in a quiet environment. Bipolar LFPs were recorded from three adjacent pairs of deep brain electrode contacts (contact 0–1, 1–2 and 2–3) with a common electrode placed on the surface of the mastoid. Any artefacts resulting from movement of the extension cable of the DBS lead were carefully identified, avoided if possible and marked on the recordings to be excluded during analysis. For patients with dystonic tremor, EMGs were simultaneously recorded using disposable adhesive Ag/AgCl electrodes (H27P, Kendall-LTP, MA, USA) placed with a tripolar configuration (active-common-reference) over the affected muscles of both body sides in each case. Signals were amplified using isolated CED 1902 amplifiers ($\times$10 000 for LFPs and $\times$1000 for EMGs; Cambridge Electronic Design, Cambridge, UK), filtered between 0.5 Hz and 500 Hz and digitized using CED 1401 mark II at a sampling rate of 2000 Hz, displayed on line and saved onto a hard disk using a custom written program in Spike2 (Cambridge Electronic Design, Cambridge, UK).

In 13 patients with pain, 13 recordings in sensory thalamus were analyzed. The resting sensory thalamic LFPs in segments of 50 s were selected for further analysis when the patients were seated