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Oscillatory subthalamic nucleus activity is modulated by dopamine during emotional processing in Parkinson's disease

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ABSTRACT

Dopaminergic denervation in Parkinson's disease (PD) leads to motor deficits but also depression, lack of motivation and apathy. These symptoms can be reversed by dopaminergic treatment, which may even lead to an increased hedonic tone in some patients with PD. Here, we tested the effects of dopamine on emotional processing as indexed by changes in local field potential (LFP) activity of the subthalamic nucleus (STN) in 28 PD patients undergoing deep brain stimulation. LFP activity from the STN was recorded after the administration of levodopa (ON group) or after overnight withdrawal of medication (OFF group) during presentation of an emotional picture-viewing task. Neutral and emotionally arousing pleasant and unpleasant stimuli were chosen from the International Affective Picture System. We found a double dissociation of the alpha band response depending on dopamine state and stimulus valence: dopamine enhanced the processing of pleasant stimuli, while activation during unpleasant stimuli was reduced, as indexed by the degree of desynchronization in the alpha frequency band. This pattern was reversed in the OFF state and more pronounced in the subgroup of non-depressed PD patients. Further, we found an early gamma band increase with unpleasant stimuli that occurred when ON but not OFF medication and was correlated with stimulus arousal. The late STN alpha band decrease is thought to represent active processing of sensory information. Our findings support the idea that dopamine enhances approach-related processes during late stimulus evaluation in PD. The early gamma band response may represent local encoding of increased attention, which varies as a function of stimulus arousal.

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1. Introduction

Intracranial recordings of oscillatory local field potential (LFP) activity from basal ganglia (BG) nuclei in patients undergoing deep brain stimulation (DBS) have largely contributed to a better understanding of the pathophysiology of movement disorders such as Parkinson's disease (PD) (Jenkinson & Brown, 2011). So far, BG activity has best been characterized in PD patients where excessively synchronized oscillations in the beta frequency range (13–35 Hz) have been related to abnormal motor processing (Hammond, Bergman, & Brown, 2007). Only recently, a functional role of the BG in human emotions has also been recognized (Temel, Blokland, Steinbusch, & Visser-Vandewalle, 2005). The subthalamic nucleus (STN) occupies a strategic position in the parallel cortex-BG loops (Alexander, Crutcher, & DeLong, 1990), receiving input via the hyperdirect pathway from motor and non-motor cortical areas (Nambu, Tokuno, & Takada, 2002). Accordingly, the STN comprises cognitive (ventral), emotional (medial) and motor (dorsal) sub-territories (Lambert et al., 2012; Parent & Hazrati, 1995). Studies examining neuronal oscillatory patterns of BG non-motor activity (for review see Marceglia, Fumagalli, & Priori, 2011; Peron, Fruhholz, Verin, & Grandjean, 2013) demonstrated a modulation of STN alpha (8–12 Hz) activity during the perception and processing of limbic information (Kühn et al., 2005) and enhanced low frequency STN activity (<10 Hz) in PD patients with impulse control disorder (Rodriguez-Oroz et al., 2011) and during conflictual decisions (Cavanagh et al., 2011; Fumagalli et al., 2011). Correspondingly, coupling of STN to non-motor cortical areas occurs in the alpha band while STN beta oscillations are coupled to motor cortical areas in PD (Litvak, Jha, et al., 2011), suggesting that non-motor processing may be indexed by modulation of low (5–13 Hz) frequency activity. It has been hypothesized that the STN processes the behavioral relevance of environmental cues (Sauleau et al., 2009) and modulates emotional processes independent from their modalities in order to modify upcoming actions (Peron et al., 2013).

Dopamine enhances motivational behavior (Wise, 2004; Witt et al., 2006) and the lack of dopamine is associated with reduced hedonic tone, depression and apathy in PD patients (Chaudhuri & Schapira, 2009; Remy, Doder, Lees, Turjanski, & Brooks, 2005), which is associated with the dopaminergic denervation of mesolimbic projections (Thobois et al., 2010). Similarly, pharmacological modulation of striatal dopamine levels in healthy humans results in euphoric or dysphoric changes with increased or decreased dopaminergic stimulation, respectively (Drevets et al., 2001; Vollm et al., 2004; Newton, Ling, Kalechstein, Uslaner, & Tervo, 2001). Furthermore, recognition of emotional facial expressions (EFE) or decoding of emotional prosody has been shown to be reduced in PD patients compared to healthy controls (for review see Gray & Tickle-Degnen, 2010).

So far, neuronal correlates of dopamine-induced modulation of emotional processing in PD are largely unknown. In our previous work, we have demonstrated that the extent of the alpha band desynchronization in the STN area correlated with the individual rating of stimulus valence (Brücke et al., 2007) and was influenced by the severity of depressive symptoms in PD patients (Huebl et al., 2011). These studies have been performed during continuous dopaminergic treatment in order to reflect a state as normal as possible. In the current study, we aimed to determine the influence of dopamine on emotional processing as indexed by changes in subthalamic oscillatory activity in PD patients. To this end, we compared changes in STN oscillatory activity during presentation of emotionally salient stimuli in two groups of PD patients ON and OFF dopaminergic treatment. Based on clinical observations, we hypothesize that hypodopaminergic states, which are commonly associated with apathy or anhedonia, are reflected by an attenuated alpha-event-related desynchronization ('alpha-ERD') to pleasant stimuli, whereas hyperdopaminergic states lead to an enhanced alpha-ERD.

2. Materials and methods

2.1. Patients and surgery

In the present study, we included 28 consecutive patients [age 62 ± 7 (mean ± standard deviation – SD) years; 10 women] with a diagnosis of idiopathic PD (duration of disease 11 ± 5 years) who had undergone functional stereotactic neurosurgery for subthalamic DBS. All patients provided written informed consent, and all measures taken during the study were approved by the local ethics committees in accordance with the declaration of Helsinki. Patient demographics and clinical and medical details are provided in Table 1. Major cognitive or affective disturbances were ruled out prior to surgery by appropriate neuropsychological (Mini Mental State Exam >26) and neuropsychiatric evaluations (Beck depression inventory – BDI <24). During the initial post-operative period with onset of continuous DBS, five of the 28 patients developed affective disturbances, namely hypomanic (cases 23, 25) and acute depressive (cases 3, 22) episodes or panic attacks (case 3) and emotional lability (15), which were resolved with long-term adjustment of stimulation parameters and dopaminergic therapy without specific further treatment (except for case 3, who needed additional antidepressant medication).

All patients were bilaterally implanted using model 3389 quadripolar DBS electrodes (Medtronic, Minneapolis, MN, USA) in the STN. Electrode contacts were numbered from 0 (most ventral) to 3 (most dorsal). Intended target coordinates for contact 0 were 11.5 mm lateral from the midline, 2.5 mm behind the midcommissural point, and 4.5 mm below the intercommissural line. Using direct visualization of the STN, the initial target coordinates were adjusted to the anatomical findings of the patient's individual brain. Intra-operative microelectrode recordings and macro-stimulation were performed in all patients to obtain further information on electrode position. Electrode placement was verified on the post-operative magnetic resonance imaging (MRI) (except for cases 13 and 18 from Vienna), using a combination of a probabilistic atlas derived from the Montreal Neurological Institute (MNI) stereotactic space with a recently digitized version of the Morel Stereotactic Atlas of