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Subthalamic stimulation, oscillatory activity and connectivity reveal functional role of STN and network mechanisms during decision making under conflict

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ABSTRACT

Inhibitory control is an important executive function that is necessary to suppress premature actions and to block interference from irrelevant stimuli. Current experimental studies and models highlight proactive and reactive mechanisms and claim several cortical and subcortical structures to be involved in response inhibition. However, the involved structures, network mechanisms and the behavioral relevance of the underlying neural activity remain debated. We report cortical EEG and invasive subthalamic local field potential recordings from a fully implanted sensing neurostimulator in Parkinson's patients during a stimulus- and response conflict task with and without deep brain stimulation (DBS). DBS made reaction times faster overall while leaving the effects of conflict intact: this lack of any effect on conflict may have been inherent to our task encouraging a high level of proactive inhibition. Drift diffusion modelling hints that DBS influences decision thresholds and drift rates are modulated by stimulus conflict. Both cortical EEG and subthalamic (STN) LFP oscillations reflected reaction times (RT). With these results, we provide a different interpretation of previously conflict-related oscillations in the STN and suggest that the STN implements a general task-specific decision threshold. The timecourse and topography of subthalamic-cortical oscillatory connectivity suggest the involvement of motor, frontal midline and posterior regions in a larger network with complementary functionality, oscillatory mechanisms and structures. While beta oscillations are functionally associated with motor cortical-subthalamic connectivity, low frequency oscillations reveal a subthalamic-frontal-posterior network. With our results, we suggest that proactive as well as reactive mechanisms and structures are involved in implementing a task-related dynamic inhibitory signal. We propose that motor and executive control networks with complementary oscillatory mechanisms are tonically active, react to stimuli and release inhibition at the response when uncertainty is resolved and return to their default state afterwards.

Introduction

Inhibitory control is a vital executive function that is needed to suppress premature actions and to block interference from irrelevant stimuli. Inhibitory control is impaired in a number of neuropsychiatric and neurological disorders and is associated with disrupted neural activity in the cortico-striatal circuitry (Antonelli et al., 2011; Lipszyc and Schachar, 2010; Richardson, 2008; Zamboni et al., 2008). Computational models as well as experimental studies in humans and primates highlight several cortical regions, particularly frontal and parietal cortices (Botvinick et al., 2004; Cohen and Ridderinkhof, 2013; Liston et al., 2006; Zavala et al., 2016) and subcortical structures, especially the basal ganglia, in inhibitory control (Aron et al., 2007; Benis et al., 2014; Cavanagh et al., 2011; Frank, 2006; Zaghloul et al., 2012). Optimal action selection in conflict situations with competing or uncertain stimulus and response relations is proposed to rely on an intact hyperdirect pathway and STN (for an overview of cortico-basal ganglia-thalamo-cortical pathways and structures, see (Jahanshahi et al., 2015)). By inhibiting the pallidial-thalamic-cortical loop, the STN is thought to suspend responses until sufficient information has been integrated and uncertainty is

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resolved (Bogacz and Gurney, 2007; Frank et al., 2007; Herz et al., 2017).

Electrophysiological recordings during inhibitory processes have demonstrated conflict and inhibition related oscillatory activity and connectivity within cortical and subcortical networks involved in reactive as well as proactive inhibition (Benis et al., 2014; Martínez-Selva et al., 2006; Zavala et al., 2015a, 2015b, 2014). Increases in cortical and subthalamic low frequency oscillations including delta and theta frequencies (2–8 Hz) and decreases in alpha/beta frequency (10–30 Hz) power have been shown to be involved in inhibitory processes and are reported to be correlated with conflict (Bastin et al., 2014; Boulinguez et al., 2009; Cavanagh and Frank, 2014; Kühn et al., 2004; Leventhal et al., 2012; Swann et al., 2012). Coherent low frequency activity has been shown between frontal midline structures and the STN (Herz et al., 2017) and beta oscillatory coupling is reported to be most prominent between STN and motor cortical structures (Accolla et al., 2016).

There are two major theoretical mechanisms discussed for response inhibition: proactive and reactive inhibitory control (Martínez-Selva et al., 2006). In the reactive model established by Frank et al. (Frank, 2006), response inhibition is implemented as response selection processes evolve. The global inhibitory signal is described as reactive in nature and is triggered by the stimulus conflict (Aron et al., 2007). In contrast, the "proactive inhibition" theory assumes that inhibition is the default mode of an executive control network responsible for basic preparatory processes, which prevents automatic responses to irrelevant signals by maintaining tonic inhibition over response processes until uncertainty is resolved (Jaffard et al., 2008).

Both theories assume a global modulatory signal suppressing all responses, rather than modulating the execution of any particular response and postulate attenuation of thalamocortical activity, with different cortical structures involved. The reactive model claims specific changes in primary motor cortex (PMC), pre-supplementary motor area (pre-SMA), the anterior cingulate cortex (ACC), and the inferior frontal gyrus (IFG) (Frank, 2006). The "proactive inhibition" hypothesis is linked to possible activation changes in medial prefrontal cortex (mPFC), Precuneus, posterior cingulate cortex (PCC), and inferior parietal cortex (IPC) (Ballanger et al., 2009; Boulinguez et al., 2009; Jaffard et al., 2008). Hence, while both models claim frontal structures to be involved, only the proactive model invokes posterior structures, which have been shown to be important for movement initiation and planning (Mattingley et al., 1998; Scherberger et al., 2005).

To elucidate the functional role of the STN in cognitive control, we collected subthalamic local field potentials (LFP) from a fully implanted sensing neurostimulator and parallel EEG recordings in patients with Parkinson's disease (PD) during a modified version of an Eriksen Flanker task inducing different levels of conflict (Van Veen and Carter, 2005). We measured whether the STN oscillatory signal reflects reaction times and stimulus conflict, whether STN DBS influences conflict processing, and explored the timecourse and topography of oscillatory connectivity between cortex and STN. Electrophysiological results are presented only for recordings without DBS.

Material and methods

Patients, surgery, electrode localization and recordings

Six participants with a mean age of 66 years (SEM ± 1.5), including 5 male 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 Ludwig Maximilian 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 LMU 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 preoperative 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 preoperative 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 Normlization 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). This allowed us to confirm stimulation and recording sites of all patients (Fig. 2 A). All but one stimulation contacts were considered to be placed within the motor STN (with distances between each contact center and nearest atlas voxel center below 0.5 mm). One came close with 0.6 mm and overall, a mean distance of 0.15 mm (SEM ± 0.05) between each stimulation contact center and nearest atlas voxel center in the motor STN was found. In all patients, the leads were connected to the implanted sensing neurostimulator (Activa PC + S, Medtronic) to record LFP bipolarly from the electrode contact above and below the single negative stimulation contact, colored in light red in Fig. 2 A. All LFP data were sampled at 422 Hz. Scalp EEG data were recorded with a 64-electrode active cap (actiCAP) with active shielding and amplified (BrainAmp DC amplifiers) using the BrainVision Recorder software (Brain Products, Munich, Germany). Two additional electrodes were placed on the superior orbit and on the outer canthus of the right eye to detect vertical and horizontal eye movements. EEG was referenced to the FCz electrode, grounded at AFz and sampled at 1000 Hz. Impedances were kept below 5 kΩ. The data was resampled to 422 Hz to match the sampling frequency of the implanted sensing neurostimulator and re-referenced to the average across all electrodes. Data traces from the sensing neurostimulator and scalp EEG recordings were synchronized using a transcutaneous electric nerve stimulator, delivering single pulses emitted via two electrodes at the scalp, producing a marked jump in the LFP and EEG signal. Experiments were recorded following overnight withdrawal of dopaminergic medication. Participants completed the decision-making task with and without DBS. Stimulation amplitudes were chosen according to the best clinical outcome (mean constant voltage: 2.71 ± 0.15 mV), stimulation frequency was 140 Hz and pulse duration was 60 μs for all recordings. The experiments were performed at least 2 months after initial programming on the same or on consecutive days within the first year after implantation.

Table 1
Clinical details. Six patients with Parkinson's disease (1 female, mean age 66.1 ± 1.5 years; disease duration 10.5 ± 1.4 years) were studied 1 month–1 year after DBS surgery.

Case	Age	Gender	Disease duration	Main symptoms	UPDRS-III ON/OFF
1	54	f	9	Equivalent	10/27
2	71	m	12	Equivalent	22/38
3	53	m	12	Equivalent	4/27
4	70	m	8	Akinetic-rigid	23/40
5	55	m	7	Equivalent	15/33
6	57	m	10	Akinetic-rigid	30/53

*Evaluation was performed OFF medication after overnight withdrawal from dopaminergic medication in random order (ON/OFF Stimulation).

Task design

Participants were seated comfortable in a dimly lit, experimental room 60 cm in front of a 21-inch TFT computer screen. The Python-based toolbox Psychopy (Peirce, 2007) was used for instructions and presentation of visual stimuli and for recording reaction times (RT). Participants

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