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Predictive timing functions of cortical beta oscillations are impaired in Parkinson's disease and influenced by L-DOPA and deep brain stimulation of the subthalamic nucleus

Impaired beta-band timing functions in PD

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ABSTRACT

Cortex-basal ganglia circuits participate in motor timing and temporal perception, and are important for the dynamic configuration of sensorimotor networks in response to exogenous demands. In Parkinson's disease (PD) patients, rhythmic auditory stimulation (RAS) induces motor performance benefits. Hitherto, little is known concerning contributions of the basal ganglia to sensory facilitation and cortical responses to RAS in PD. Therefore, we conducted an EEG study in 12 PD patients before and after surgery for subthalamic nucleus deep brain stimulation (STN-DBS) and in 12 age-matched controls. Here we investigated the effects of levodopa and STN-DBS on resting-state EEG and on the cortical-response profile to slow and fast RAS in a passive-listening paradigm focusing on beta-band oscillations, which are important for auditory–motor coupling. The beta-modulation profile to RAS in healthy participants was characterized by local peaks preceding and following auditory stimuli. In PD patients RAS failed to induce pre-stimulus beta increases. The absence of pre-stimulus beta-band modulation may contribute to impaired rhythm perception in PD. Moreover, post-stimulus beta-band responses were highly abnormal during fast RAS in PD patients. Treatment with levodopa and STN-DBS reinstated a post-stimulus beta-modulation profile similar to controls, while STN-DBS reduced beta-band power in the resting-state. The treatment-sensitivity of beta oscillations suggests that STN-DBS may specifically improve timekeeping functions of cortical beta oscillations during fast auditory pacing.

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1. Introduction

Akinesia, the inability to initiate and execute movements, is a key aspect of impaired motor performance in patients suffering from Parkinson's disease (PD). Once set in motion, kinetic function in PD is abnormally slow and reduced in amplitude. Furthermore, dynamic motor output of PD patients shows a disturbed temporal coordination, resulting in a set of characteristic movement irregularities (Sacks, 1999). Gait and speech of PD patients are often hastened, rapid alternating movements are difficult to perform, and motor synchronization to sensory stimuli is globally impaired. A candidate neuronal mechanism involved in these dysregulations of motor rhythmicity in PD patients may encompass pathological levels of oscillatory brain activity within coupled subcortical and cortical networks (Brown, 2003; Nagasaki et al., 1978).

A characteristic signature of ongoing neuronal activity in the dopamine-depleted motor circuitries of PD patients is abnormal coupling at beta frequencies (13–30 Hz). Beta activity is excessively synchronized within and between functionally interconnected nodes in the basal ganglia (BG), thalamus and cortex, eventually resulting in impaired motor function (Hutchison et al., 2004; Kühn et al., 2006; Little et al., 2012; Sharott et al., 2014). Both dopaminergic medication and deep brain stimulation of the subthalamic nucleus (STN-DBS) reduce beta-band coupling within and between structures of this functional loop in PD patients. At the same time, these neuromodulatory

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interventions restore physiological motor output, supporting the functional significance of beta oscillations for information processing in the motor domain (Engel and Fries, 2010; Jenkinson and Brown, 2011). Beyond the antikinetic effects of elevated beta-band activity in the resting brain state, their dynamic modulation is impaired in PD as well (Doyle et al., 2005). Impaired beta modulation may lead to deficient dynamic scaling and sequencing of complex sensorimotor processes such as gait (Singh et al., 2013), speech (Hebb et al., 2012) and repetitive movements (Joundi et al., 2013).

External sensory stimuli can temporarily ameliorate some of the motor disabilities of PD patients (Cunnington et al., 1995; Martin, 1967). As an example, rhythmic auditory stimulation (RAS) improves dysrhythmic locomotion and is frequently used to treat gait disturbances in advanced stages of PD (McIntosh et al., 1997). However, sensory facilitation by RAS depends on the stimulation frequency — with slower presentation rates being more effective than fast rhythms (Enzensberger and Fischer, 1996). Hitherto, little is known concerning the neural processing of RAS in PD patients. More specifically, BG-cortex circuits play a critical role modulating beta-band activity during synchronization tasks as timekeeper for movements (Bartolo et al., 2014; Rao et al., 1997; Teki, 2014), but it remains unknown how STN-DBS and dopaminergic medication influence the cortical response profile to RAS in the absence of overt movement.

As a first step, we re-addressed the question whether treatment with levodopa or STN-DBS induces significant changes in ongoing EEG activity focusing, in particular, on the beta-band. To this end, we analyzed the resting state EEG of patients with advanced PD before (DOPA-OFF versus DOPA-ON) and after STN-DBS surgery (OFF-DBS versus ON-DBS). In order to examine the specific influence of BG circuit modulation on rhythm-related auditory processing, we then explored the neurophysiological signatures of RAS in a passive listening paradigm with slow (≤2 Hz) and fast (≥4 Hz) stimulus presentation rates under these four experimental conditions. Since beta-oscillatory signals reflect timekeeping functions in healthy people (Fujioka et al., 2012), we hypothesized that RAS would reveal an altered beta-band response profile in patients with PD.

2. Material and methods

All statistical values are given as mean ± SD unless noted otherwise. Auditory evoked potential analysis of this dataset has been reported elsewhere (Gulberti et al., 2015).

2.1. Patients & control participants

The present investigation was conducted in agreement with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1967) and the local ethics committee approved the procedures. All participants provided written informed consent. Twelve patients (7 female, 5 male, mean age: 61 ± 6 years) with a diagnosis of advanced idiopathic PD (mean disease duration: 14 ± 3 years, Hoehn & Yahr stage: 3 ± 1; Hoehn and Yahr, 1967) and twelve healthy control persons matched in sex, age and education (8 female, 4 male, mean age: 65 ± 8 years) participated. All participants declared normal hearing and normal or corrected-to-normal vision. Patients underwent bilateral microelectrode-guided implantation of DBS electrodes in the STN. Pre-operatively, all PD patients showed a significant improvement of the motor-subscore (III) of the Unified Parkinson's Disease Rating Scale (Fahn et al., 1987) following intake of levodopa. The mean motor score after overnight withdrawal of anti-parkinsonian medication was 32 ± 12, while after intake of levodopa it was reduced to 18 ± 9 ($t(11) = -5.54$; $p = 0.0002$; paired t-test). This was a mean symptom improvement of 44%. Pre-operatively, the daily levodopa-equivalent dose was 1132 ± 420 mg. During the period of post-operative recordings, it was reduced to 663 ± 354 mg ($t(22) = 2.96$; $p = 0.0073$; paired t-test; conversion factors used for the calculation of levodopa equivalent daily dose after Tomlinson et al., 2010). Importantly, all patients demonstrated an adequate global intellectual capacity, when tested with the Mini-Mental Status Exam (Folstein et al., 1975; mean score: 29 ± 1) and the Mattis Dementia Rating Scale (Mattis, 1988; mean score: 143 ± 0.5). Furthermore, they fulfilled other inclusion criteria for STN-DBS, such as no structural alterations on magnetic resonance imaging (MRI), and no concomitant severe medical comorbidities. Further clinical details are summarized in Table 1.

2.2. Surgical procedures

For all patients DBS electrodes (model 3389, Medtronic, Minneapolis, MN, USA) and stimulators (Kinetra model 7428 in 7 patients and Activa PC model 37,601 in 5 patients, Medtronic, Minneapolis, MN, USA) were implanted at the Department of Neurosurgery at the University Medical Center Hamburg-Eppendorf, Germany. In short, an MRI-compatible Zamorano–Dujovny frame (Stryker Leibinger) was tightly secured with pins on the patient's head. Gadolinium-enhanced volumetric T1 MRI and T2-weighted spin echo MRI sequences were first acquired, and were then fused with computerized tomography scans by means of iPlan (Brainlab), a commercial treatment planning software. Through this procedure, both commissures, the STN-nigra complex and blood vessels could be delineated with high resolution. A reference line connecting the anterior and posterior commissure (AC–PC line) was then determined. The intended target coordinates for the STN were 11.5–12.5 mm from the midline, 1–2 mm behind the midcommissural point and 2 mm below the line connecting anterior and posterior commissure. For the surgical implantation of the electrodes, burr holes of 8–10 mm diameter were fashioned 1–3 cm anterior to the left and right coronal suture. Further details concerning the surgical procedure are reported in Hamel et al. (2003).

Successful placement of the implanted DBS electrodes in the region of the STN was assessed by intra-operative microelectrode recordings, by effective intra-operative macrostimulation, by stereotactic reconstruction of electrode contacts on post-operative stereotactic CT scans fused with pre-operative MRIs, and by a significant improvement in the post-operative UPDRS motor score in DOPA-OFF condition: ON-DBS (20 ± 8) vs. OFF-DBS (40 ± 10; $t(9) = -7.89$; $p < 0.0001$; paired t-test). Two patients were excluded from this paired t-test due to missing post-operative UPDRS scores. Post-operatively, none of the patients showed signs of accidental stimulation of fiber tracks running in the neighboring internal capsule or lemniscal radiation.

2.3. Protocol

The first experimental sessions took place 6 ± 5 days before the implantation of bilateral STN-DBS electrodes for treatment of PD, the second experimental sessions 5 ± 2 months following DBS surgery. In the pre-operative recording sessions, patients were assessed in (i) DOPA-ON and (ii) DOPA-OFF conditions. These two pre-operative recordings always took place on two subsequent days and the order in which the two conditions were recorded was counterbalanced. PD patients were tested after an overnight period of withdrawal from medication (DOPA-OFF condition). It is of note that all post-operative recordings also took place after overnight withdrawal of anti-parkinsonian medication on two different days. Post-operatively, the two experimental conditions were: (iii) ON-DBS, i.e., during bilateral therapeutic STN-DBS with high-frequencies (130–240 Hz) and (iv) OFF-DBS, i.e., with the DBS device switched off. For each subject, stimulation contacts, amplitude and pulse duration were the same as for therapeutic high-frequency stimulation (see Table 1). After switching off the therapeutic high-frequencies DBS, a period of time ≥25 min was elapsed before starting the recordings in the OFF-DBS condition. This period has previously been demonstrated to be long enough to induce a significant worsening of motor symptoms following

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