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The impact of Parkinson's disease and subthalamic deep brain stimulation on reward processing

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ABSTRACT

Background: Due to its position in cortico-subthalamic and cortico-striatal pathways, the subthalamic nucleus (STN) is considered to play a crucial role not only in motor, but also in cognitive and motivational functions. In the present study we aimed to characterize how different aspects of reward processing are affected by disease and deep brain stimulation of the STN (DBS-STN) in patients with idiopathic Parkinson's disease (PD).
Methods: We compared 33 PD patients treated with DBS-STN under best medical treatment (DBS-on, medication-on) to 33 PD patients without DBS, but optimized pharmacological treatment and 34 age-matched healthy controls. We then investigated DBS-STN effects using a postoperative stimulation-on/ -off design. The task set included a delay discounting task, a task to assess changes in incentive salience attribution, and the Iowa Gambling Task.
Results: The presence of PD was associated with increased incentive salience attribution and devaluation of delayed rewards. Acute DBS-STN increased risky choices in the Iowa Gambling Task under DBS-on condition, but did not further affect incentive salience attribution or the evaluation of delayed rewards.
Conclusion: Findings indicate that acute DBS-STN affects specific aspects of reward processing, including the weighting of gains and losses, while larger-scale effects of disease or medication are predominant in others reward-related functions.

1. Introduction

Reward processing comprises perception, salience attribution, and reaction to stimuli that signal reward or punishment. Conveyed via learning mechanisms, it facilitates behavioral adaption to positive or negative feedback. The present study aimed to characterize different aspects of reward processing as a function of disease and deep brain stimulation of the subthalamic nucleus (DBS-STN) in patients with idiopathic Parkinson's disease (PD).

Via the cortico-subthalamic and cortico-striatal pathways, the STN receives direct and indirect cortical information not only from motor, but also prefrontal, orbitofrontal and anterior cingulate cortices (Haynes and Haber, 2013), and is therefore considered to affect motor, as well as cognitive and motivational functions (Temel et al., 2005). A prominent functional model of the STN proposes that it modulates the timing of a response, preventing premature responding especially under conflicting motivational response options (Frank, 2006). In line with this, STN lesions in rats result in an increased motor impulsivity or impulsive action (Baunez et al., 1995; Uslaner and Robinson, 2006). Of note, in rodents opposite effects have been reported for impulsive choice, a form of impulsivity that refers to impulsivity in decision-making processes (Winstanley et al., 2006) rather than to behavioral disinhibition and that is commonly assessed using delay discounting

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tasks. Having the choice between a soon, but small, or a larger, but delayed reward, rats with STN lesions preferred the delayed option, indicating a decreased impulsive choice (Uslaner and Robinson, 2006; Winstanley et al., 2005). It has been discussed that this effect is caused by an increased incentive salience of the delayed reward (Uslaner and Robinson, 2006). While to date there are no studies on the influence of DBS-STN on delay discounting in humans, the influence of PD has been investigated, revealing a complex interplay between disease effect, dopaminergic medication and individual predispositions: while patients with impulsive symptoms and dopaminergic medication showed increased discounting rates, this effect was not as clear in patients without impulsive symptoms and without medication (Housden et al., 2010; Leroi et al., 2013; Milenkova et al., 2011; Voon et al., 2010). Notably, no evidence on decreased discounting rates in PD patients is available.

One explanation for a shift to a more impulsive choice pattern might be found in an altered incentive value attribution. The incentive salience of an object describes how much we "want" it, a quality that can be differentiated from how we react to that object that is from how much we "like" it (Berridge and Robinson, 1998). In order to see whether incentive value attribution is affected in patients with PD and DBS-STN, we included a task in which participants were asked to ascribe a monetary value to certain everyday objects.

If DBS-STN affects the reward system by altering valuation processes, stimulation should also affect the performance in an Iowa Gambling Task (IGT), a decision-making task requiring the simultaneous weighting of gains and losses in order to develop an optimal gambling strategy in the long run. For PD patients without DBS, decreased performance with more risky choices has repeatedly been reported (Kobayakawa et al., 2010, 2008; Mimura et al., 2006; Pagonabarraga et al., 2007; Perretta et al., 2005). Several findings indicate that this impairment is related to the intake of dopaminergic medication: it is stronger for PD patients that exhibit pathologic gambling (considered as hyper-dopaminergic symptom) (Rossi et al., 2010) and has not been found in PD patients with symptoms of apathy (considered as hypo-dopaminergic symptom) (Martínez-Horta et al., 2013) and in de novo PD patients that do not have dopaminergic medication yet (Poletti et al., 2010). However, the data are more inconsistent concerning the effect of acute DBS-STN in PD: while some studies did not find pronounced effects on the overall performance in the IGT (Castrioto et al., 2015; Czernecki et al., 2005; Pinkhardt et al., 2012), increased risky choices particularly during the last block of the experiment under DBS-on condition have been reported (Oyama et al., 2011).

Delineating disease-related changes from stimulation effects, we compared 33 PD patients with DBS-STN (PD-DBS) under best medical treatment (DBS-on, medication-on) to 33 PD patients without DBS, but optimized pharmacological treatment (PD-nonDBS) and 34 age-matched healthy controls (HC). Based on previous evidence we expected stronger devaluation of delayed rewards in a delay discounting task (Milenkova et al., 2011) and impaired performance in the IGT (Mimura et al., 2006; Perretta et al., 2005) for PD patients. Regarding DBS-STN effects, we hypothesized weaker devaluation of delayed rewards (Uslaner and Robinson, 2006; Winstanley et al., 2005), and increased incentive salience attribution (Serranová et al., 2011) under DBS-on condition, as well as impaired IGT performance (Oyama et al., 2011).

2. Methods

2.1. Sample

PD patients were diagnosed with idiopathic PD according to UK Brain Bank criteria (Litvan et al., 2003). PD-DBS had a stable postoperative condition of at least three months after surgery. Exclusion criteria comprised for all subjects significant cognitive deficits (Mini-Mental State Examination (MMSE) ≤ 24, (Folstein et al., 1975)), for all PD patients the presence of other neurological and impulse control disorders (based on expert opinion of the treating neurologist); for PD-DBS patients the non-tolerance of a transient deactivation of DBS electrodes and for HC presence of any neurological or current (past 12-months) psychiatric disorders (DSM-IV-TR criteria (Wittchen and Pfister, 1997)). HC and PD-nonDBS were matched to PD-DBS for gender, age and education.

2.2. Stereotactical electrode implantation procedure

Trajectories for the STN were planned on the basis of the following coordinates on both hemispheres with individual adjustment to target points visible in T2-sequences: x (lateral distance from the midline)$=12$, y (anteroposterior distance from the AC)$=3$, and z (height relative to the AC line)$=4$. Surgery was done under local anesthesia using the ZD stereotactic system. The target point was verified during the surgery by microelectrode recording (ISIS MER System, Inomed) and intraoperative neurological testing of stimulation effects. Electrodes (Medtronic 3389) were implanted and leads were fixed at the burr hole. The pulse generator (Activa PC Modell 37601; Medtronic) was implanted infraclavicularly or abdominally (according to patient preference) and activated.

2.3. Procedure

Testing took place on two different testing days. Each of them lasted 2–3 h and the minimal time interval between both days was 2 weeks. PD-DBS completed one session under DBS-on/medication-on and the other under DBS-off/medication-on condition (counterbalanced order). PD-nonDBS completed both sessions under medication-on and also for HC were both visits identical. To control for learning effects, clinical and healthy control data were matched to the respective PD-DBS session (e.g. if PD-DBS session 1 was "DBS-on" stimulation, session 1 data of the corresponding controls were matched to "DBS-on" and session 2 data to "DBS-off"). On both visits participants completed a delay discounting task, a task on the Incentive Value of Everyday Objects and the Iowa Gambling Task. Motor symptoms were assessed using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) (Movement Disorder Society Task Force, 2003). In order to control for phasic effects of dopamine medication, assessment time was adjusted to the individual dosing regimen, so that all patients took their regular intake of medication at the beginning of each test session. After modulation of stimulation electrodes, a waiting period of 1 h was applied (also for HC) before starting the tasks.

On the first visit all participants were furthermore screened for neuropsychiatric symptoms using the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), the Apathy Evaluation Scale (Clinician version, AES-C) (Marin et al., 1991) and the Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995). PD patients also completed the Questionnaire for Impulsive–Compulsive Disorders in Parkinson's Disease (QUIP) (Weintraub et al., 2009). All questionnaires were completed before manipulation of the electrodes. The protocol was approved by the ethics committee of the Technische Universität Dresden and all participants gave their written informed consent.