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Cortico-muscular coherence in advanced Parkinson's disease with deep brain stimulation

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HIGHLIGHTS

- Deep brain stimulation (DBS) modifies the cortico-muscular coherence (CMC) in advanced Parkinson's disease with high individual variability.
- No clear correlation between CMC and total motor performance was detected.
- CMC between 13 and 25 Hz was associated with better UPDRS (Unified Parkinson disease scores) results at the group level in both DBS on and off conditions.

ABSTRACT

Objective: Cortico-muscular coherence (CMC) is thought to reflect the interplay between cortex and muscle in motor coordination. In Parkinson's disease (PD) patients, levodopa has been shown to enhance CMC. This study examined whether subthalamic nucleus (STN) deep brain stimulation (DBS) affects the CMC in advanced PD.
Methods: Magnetoencephalography (MEG) and electromyography (EMG) measurements were done simultaneously both with DBS on and off to determine the CMC during wrist extension. The spatiotemporal signal space separation (tSSS) was used for artifact suppression.
Results: CMC peaks between 13 and 25 Hz were found in 15 out of 19 patients. The effect of DBS on CMC was variable. Moreover, the correlation between CMC and motor performance was inconsistent; stronger CMC did not necessarily indicate better function albeit tremor and rigidity may diminish the CMC. Patients having CMC between 13 and 25 Hz had the best motor scores at the group level.
Conclusions: DBS modifies the CMC in advanced PD with large interindividual variability.
Significance: DBS does not systematically modify CMC amplitude in advanced PD. The results suggest that some components of the CMC may be related to the therapeutic effects of DBS.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder with cardinal motor symptoms of bradykinesia, rigidity and tremor. Subthalamic nucleus (STN) deep brain stimulation (DBS) is a well documented treatment for advanced PD, although understanding of its mechanism of action is still incomplete.

Cortico-muscular coherence (CMC) is thought to reflect the interplay between cortex and muscle in motor coordination. CMC is calculated between simultaneous magnetoencephalography (MEG)/electroencephalography (EEG) and electromyography (EMG) recordings. CMC in the 12–33 Hz band has been found during isometric contraction in healthy subjects between motor cortex and different muscles (e.g. (Conway et al., 1995; Salenius et al., 1997; Gross et al., 2000)). In a precision grip task, the level of coherence depends on the performed task (Kilner et al., 2000). High CMC may (Kristeva et al., 2007) or may not (Johnson et al., 2011) correlate with precise motor performance. CMC amplitude

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decreases if attention is divided during muscle activation (Kristeva-Feige et al., 2002; Johnson et al., 2011).

PD patients withdrawn from levodopa treatment had abnormally weak CMC at 15–30 Hz during isometric contraction compared with healthy controls, and administration of levodopa strengthened the 15–30 Hz CMC in six out of eight patients. However, the effect sizes were highly variable between the patients, and two patients (25%) did not have clear CMC in the 15–30 Hz range (Salenius et al., 2002). In de novo PD patients or early-stage medicated PD patients, CMC does not differ from healthy controls (Pollok et al., 2012).

DBS-induced artifacts complicate the studies of the effects of DBS on CMC in PD. However, a novel artifact suppression algorithm (Taulu and Simola, 2006) has enabled DBS studies in conjunction with MEG (Park et al., 2009; Airaksinen et al., 2011, 2012). So far, there are two MEG publications which have reported CMC results in PD patients with DBS. In one study with three patients, STN-DBS was found to increase the 10–30 Hz range CMC amplitude for the tremorous hand; this increase was associated with amelioration of tremor by DBS (Park et al., 2009). In another study with one patient, DBS suppressed both the resting and postural tremor and coherence between MEG and EMG from a resting hand peaking at 4 Hz and 8 Hz (Connolly et al., 2012). A slight increase of EEG-EMG CMC during DBS on vs. off in the 15–20 Hz range was observed in an average of eight patients studied eight days after DBS implantation (Weiss et al., 2012).

We studied the CMC changes induced by DBS in 19 patients to see if the previously described effects can be generalized to a larger patient population. We hypothesized that DBS, similarly to levodopa, would increase CMC in the low beta band and that CMC would be correlated with motor symptoms during DBS in advanced PD.

2. Patients and methods

The study was approved by the Ethics Committee of Helsinki University Central Hospital, and all patients gave informed written consent. We recorded MEG from 28 advanced PD patients, who had bilateral STN DBS (Kinetra or Activa PC Neurostimulators, Medtronic Inc., Minneapolis, MN, USA). The data of nine patients were rejected. Two patients could not tolerate the DBS off state during the measurement, accurate monitoring of head position was not possible in one patient, and MEG amplifiers were saturated by strong artifacts related to dystonic movements in one patient. One patient was excluded because he had undergone thalamotomy of the right hemisphere 14 years before the DBS implantation. Four patients were excluded as they were measured within 4 months after the implantation. The characteristics of the 19 analyzed patients are shown in Table 1. The main reason for DBS implantation was severe daily motor fluctuations and dyskinesias. Fifteen patients had the rigid-akinetic and four had the tremor subtype of PD. The mean age of the patients was 57 (±10) years. Diagnosis of PD was made 12.5 (±5) years before the implantation of the bilateral STN DBS. The MEG measurements were done 11.8 (±8.4) months after the implantation (range 4.5–25 months). The patients did not have clinical signs of dementia or depression. All patients used their regular antiparkinsonian medication during the MEG measurements. To calculate the levodopa equivalent daily dose (LEDD), the following formula was used: 100 mg L-dopa = 130 mg controlled release L-dopa = 70 mg L-dopa + COMT inhibitor = 1 mg pramipexole = 5 mg ropinirole (Mamikonyan et al., 2008) = 4 mg rotigotine (Poewe et al., 2007).

A 306-channel neuromagnetometer (Elekta Neuromag®, Elekta Oy, Helsinki, Finland) was used to record neuromagnetic activity. The patients were seated under the device and the head position was determined using the vendor-supplied head position indicator system in the beginning of the data recording. Patients were instructed to extend the wrist of the more affected upper limb. Simultaneously, muscle activity was recorded with surface EMG placed over the activated extensor carpi radialis longus muscle. The wrist was extended five times, each time for one minute, with a 20-s rest periods between the extensions. The patients were instructed to activate or relax the wrist. The recording passband was 0.03–330 Hz and the sampling rate 1012 Hz for both MEG and EMG. The MEG measurements were done twice. In the first measurement DBS was on; thereafter, DBS was switched off in the shielded room and the measurement was repeated. The EMG electrodes were the same for both measurements. With one patient, the order of measurement was reversed. The positioning of this patient into the MEG device was difficult and unpleasant for the patient due to rigidity when DBS was off: therefore, the order of recordings was not balanced in the whole patient series.

The spatiotemporal signal space separation (tSSS) (Taulu and Simola, 2006) method with an 8-s time window and a subspace correlation limit of 0.9 (Medvedovsky et al., 2009) was applied to suppress the strong magnetic artifacts before data analysis. In addition to the actual electric stimulation artifact, large artifacts are induced e.g. from the pulse generator and the implanted wires which move due to respiration. MaxFilter™ was used for the tSSS operation.

Power spectral density (PSD) values of MEG and rectified EMG and the MEG–EMG coherence spectra were calculated for each patient both in the DBS on and off conditions. The spectra were calculated using Welch's method with 50% overlapping 1024-point Hanning windows, resulting in a frequency resolution of about 1 Hz. The coherence was calculated from separate wrist extension periods by combining the individual periods and then calculating the coherence from the combined signal. The number of averaged segments used for coherence calculations varied in the range 106–597 (mean 451 ± 118).

The coherence was calculated between the EMG signal and each MEG gradiometer pair in turn. The location of the CMC maximum peak within each frequency band was then determined from a selection of 15 gradiometer pairs over the sensorimotor cortex contralateral to the activated hand (Fig. 1).

The PSD (see Fig. 2) was normalized by dividing it with the average PSD between 3 and 48 Hz. The grand averages were obtained by averaging these normalized PSDs over the patients. The averaged spectra were compared with DBS on and off for 6–13 Hz and 13–25 Hz bands.

To compare the results between the DBS on and off conditions at sensor level, the head positions were first equalized by using the multipole-based method described in Taulu et al. (2005), implemented in Elekta MaxFilter™ software. The coherence spectra were then inspected. Peak strengths and frequencies were then determined from the planar gradiometer pair showing the largest response over the sensorimotor cortex. The coherence spectra were divided into 4–6 Hz, 6–13 Hz and 13–25 Hz frequency bands.

Time-shifted coherence (coherence calculated by shifting EMG data 3 s in relation to the MEG data) was used for defining the statistical significance level. This time shift is expected to destroy any true EMG–EMG coherence in the data. The significance level was set at 99% of the time-shifted coherence (Salenius et al., 2002).

UPDRS III (motor) scores (abbreviated in the following as UPDRS scores) were measured just before the MEG measurement (DBS on) and just after the measurement (DBS off). The UPDRS values were not documented from one patient with DBS on and from another with DBS off. Furthermore, in one patient the tremor score distribution between extremities was not recorded when DBS was off.

The correlations were calculated between CMC frequency/amplitude and the following UPDRS scores (separately for DBS on and off): total (items 18–31), tremor (items 20–21), rigidity (item 22), bradykinesia (items 23–26) or rigidity-bradykinesia (items