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Subthalamic oscillatory activity and connectivity during gait in Parkinson's disease

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ABSTRACT

Local field potentials (LFP) of the subthalamic nucleus (STN) recorded during walking may provide clues for determining the function of the STN during gait and also, may be used as biomarker to steer adaptive brain stimulation devices. Here, we present LFP recordings from an implanted sensing neurostimulator (Medtronic Activa PC + S) during walking and rest with and without stimulation in 10 patients with Parkinson's disease and electrodes placed bilaterally in the STN. We also present recordings from two of these patients recorded with externalized leads. We analyzed changes in overall frequency power, bilateral connectivity, high beta frequency oscillatory characteristics and gait-cycle related oscillatory activity. We report that deep brain stimulation improves gait parameters. High beta frequency power (20-30 Hz) and bilateral oscillatory connectivity are reduced during gait, while the attenuation of high beta power is absent during stimulation. Oscillatory characteristics are affected in a similar way. We describe a reduction in overall high beta burst amplitude and burst lifetimes during gait as compared to rest off stimulation. Investigating gait cycle related oscillatory dynamics, we found that alpha, beta and gamma frequency power is modulated in time during gait, locked to the gait cycle. We argue that these changes are related to movement induced artifacts and that these issues have important implications for similar research.

1. Introduction

Recordings of local field potentials (LFP) in the basal ganglia of patients with Parkinson's disease (PD) have demonstrated oscillations at several frequencies, of which the beta band has gained most attention (Stein and Bar-Gad, 2013). Although the functional and pathological role of (beta) oscillations are still debated (Espenhahn et al., 2017; Eusebio and Brown, 2009; Gross et al., 2005; Pfurtscheller et al., 1996; Raz et al., 1996), beta power has been shown to be correlated with akinetic-rigid symptoms (Hammond et al., 2007; Kühn et al., 2006b; Neumann et al., 2016) in human patients as well as in animal models of parkinsonism (Costa et al., 2006; Mallet et al., 2008; Sharott et al., 2005). Beta oscillations are also reported to be reduced in amplitude after levodopa intake and are attenuated by STN deep brain stimulation (DBS) in a stimulation intensity dependent manner (Kühn et al., 2008a, 2008b; Oswal et al., 2016; Quinn et al., 2015; Trager et al., 2016; Weiss et al., 2015).

Local field potentials are investigated as biomarkers for adaptive closed-loop stimulation in PD (Cagnan et al., 2013; Johnson et al., 2016; Little et al., 2013a; Piña-Fuentes et al., 2017; Tinkhauser et al., 2017a). When considering oscillatory activity as a feedback signal, it is important to understand its functional role as well as its contributions to the genesis of clinical symptoms. Cortical as well as subcortical beta has been shown to be involved in a series of neural processes underlying cognitive functioning and motor behavior (Frank, 2006; Frank et al., 2007; Herz et al., 2017a; Meijer et al., 2016; Tan et al., 2014a, 2014b; Te Woerd et al., 2015; Williams et al., 2005; Zavala et al., 2013). Beta modulations are reported to be correlated with decision thresholds and reaction times as well as with grip force (Hell et al., 2018; Herz et al., 2017b; Tan et al., 2016). Beta is decreased in amplitude during motor imagery (Kühn et al., 2006a; Marceglia et al., 2009) and movements (Joundi et al., 2013; Kühn et al., 2004; Litvak et al., 2012), while this mechanism probably fails as bradykinesia increases (Steiner et al., 2017). While beta power is attenuated prior, during and shortly after movements followed by a rebound after movement termination, low frequencies in the theta range and gamma frequencies exhibit increases at movement onset (Cassidy et al., 2002; Chung et al., 2001; Foffani et al., 2005, 2003; Fogelson et al., 2005; Kane et al., 2009; Özkurt et al., 2011; Priori et al., 2002; Tan et al., 2014a, 2014b).

Reports of beta band suppression during movement are ubiquitous,

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but investigations of the modulation of beta during gait are rare and conflicting (Quinn et al., 2015; Singh et al., 2013; Storzer et al., 2017). Quinn et al. report that subthalamic beta power was relatively similar during lying, sitting, standing, and during forward walking and that akinetic-rigid PD subjects tended to exhibit decreased beta power when walking, while tremor dominant subjects did not. Storzer et al. report, that patients without freezing of gait show a suppression of beta power in both bicycling and walking, while this suppression was stronger for bicycling. Both Singh and Storzer report a movement-induced, narrowband power increase in the low beta band during walking in patients with freezing of gait, time-locked to the onset of gait.

In this study, we used a sensing neurostimulator (Activa PC + S®, Medtronic, plc.) connected to electrodes implanted bilaterally in the STN's of 10 patients with PD as well as recordings from externalized leads in two of the same patients. We investigated subthalamic oscillatory activity during continuous gait, while also comparing neural activity during gait and sitting and standing rest. Recordings were made off stimulation, with stimulation at half the clinical most beneficiary amplitude and stimulation with full amplitude. Kinematic parameters were recorded with inertial sensor units and subsequently analyzed in parallel to the electrophysiological activity to reconstruct gait-cycle related oscillatory activity. Our main aim was to discuss whether and how subthalamic frequency content changes during walking across the gait cycle as compared to rest.

2. Material and methods

2.1. Patients, surgery, electrode localization

Ten participants with a mean age of 61.7 years (SEM ± 2.1), including 9 males and one female patient with Parkinson's disease (PD) took part in this study and gave their written informed consent. The protocol was approved by the Ethics Committee of the medical faculty of the University of Munich. Clinical details of all participants are provided in Table 1. All patients underwent implantation of DBS leads (model 3389; Medtronic Neurological Division, MN, USA) with 4 ring electrodes in the left and right STN for the treatment of advanced Parkinsonism at the Department of Neurosurgery at the hospital of the University of Munich. Initial stereotactic coordinates were 12 mm lateral, 3 mm posterior and 4 mm below the midpoint of the AC-PC line. Coordinates were adjusted by direct visualization of the STN on individual pre-operative T2-weighted MRI scans. Intraoperative single cell recordings and macrostimulation guided the final placement of the electrode leads. The exact position of the DBS electrodes in relation to the subthalamic target structures were determined based on the pre-operative T2-weighted MRI and postoperative CT scans, using the Lead DBS toolbox (Horn and Kühn, 2015) and 3DSlicer software (www.slicer.org). MRT and CT were aligned manually using 3DSlicer software, co-registered using a two-stage linear registration (rigid followed by affine) as implemented in Advanced Normalization Tools (Avants et al., 2008) and normalized to MNI space (MNI ICBM Nonlinear 2009b template), (Fonov et al., 2011). To visualize the STN, we used an atlas to outline the STN and its putative subdivisions, the motor, the associative and the limbic area (Accolla et al., 2014).

2.2. LFP recordings and kinematic measurements

In all patients, the leads were connected to the implanted sensing neurostimulator (Activa PC + S®, Medtronic, plc.) to record LFP's bipolarly from the electrode contact above and below the single negative stimulation contact, colored in light red (Fig. 1). The stimulation contact was chosen according to best clinical outcome. All LFP data were sampled at 422 Hz. We additionally recorded LFP data from externalized leads during the same conditions in two of these patients before implantation of the neurostimulator. Here, sutbhalamic LFP were recorded from the four contacts of the implanted stimulation electrodes in bipolar fashion using Brain Vision Recorder software and Brainamp amplifiers (Brain Products GmbH, Gilching, Germany). The bipolar pair containing the later stimulation electrode was chosen for evaluation. The experiments with externalized recording were performed two days after the initial surgery and the experiments with internal sensing equipment were performed at least 2 months after initial programming on the same or on consecutive days within the first year after implantation. We had to exclude recordings from one subject, as the LFP's were severely contaminated with ECG artifacts.

Movement parameters were recorded using inertial sensor units. We used a research prototype measurement and recording system with one analog gyroscope (IDG500, Invensense, Sunnyvale, CA, USA) and two analog accelerometers (ADXL335, Analog devices, Norwood, MA, USA) on each shank and each thigh to record kinematic profiles. Data were collected by a microprocessor (ATXMEGA 128, Atmel, San Jose, CA, USA) with 16 analog-digital converters (12-bit) connected to an SD-card for data storage. Data from the sensors were collected at 200 Hz. Synchronization of gait and LFP data was achieved by a transcutaneous electric nerve stimulator (TENS) device which was triggered at the beginning and before the end of the recording by the gait recording processor and delivered electric impulses between right mastoid and left shoulder which were recorded by the neurostimulator.

2.3. Task design

LFPs were recorded during sitting (2 min), standing rest (2 min) and free walking (approx. 125 m) along a hallway. Experiments were recorded following overnight withdrawal of dopaminergic medication

Table 1
Clinical details.
Ten patients with Parkinson's disease (1 female, mean age 61.7 ± 2.1 years; disease duration 9.8 ± 0.9 years) were studied 1 month – 1 year after DBS surgery.

Case	Age	Gender	Disease duration	Main symptoms	UPDRS-III ON/OFF	Tremor ON/OFF	Rigor ON/OFF	Gait ON/OFF	Lateralization Right/left
1	66	m	9	Equivalent	51/78	0/5	5/10	2/3	25/20
2	64	m	16	AR	23/73	0/0	3/9	1/3	23/20
3	61	m	8	TD	17/44	11/24	1/5	1/2	16/10
4	54	f	8	Equivalent	10/27	3/6	1/5	1/1	13/6
5	71	m	12	Equivalent	22/38	9/10	4/5	1/1	11/14
6	53	m	12	Equivalent	4/27	0/6	0/5	1/1	13/6
7	70	m	8	AR	23/40	0/0	7/11	1/2	15/15
8	55	m	7	Equivalent	15/33	4/10	3/8	1/2	3/12
9	66	m	11	Equivalent	26/75	6/18	1/12	2/2	7/11
10	57	m	7	AR	30/53	0/0	5/13	1/1	10/9

Evaluation was performed OFF medication after overnight withdrawal from dopaminergic medication in random order (ON/OFF DBS); Tremor score reflects the total score on all ratings in items 15–18 in the UPDRS III, rigor score reflects all ratings on item 3 and gait item 10, lateralization score reflects all scores that allow for the assessment of lateralization of Parkinsonian symptoms, including item 3–8, 15–17.