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Chronic stress-like syndrome as a consequence of medial site subthalamic stimulation in Parkinson's disease

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Abstract Considering the functional organization of the subthalamic nucleus (STN), we hypothesized that subthalamic deep brain stimulation (STN-DBS) in Parkinson's disease might have a differential impact on the hypothalamic-pituitary-adrenal axis in relation to the position of active stimulating contact within the STN. In addition, we searched for any STN-DBS-related morning plasma cortisol changes in association with postoperative anxiety and weight gain. A plasma cortisol measurement was performed on the day of initiation of bilateral STN-DBS and repeated after 1 and 17 months in twenty patients with advanced Parkinson's disease. The body weight change and anxiety scores following the implantation were assessed as well. The electrode positions in the STN were determined on T1-weighted magnetic resonance images. After initiation of stimulation, cortisol levels significantly decreased and the cortisol changes after 1 and 17 months strongly correlated with the position of active contact in the subthalamic area. Patients with at least one contact located more medially in the STN experienced a significantly greater decrease of cortisol than those with one or both active contacts more laterally. Furthermore, the lower cortisol levels were strongly associated with higher trait anxiety and

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weight gain. These changes mimicked the effects of chronic stress and suggest the disturbing impact of STN-DBS on limbic and motivational systems.

1. Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is currently recognized as a standard and highly effective method for the treatment of motor manifestations of advanced Parkinson's disease (PD). Besides motor improvement, non-motor effects of STN-DBS have been reported, such as weight gain and various cognitive, emotional or motivational disturbances (Peron et al., 2013; Serranova et al., 2011). These observations are consistent with research indicating that the STN serves as an important integrative structure for both motor and limbic processing (Baunez et al., 2011; Haegelen et al., 2009). Furthermore, the clinical effects of stimulation have been shown to depend on the position of the active electrode within the STN in a manner that reflects the functional organization and connectivity of the STN (Herzog et al., 2004). Accordingly, we have observed that the degree of weight gain as well as motor improvement is related to the position of stimulating contact in the mediolateral direction within the subthalamic area, respectively (Ruzicka et al., 2012b).

Extensive research in recent years has further revealed the very close clinical and neurobiological relationship among decision-making, body-weight regulation, the reward system and fear-stress circuits controlling the hypothalamic-pituitary-adrenal (HPA) axis (Dallman, 2010; Davis et al., 2004; Tryon et al., 2013; Volkow et al., 2012). Nevertheless, while weight gain following STN-DBS and its putative underlying mechanisms have been extensively reported and debated in the literature (Kistner et al., 2014; Novakova et al., 2007; Rieu et al., 2011; Ruzicka et al., 2012a), there have been few studies, with mixed findings, examining the effect of DBS on the HPA axis, stress and anxiety (Chang et al., 2012; de Koning et al., 2013; Novakova et al., 2007; Seifried et al., 2013). As we have previously observed a persistent decrease of morning plasma cortisol with the onset of chronic stimulation (Novakova et al., 2007; Ruzicka et al., 2012a), we elected to further investigate possible impact of STN-DBS on the endocrine system.

Considering the spatially distributed organization of the STN (Lambert et al., 2012), the primary aim of this study was to assess whether changes of morning plasma cortisol levels depend on the position of an active electrode in the STN, which would corroborate the heterogeneity of this nucleus and confirm the impact of DBS on the HPA axis. To the best of our knowledge, hormonal levels with respect to the position of the active implanted electrode have never been studied before. As STN-DBS may also influence the HPA axis indirectly via the fear-stress circuits of the limbic system, we hypothesized that decreased DBS-related cortisol should be accompanied by increased anxiety; a relationship previously conceptualized as a state of chronic fear and stress (Davis et al., 2010). Based on current knowledge of close association between anxiety disorders and overweight habitus (Gariepy et al., 2010; Perkonigg et al., 2009), we further hypothesized that cortisol alterations and anxiety may be associated with DBS-related weight gain.

2. Materials and methods

2.1. Subjects

Twenty patients with advanced PD (6 women, 14 men; mean age 56.6 ± (SD) 5.8 years; disease duration 13.2 ± 4.5 years) selected for treatment with STN-DBS were included in the present study. All patients were diagnosed with idiopathic PD based on the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria for Parkinson's Disease (Hughes et al., 2002). Patient demographic and clinical data are summarized in Table 1 and in our previous publication (Ruzicka et al., 2012b). Patients with dementia and/or severe depression were excluded on the basis of psychiatric examination and neuropsychological testing (Mattis Dementia Rating Scale score $\leq$ 123, Beck Depression Inventory Second Edition score of $\geq$30). All patients provided written, informed consent for participation in the study and the study was approved by the Ethics Committee of the General University Hospital in Prague, Czech Republic.

2.2. Surgical procedure and postoperative management

Bilateral DBS electrode implantation (model 3389, Medtronic, Minneapolis, MN, USA) was performed under local anesthesia and guided by stereotactic magnetic resonance. Microelectrode recordings and test stimulation procedures were performed as described previously (Machado et al., 2006). Stimulation was initiated one month following implantation (TIME 0) and stimulation parameters were individually adapted to obtain the best motor outcome. Motor status was assessed using the motor subscore of the Unified Parkinson's Disease Rating Scale (UPDRS-III). Each subject was examined in the morning in the off medication state with the stimulator off (sOFF) and again at least 30 min after switching the stimulator on (sON). STN-DBS was clinically effective in all patients as the UPDRS-III score decreased from 36.7 ± (SD)9.6 (sOFF) to 17.8 ± 5.5 (sON) ($T = 7.3$, $p < 10^{-7}$) on the first day of stimulation. The change of motor status was calculated as the percentage change of UPDRS-III scores (100 − 100sON/sOFF). Patients were then regularly seen at visit 1, 3, 5, 11 and 17 months after STN-DBS initiation (TIME 1, 3, 5, 11, 17). At month 17 after initiation of stimulation (TIME 17), the average stimulation parameters were 2.8 ± 0.5 V, 60−120 ms and 130 Hz. During the study period, the stimulation intensity was gradually increased while dopaminergic medication was in most cases reduced to further ensure the best control of PD manifestations. Stimulation intensity (STIM) was calculated as the mean of arithmetic products of all