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MODULATION OF LOCAL FIELD POTENTIAL POWER OF THE SUBTHALAMIC NUCLEUS DURING ISOMETRIC FORCE GENERATION IN PATIENTS WITH PARKINSON'S DISEASE

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Abstract—Investigations of local field potentials of the subthalamic nucleus of patients with Parkinson's disease have provided evidence for pathologically exaggerated oscillatory beta-band activity (13–30 Hz) which is amenable to physiological modulation by, e.g., voluntary movement. Previous functional magnetic resonance imaging studies in healthy controls have provided evidence for an increase of subthalamic nucleus blood-oxygenation-level-dependant signal in incremental force generation tasks. However, the modulation of neuronal activity by force generation and its relationship to peripheral feedback remain to be elucidated. We hypothesised that beta-band activity in the subthalamic nucleus is modulated by incremental force generation. Subthalamic nucleus local field potentials were recorded intraoperatively in 13 patients with Parkinson's disease (37 recording sites) during rest and five incremental isometric force generation conditions of the arm with applied loads of 0–400 g (in 100-g increments). Repeated measures analysis of variance (ANOVA) revealed a modulation of local field potential (LFP) power in the upper beta-band (in 24–30 Hz; $F_{(3.042)} = 4.693$, $p = 0.036$) and the gamma-band (in 70–76 Hz; $F_{(4)} = 4.116$, $p = 0.036$). Granger-causality was computed with the squared partial directed coherence and showed no significant modulation during incremental isometric force generation. Our findings indicate that the upper beta- and gamma-band power of subthalamic nucleus local field potentials are modulated by the physiological task of force generation in patients with Parkinson's disease. This modulation seems to be not an effect of a modulation of peripheral feedback.

Key words: deep brain stimulation (DBS), intraoperative recordings, Granger-causality, squared partial directed coherence, closed-loop stimulation, basal ganglia.

INTRODUCTION

Motor system neuroscience has aimed at a more profound understanding of the functions of the basal ganglia (BG) (Alexander et al., 1990; Bergman et al., 1998; Jahanshahi et al., 2002; Levy et al., 2002; Brown, 2003; Reck et al., 2009b; Pedrosa et al., 2012). Studies of patients with Parkinson's disease (PD) have provided important insights into the physiological and pathophysiological role of basal ganglia–cortical loops in movement generation (Hallett and Khoshbin, 1980; Brown and Marsden, 1998; Berardelli et al., 2001; Pope et al., 2006; Reck et al., 2009a).

Various single-cell studies of human and non-human primates have revealed that the subthalamic nucleus (STN) plays a vital role in the control of movement parameters like, e.g., direction (Williams et al., 2005b), amplitude and velocity of movements (Georgopoulos et al., 1983), and force (Delong et al., 1984). The involvement of BG in force generation was further suggested by lesional (Theodosopoulos et al., 2003; Aparicio et al., 2005) as well as low (Chen et al., 2011) and high frequency (Levy et al., 2002; Alberts et al., 2008) deep brain stimulation (DBS) studies which described altered force generation dynamics and maximum force amplitude. Imaging studies using functional magnetic resonance imaging (fMRI) have shown an increased blood-oxygenation-level-dependent (BOLD) signal within the STN of healthy human subjects during the generation of a series of force pulses (Pope et al., 2005; Vaillancourt et al., 2007) and incremental isometric force (Spraker et al., 2007).

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Abbreviations: A, anterior; ANOVA, analysis of variance; BG, basal ganglia; BOLD, blood-oxygenation-level-dependent; C, central; CI, confidence interval; CT, computed tomography; DBS, deep brain stimulation; DTF, directed transfer function; EDC, M. extensor digitorum communis; EEG, electroencephalography; EMG, electromyogram; f, female; FDI, first dorsal interosseus; FDL, M. flexor digitorum superficialis; FFT, fast Fourier transform; fMRI, functional magnetic resonance imaging; HSD, honest significance difference; IFG, isometric force generation; L, lateral; LFP, local field potential; m, male; M, medial; P, posterior; PD, Parkinson's disease; PET, positron emission tomography; rCBF, regional cerebral blood flow; SD, standard deviation; SNr, substantia nigra pars reticulata; sPDC, squared partial directed coherence; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale; ZI, zona incerta.

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The wealth of these data indicating a substantial role of the STN in the generation of force is, however, contrasted by the lack of knowledge regarding the neural mechanisms underlying this contribution.

Local field potential (LFP) studies have provided evidence for a modulation of neuronal oscillatory activity of the beta- (13–30 Hz) and the 60–80 Hz gamma-band by physiological tasks like voluntary movement preparation and execution in patients with PD (Cassidy et al., 2002; Kuhn et al., 2004; Alegre et al., 2005; Doyle et al., 2005; Foffani et al., 2005). Based on these observations of LFP studies indicating a modulation of STN beta- and gamma-band power during voluntary movement and on single-cell, DBS and imaging studies implying a crucial role of the STN for force generation, we hypothesised that beta- and gamma-band activity is modulated by isometric force generation (IFG).

Finally, we were interested in whether a modulation of STN LFP power during the execution of IFG conditions was interrelated with a modulation of the directionality of information flow between the muscle electromyogram (EMG) and STN LFPs. Previously, a bi-directional information flow between muscle and brain was observed in healthy subjects between electroencephalography (EEG) and forearm muscle EMGs, however no interrelation was reported between force generation levels in a hold–ramp–hold task and a modulation of Granger-causality between forearm EMG and EEG activity (Witham et al., 2011). In STN LFP studies, during the main parkinsonian symptom more 'afferent' Granger-causality connections (from forearm EMGs to STN LFPs) were detected during rest (Florin et al., 2010, 2012). Wang and co-workers observed significantly more 'afferent' information flow from forearm muscle EMG and STN LFPs during periods of continuing resting tremor compared to periods of intermittent resting tremor (Wang et al., 2007). We interpreted their data as an activation of quiescent pathways between muscle and STN during an allometric movement. Even though an involuntary movement during tremor is not directly comparable to a voluntary movement during an IFG task, this study indicates movement-related changes of Granger-causality between STN LFPs and forearm muscle EMGs. Based on this observation we hypothesised an activation of 'afferent' pathways, e.g., via circuits activated by muscle stretch receptors, during a movement task with IFG.

EXPERIMENTAL PROCEDURES

Patients and clinical characteristics

Thirteen patients with idiopathic PD (five females and eight males) diagnosed according to the British Brain Bank criteria (Hughes et al., 1992) with a mean age of 59.6 years (±9.8 years) participated in this study (Table 1). Mean disease duration was 9.5 years (±5.0 years). All patients had motor symptoms consisting of bradykinesia, resting tremor and/or rigidity.

No clinically relevant cognitive impairments were observed prior to surgery and preoperative selection criteria were fulfilled in accordance with our internal hospital protocols as well as the consensus recommendations of the German Deep Brain Stimulation Association (Hilker et al., 2009) and the Movement Disorders Society (Lang et al., 2006). All patients gave their informed written consent for intraoperative recordings. The study was approved by the local ethics committee (Study No. 08-158, Cologne) and carried out in accordance with the Declaration of Helsinki.

Planning and implantation

Bilateral STN electrode implantation was performed at the Department of Stereotaxy and Functional Neurosurgery of the University Hospital Cologne. Prior to the operation procedure L-DOPA and dopamine agonists were withdrawn for a minimum of 12 h and 3–4 days respectively, thus patients were implanted during defined medication OFF-state.

Preoperative STN targeting was performed by senior stereotactic neurosurgeons (V.S., M.M.) based upon functional coordinates using the Schaltenbrand and Wahren atlas (Schaltenbrand, 1977), stereotactic cranial computed tomography (CT), stereotactic high-resolution magnetic resonance imaging (MRI, T1, T2 and T2*), fusioned CT/MRI images (Ende et al., 1992), and on visual inspection (Voges et al., 2002).

Intraoperatively, STN targeting was confirmed electrophysiologically with up to five microelectrode recordings on the basis of characteristic firing patterns allowing a differentiation of the STN's proximal boundary to the zona incerta (ZI) and its distal boundary to the substantia nigra pars reticulata (SNr; Hutchison et al., 1998).

Intraoperative recordings

Intraoperative single-cell and LFP recordings of the STN were performed in all 13 patients (14 hemispheres) with bilateral recordings only in one patient. Recordings were limited to one hemisphere in most patients due to fatigue and anatomical constraints by, e.g., blood vessels. Recordings were performed during the implantation of electrodes with combined micro–macroelectrodes using the Inomed ISIS MER system (INOMED Corp., Teningen, Germany; ISIS MER system software 2.4beta). These micro–macroelectrodes (INOMED Corp., No. 230767) consist of a distal microelectrode tip (Ø 4 μm) and a macroelectrode ring localised 1 mm proximally (Ø 800 μm). The microelectrode is a high-impedance electrode (about 1–2 MΩ) made of tungsten and can thus record single-cell activity, whereas the macroelectrode is a low impedance electrode (about 1 kΩ) made of stainless steel which can record LFPs. Simultaneous surface EMGs were recorded from the M. extensor digitorum communis, M. flexor digitorum longus and the M. interosseus dorsalis I (EDC, FDL and FDI).

All data recordings were performed intraoperatively with a sampling rate of 2.5 kHz. LFPs were pre-amplified with a factor of 2000 (Florin et al., 2008). A hardware high-pass filter of 0.5 Hz and low-pass filter of 1 kHz was applied during all data recording.

Combined single unit and LFP recordings were performed on 3–5 trajectories for each hemisphere. In some hemispheres fewer than five trajectories were used due to unfavourable individual anatomy and resulting surgical constraints. The electrodes were arranged in the Ben-Gun approach consisting of a square array of micro-macroelectrodes separated by 2 mm on central, anterior, posterior, medial, and lateral positions (CAMPL).

In order to implement a mapping of the STN boundary with respect to the ZI, recordings were performed in consecutive 1-mm steps starting at 6 mm above target point until reaching the planned target point in the dorsolateral STN. The intraoperative paradigm was carried out at the preoperatively planned target point if single-cell recordings indicated that at