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Analysis of simultaneous MEG and intracranial LFP recordings during Deep Brain Stimulation: a protocol and experimental validation

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HIGHLIGHTS

- Setup for MEG and intracranial recordings during Deep Brain Stimulation is described.
- Phantom experiment showed correct recovery of oscillatory sources despite artefacts.
- The method is applied to real data from a patient with Parkinson's Disease.
- Cortico-subthalamic coherence profiles on and off stimulation were comparable.

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ABSTRACT

Background: Deep Brain Stimulation (DBS) is an effective treatment for several neurological and psychiatric disorders. In order to gain insights into the therapeutic mechanisms of DBS and to advance future therapies a better understanding of the effects of DBS on large-scale brain networks is required.
New method: In this paper, we describe an experimental protocol and analysis pipeline for simultaneously performing DBS and intracranial local field potential (LFP) recordings at a target brain region during concurrent magnetoencephalography (MEG) measurement. Firstly we describe a phantom setup that allowed us to precisely characterise the MEG artefacts that occurred during DBS at clinical settings.
Results: Using the phantom recordings we demonstrate that with MEG beamforming it is possible to recover oscillatory activity synchronised to a reference channel, despite the presence of high amplitude artefacts evoked by DBS. Finally, we highlight the applicability of these methods by illustrating in a single patient with Parkinson's disease (PD), that changes in cortical-subthalamic nucleus coupling can be induced by DBS.
Comparison with existing approaches: To our knowledge this paper provides the first technical description of a recording and analysis pipeline for combining simultaneous cortical recordings using MEG, with intracranial LFP recordings of a target brain nucleus during DBS.

1. Introduction

Deep Brain Stimulation (DBS) is a way of treating neurological and psychiatric disorders that involves electrical stimulation of subcortical brain regions through chronically implanted macroelectrodes. One condition in which DBS therapy has proven to be particularly effective is Parkinson's Disease (PD) (Deuschl et al., 2006). In PD, the most commonly targeted brain region for DBS is the subthalamic nucleus (STN), but other less frequently implanted sites include the thalamus, the pedunculopontine nucleus and the globus pallidus (Lukins et al., 2014).

Each DBS procedure presents a unique opportunity to gain valuable translational insights about electrophysiological brain activity in pathological disease states (Oswal et al., 2013a). DBS electrodes are sometimes externalised post-operatively to verify correct electrode placement prior to stimulator implantation. This enables local field potential recordings from the target nuclei. As a result, it has

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been possible to gain valuable information about the clinical and functional correlates of oscillatory activity within the STN in PD. An additional role of such recordings has been to shed light on the local therapeutic mechanisms of DBS. For example, it has been possible to show that DBS reduces beta band activity within the STN (Eusebio et al., 2011; Rossi et al., 2008), and furthermore that the extent of beta reduction correlates with clinical improvement (Kühn et al., 2009, 2006; Ray et al., 2008; Chen et al., 2010). Such insights are being translated into improved clinical therapies, as highlighted by a seminal study of adaptive DBS in the Parkinsonian non-human primate (Rosin et al., 2011), and recent pilot work also suggesting that adaptive DBS, triggered to beta band amplitude, may potentially be better than conventional DBS at ameliorating Parkinsonian symptoms in patients (Little et al., 2013). Despite these promising early insights, many questions remain yet to be answered about the neuromodulatory effects of DBS on long-range brain networks. Magnetoencephalography (MEG) may provide a powerful approach for imaging brain networks during DBS.

Previous work using simultaneous MEG and resting intracranial LFP recordings has shown the existence of two spatially and spectrally distinct networks between the STN and cortical regions in PD (Litvak et al., 2010, 2011a; Hirschmann et al., 2011). An alpha band network exists between the STN and temporo-parietal and brainstem regions, whilst a beta band network exists between the STN and motor/premotor regions. Furthermore, the initiation of movement is accompanied by a dopamine dependent reduction in coherence in the alpha network and a concomitant emergence of gamma band synchrony between the STN and primary motor cortex (Oswal et al., 2013b; Litvak et al., 2012). The identified resting state networks may play an important role in the pathophysiology of PD, highlighted by the fact that dopamine dependent modulations in their activities correlate with dopamine related improvements in clinical scores. Although such correlations by no means imply causation, their presence is highly informative. It is worthwhile noting that even in the absence of DBS, these recordings are severely contaminated by the presence of high amplitude artefacts related to the presence of ferromagnetic extension wires from the DBS electrodes to the recording equipment. However, source space analysis using beamformers enables effective suppression of such artefacts, allowing for valid physiological inferences to be made (Litvak et al., 2010; Oswal et al., 2014). Non-ferromagnetic extension wires have recently been made available, but they are not approved for clinical use in the UK at present (Hirschmann et al., 2011).

Although it has been possible to simultaneously stimulate and record from the STN, and also to record from the STN during concurrent MEG, no methods have as yet been developed to combine these two approaches and allow simultaneous MEG and intracranial LFP recordings during DBS. The utility for such recordings is clear, since they would enable the characterisation of both local effects of DBS and of the effects of DBS on connectivity between target nuclei and distal brain regions. Such information could benefit current understanding of the therapeutic mechanisms of DBS in addition to informing future developments in DBS technologies.

In this paper we describe the experimental setup for simultaneous MEG and intracranial LFP recordings during DBS. We also detail the analysis procedure making it possible to recover coherence between the LFP and the MEG in the presence of stimulation, despite artefacts due to ferromagnetic extension wires, and those due to DBS currents that will not be obviated by the use of non-ferromagnetic extension wires. The proposed methods are validated using a dipole phantom and applied to data from a single PD patient with electrodes in the STN.

2. Methods

2.1. Simultaneous MEG and LFP recordings

All the MEG recordings described in the present paper were performed using a CTF 275-channel MEG system (CTF/VSM MedTech, Vancouver, Canada). An important advantage of this system is the high dynamic range of its sensors and their robustness to strong external interferences.

In our previous studies we used the EEG system integrated in CTF-MEG to record the intracranial data (Litvak et al., 2011a, 2012; Oswal et al., 2013b). Our rationale for moving away from this approach was that the recording equipment was not isolated from the mains power supply and thus did not comply with newer and more rigorous local safety standards. The approach we use in the present study is to record LFP and other electrophysiological measurements from the patient using a battery-powered and optically isolated BrainAmp system (Brain Products GmbH, Gilching, Germany). The challenge that this approach poses is fusing the EEG and MEG data with minimal timing distortions. For this purpose we propose to use a synchronisation signal recorded on both systems. The optimal type of signal is random white noise because it can only be matched in a unique way.

Any noise generator capable of producing wide-band noise with an appropriate amplitude can be used. Our generator was built utilising an 8.2 V Zener diode biased close to its avalanche region. This was achieved using a variable potentiometer, while an oscilloscope was used to ensure the maximum noise was produced. The noise was amplified to 500 mV peak-to-peak range. To control the exact output amplitude a variable resistor on the output was included. Note that connecting the noise generator with cables to both the MEG and the EEG amplifier would create a breach in the optical isolation and defeat its purpose. Fortunately, the BrainAmp system provides a solution by combining two optically isolated amplifiers into one system with synchronous sampling—accordingly one of these amplifiers was used to record the noise signal, whilst the other was used to record physiological activity.

Fig. 1 details our experimental set up. We note that it is possible to record the white noise and the physiological signals (LFP, EEG, EOG, EMG) in either a monopolar or a bipolar fashion. For the purposes of our experiment we recorded physiological signals bipolarly (using an 8 channel bipolar ExG BrainAmp amplifier), since our stimulation-record amplifier was designed to give bipolar outputs. The white noise was recorded using a 32 channel monopolar BrainAmp MR plus amplifier. Our set up was approved by the MEG safety board of the Wellcome Trust Centre for Neuroimaging, following extensive in-house safety testing.

2.2. Simultaneous stimulation and LFP recording

In this section we detail our approach for simultaneous DBS and LFP recording during MEG. We used a purpose built stimulation-record amplifier that was a variant of the design used in previous studies not involving MEG (Eusebio et al., 2011; Little et al., 2013; Rossi et al., 2007).

This design is based on the idea that when stimulating one of the two middle contacts (contact 1 or 2) monopolarly while recording from the two adjacent contacts of the DBS electrode (0 and 2 or 1 and 3, respectively) one can use the common mode rejection property of the front stage differential amplifier to reduce the DBS artefact and line noise. Both these signals are seen similarly by the recording contacts. The stimulation-record amplifier is used in combination with a clinically approved external DBS stimulator (type 3628, Medtronic Inc., Minneapolis,