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Somatomotor mu rhythm amplitude correlates with rigidity during deep brain stimulation in Parkinsonian patients

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HIGHLIGHTS

- The spatiotemporal signal space separation (tSSS) method makes magnetoencephalography (MEG) measurements feasible in deep brain stimulation (DBS) patients.
- During DBS, rigidity correlated with somatomotor mu rhythm strength when eyes were open.
- The peak frequency of occipital alpha rhythm correlated negatively with Unified Parkinson's Disease Rating Scale (UPDRS) total motor and rigidity subscores.

ABSTRACT

Objective: Parkinsonian patients have abnormal oscillatory activity within the basal ganglia-thalamocortical circuitry. Particularly, excessive beta band oscillations are thought to be associated with akinesia. We studied whether cortical spontaneous activity is modified by deep brain stimulation (DBS) in advanced Parkinson's disease and if the modifications are related to the clinical symptoms.
Methods: We studied the effects of bilateral electrical stimulation of subthalamic nucleus (STN) on cortical spontaneous activity by magnetoencephalography (MEG) in 11 Parkinsonian patients. The artifacts produced by DBS were suppressed by tSSS algorithm.
Results: During DBS, UPDRS (Unified Parkinson's Disease Rating Scale) rigidity scores correlated with 6–10 Hz and 12–20 Hz somatomotor source strengths when eyes were open. When DBS was off UPDRS action tremor scores correlated with pericentral 6–10 Hz and 21–30 Hz and occipital alpha source strengths when eyes open.
Occipital alpha strength decreased during DBS when eyes closed. The peak frequency of occipital alpha rhythm correlated negatively with total UPDRS motor scores and with rigidity subscores, when eyes closed.
Conclusion: STN DBS modulates brain oscillations both in alpha and beta bands and these oscillations reflect the clinical condition during DBS.
Significance: MEG combined with an appropriate artifact rejection method enables studies of DBS effects in Parkinson's disease and presumably also in the other emerging DBS indications.

1. Introduction

Abnormal oscillatory activity occurs within the basal ganglia of patients with Parkinson's disease (PD). This abnormal activity is modified by activity in cerebello–thalamo–cortical neural loops (Schnitzler and Gross, 2005). Stimulation of different parts of this system may resume the normal unsynchronized activity in the basal ganglia circuitry and reduce the clinical symptoms of PD. One important hub of this network is the subthalamic nucleus (STN). STN stimulation effectively ameliorates several PD symptoms (Krack et al., 2003).

Oscillatory activity in the STN has been studied from electrodes implanted into the STN of PD patients. STN 11–35 Hz oscillatory activity is decreased prior to movement and increased during

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voluntary suppression of movements (Kuhn et al., 2004). Clinical improvement of akinesia-rigidity by levodopa therapy is associated with a reduction in STN 8–35 Hz activity, whereas improvement of tremor is not (Kuhn et al., 2006). STN 15-Hz oscillations tend to correlate with improvement of rigidity in response to medication, whereas about 25 Hz oscillations are significantly associated with improvement of axial bradykinesia by DBS (Zaidel et al., 2010). Activity and firing rate of the STN neurons may increase with progression of PD (Remple et al., 2011). Local field potentials (LFPs) in the STN are coherent with scalp electroencephalography (EEG), predominantly in the 8–13-Hz and 21–32 Hz range (Fogelson et al., 2006). The EEG somatomotor mu rhythm, including beta band oscillations over the sensorimotor cortices is suppressed by movement or even by imaging movement (Chatrian et al., 1959). EEG mu rhythm suppression during movement appears to begin earlier when STN DBS is on rather than off (Devos et al., 2004). Recordings of LFPs from the STN during DBS have revealed conflicting results; both suppression of beta activity (Eusebio et al., 2011) and unaltered beta activity but also increased low-frequency oscillations (Rossi et al., 2008) have been reported.

Magnetoencephalography (MEG) recordings have demonstrated that the motor cortex activity is affected by tremor (Mäkelä et al., 1993), and is involved (Volkmann et al., 1996; Timmermann et al., 2003) in the tremor-generating network in PD. Spectra of spontaneous MEG in patients with PD display increased theta, low alpha band and, contrary to STN recordings, decreased beta band activity. These spectral differences are not changed by levodopa therapy (Stoffers et al., 2007). MEG has demonstrated abnormal coupling of sensorimotor areas oscillating predominantly at 8–12 Hz in PD (Timmermann et al., 2003).

Recent publications have suggested a dominant role for cortical oscillatory activity in driving STN activity both in animal models (Gradinaru et al., 2009) and in patients (Marsden et al., 2001; Fogelson et al., 2006; Litvak et al., 2011). MEG is an excellent tool for non-invasive studies for cortical electrophysiology. However, severe electromagnetic artifacts generated by the stimulator have prevented MEG studies in patients with DBS. Recent reports, however, showed that application of beamformer analysis (Litvak et al., 2010, 2011), or use of non-magnetic DBS cables (Hirschmann et al., 2011) result in data that allows correlation of MEG signals with LFPs from STN. These recordings have revealed a rich pattern of connectivity between STN and MEG cortical oscillations. However, these studies do not permit the direct analysis of the stimulation effects on MEG, as STN stimulation has not been performed simultaneously with MEG recordings. Moreover, STN recordings are usually available only a few days after the operation, before the connection of the electrodes to the subcutaneous pulse generator, when the "stun effect" from the microlesion caused by the operation is still present (e.g., Eusebio et al., 2011).

The spatiotemporal signal space separation (tSSS) method (Taulu and Simola, 2006) suppresses magnetic artifacts originating from distant or nearby sources in MEG recordings (Taulu and Hari, 2009). The method utilizes Maxwell's equations and exact information about the geometry of the sensor array to decompose the multichannel MEG signals into a device-independent representation. The measured signals are then divided into two spatial parts by the signal space separation (SSS) method (Taulu and Kajola, 2005). The tSSS algorithm recognizes the temporally correlated signal components between the inside and outside or residual parts of the signal and removes them from the data (Taulu and Simola, 2006). This method has been utilized successfully to remove magnetic artifacts caused by DBS (Park et al., 2009; Airaksinen et al., 2011) and by vagus nerve stimulation (Tanaka et al., 2009; Carrette et al., 2011).

Herein we report the effects of ongoing STN DBS on cortical spontaneous MEG activity in the somatomotor and occipital regions by applying the tSSS algorithm. We hypothesized that STN DBS would modify somatomotor beta activity in PD patients showing clinical improvement, particularly in rigidity.

2. Patients and methods

Sixteen PD patients with bilateral STN DBS (Kinetra®, Medtronic) were measured with MEG. The study was accepted by the Ethics Committee of the Department of Neurology, Helsinki University Central Hospital. All patients gave informed written consent. Five patients were excluded from the data analysis. For one patient, head coordinate data for source modeling was not available. One patient did not tolerate turning off the DBS. In one patient, artifacts could not be effectively removed by tSSS because of too many saturated MEG sensors. Two patients were omitted because of missing UPDRS (Unified Parkinson's Disease Rating Scale) scores.

The mean age of the 11 analyzed patients (6 females, 5 males) was 61 years (49–75 years). The patients did not present clinical signs of dementia or depression. One patient had undergone thalamotomy of the right hemisphere 14 years before the bilateral STN DBS implantation. All patients used their normal antiparkinsonian medication during the measurements. In 2 patients, the DBS frequency was adjusted from 160 Hz to 130 Hz during measurements to avoid the interference with the head position indicator coils used in MEG. Otherwise, the stimulation parameters were not changed from the optimized therapeutic settings of each patient. The clinical details of patients and stimulation parameters are presented in Table 1.

The recordings were first performed when bilateral DBS was on. Thereafter, the stimulator was turned off in the shielded room. The head position was remeasured before the measurement with DBS off. UPDRS motor scores were defined before the start of the measurement with DBS on and after the patient had been taken out from the shielded room with DBS off.

MEG measurements were performed with a 306-channel Elekta Neuromag® MEG device (Elekta Oy, Helsinki, Finland) in a magnetically shielded room (Euroshield, Eura, Finland). The recording passband was 0.03–330 Hz and the sampling rate 1011 Hz. Spontaneous activity was recorded for 3 min when the patient's eyes were closed and 5 min with eyes open.

The exact location of the head relative to the sensors was determined by the head position indicator coils placed on the scalp. The location of the coils with respect to landmarks on the head was determined with a 3-D digitizer (Polhemus™).

The magnetic artifacts caused by DBS were removed by tSSS-method (Taulu and Simola, 2006) with an 8 s raw data buffer and subspace correlation limit of 0.8 (Medvedovsky et al., 2009; Carrette et al., 2011).

Spontaneous 140 s MEG data periods were analyzed in the frequency domain, except for one data set of one patient that contained only 47 s of acceptable data. To detect the interesting spectral ranges, the fast Fourier transform (FFT) spectra were calculated from the signals (Fig. 1). The FFT length was 512 samples (frequency resolution approximately 2 Hz). Thereafter, the spectral peaks were scrutinized: tSSS effectively suppressed most DBS artifacts but left some narrow interference peaks in the spectra (Fig. 2). Most probably the peaks were produced by the high-frequency interference from the DBS that was not sufficiently suppressed by the applied anti-aliasing filter parameters of the MEG, and therefore appeared at lower frequencies in the sampled signal. These artifacts were more evident in monopolar stimulation. The peak frequency of the lowest detected spurious, maybe aliased, peak was 20.7 Hz (Fig. 2). This spurious peak cannot, however, be simply explained by an aliased DBS-interference component.

The sources of oscillatory activity were localized from the MEG data by the frequency domain minimum current estimate (MCEfd)