Univerzita Karlova v Praze

1. lékařská fakulta

Studijní program: Biomedicína

Studijní obor: Neurovědy

MUDr. Filip Růžička

Neuroanatomical aspects of non-motor effects of deep brain stimulation

Neuroanatomické aspekty non-motorických efektů hluboké mozkové stimulace

Disertační práce

Školitelé:

Doc. MUDr. Robert Jech, Ph.D., Prof. MUDr. Evžen Růžička, DrSc.

Praha, 2014

Prohlášení:

Prohlašuji, že jsem závěrečnou práci zpracoval samostatně a že jsem řádně uvedl a citoval všechny použité prameny a literaturu. Současně prohlašuji, že práce nebyla využita k získání jiného nebo stejného titulu.

Souhlasím s trvalým uložením elektronické verze mé práce v databázi systému meziuniverzitního projektu Theses.cz za účelem soustavné kontroly podobnosti kvalifikačních prací.

V Praze, 19.6.2014

Filip Růžička

Identifikační záznam:

Filip Růžička: Neuroanatomické aspekty non-motorických efektů hluboké mozkové stimulace.

Praha, 2014.

Počet stran 114

Disertační práce (Ph.D.). Univerzita Karlova v Praze, 1. lékařská fakulta, Neurologická klinika.

Školitel: Prof. MUDr. Evžen Růžička, DrSc, Doc. MUDr. Robert Jech, PhD.

Acknowledgement:

I am very grateful for having Associate Professor Robert Jech and Professor Evžen Růžička as my supervisors. Without their mentoring, confidence and guidance, this work would not have been possible.

I would also like to thank the following individuals for their friendship and encouragement: Tereza Serranova, Tomáš Sieger, Martin Voleman, Markéta Fialová, Anna Rezková, Lucie Nováková, Aaron Rulseh.

Finally, I want to thank my mother, who constantly believed in me, listened to me and supported me during hard times.

Souhrn

Hluboká mozková stimulace subthalamického jádra (DBS STN) představuje standardní součást terapie středních stádií Parkinsonovy nemoci vedoucí k podstatnému zlepšení a stabilizaci hybnosti pacienta. Mezi nežádoucí účinky stimulace patří její vliv na afektivní a kognitivní funkce. Velmi častý je i nárůst tělesné hmotnosti. Mechanismus těchto změn není jasný, ale mohl by souviset s pozicí stimulujícího kontaktu v STN.

Cíle práce: Vzhledem k funkční organizaci subthalamického jádra, kde mediální část je zapojena k limbickému systému, střední část má vztah k asociačním strukturám a laterální část STN k motorickým oblastem mozku, bylo naším hlavním cílem zjistit, zda nárůst tělesné hmotnosti a změna funkce hypotalamicko-hypofyzární osy závisí na poloze stimulujícího kontaktu hluboké mozkové stimulace v tomto jádře. Naším vedlejším cílem bylo ověřit, zda změna funkce hypotalamicko-hypofyzární osy souvisí s pooperačním nárůstem hmotnosti a úzkostností.

Metodika: Studie 1- Hmotnost byla měřena v pravidelných intervalech u 20 pacientů s Parkinsonovou nemocí během 18-ti měsíců po operaci. Poloha stimulující elektrody byla hodnocena na základně vyšetření magnetickou rezonancí mozku (1.5T) s využitím T1 vážené sekvence. Studie 2- Plazmatický kortizol byl měřen u 20 pacientů ze studie 1, nejdříve v den zahájení stimulace DBS STN, a poté za 1 a 17 měsíců. Úzkost a úzkostnost byla měřena pomocí dotazníků STAI (State-Trait Anxiety Inventory) 1 rok po operaci.

Výsledky: Studie 1- Zjistili jsme, že vzdálenost aktivního stimulujícího kontaktu od stěny III. mozkové komory signifikantně korelovala jak s nárůstem hmotnosti, tak se zlepšením motorického stavu pacientů měřeným na kontralaterální části těla pomocí UPDRS-III skóre. Studie 2- Po zahájení stimulace DBS-STN došlo k významnému poklesu kortizolu měřeného za 1 a 17 měsíců od operace. U pacientů s alespoň jedním kontaktem více mediálně byl pozorován podstatně větší pokles hladiny plazmatického kortizolu než u pacientů s oběma kontakty laterálně. Nadto, pooperačně stimulací indukovaná nižší hladina kortizolu byla spojena s větší úzkostností a větším nárůstem hmotnosti, což naznačuje možný vliv stimulace na oblast jádra zapojenou do limbického systému.

Závěr: Zjistili jsme, že mediální pozice aktivního kontaktu DBS STN je spojena s větším nárůstem hmotnosti, akcentací úzkostnosti a nižším ranním plazmatickým kortizolem, což naznačuje lokální vliv stimulace na limbické struktury**.**

Summery

The underlying mechanisms of weight gain and other affective and cognitive changes after initiation of deep brain stimulation in Parkinson's disease are still unclear. Considering the functional organization within the subthalamic nucleus (STN); limbic, associative and sensorimotor regions residing in the medial, central and later STN respectively, we hypothesized that weight gain may be related to medial localization of stimulation, while motor improvement may be related to lateral localization of stimulation within the STN **(study 1).** We further hypothesized that stimulation close to the limbic and associative part of the STN may be associated with negative impact on limbic system leading to enhanced anxiety and changes in the hypothalamic-pituitary-adrenal axis (HPA)(**study 2).** Therefore, the primary aims our study were to assess changes in body weight **(study 1)** and the hypothalamic-pituitary-adrenal axis (HPA) **(study 2)** in relation to the position of the active stimulating contact within the nucleus. The secondary goals were to elucidate whether morning plasma cortisol changes after the initiation of stimulation are related to postoperative anxiety and weight gain. **Study 1.** Regular body-weight measurements were performed in 20 patients with advanced Parkinson's disease within a period of 18 months after implantation. T1-weighted (1.5T) magnetic resonance images were used to determine electrode position within the STN and the Unified Parkinson's disease rating scale (UPDRS-III) was used for motor assessment. We observed weight gain inversely related to the distance of contacts from the wall of the third ventricle, and patients with at least one contact located medially in the STN experienced significantly greater weight gain than those with both active contacts located laterally. On the contrary, motor improvement was related to the lateral part of the STN. **Study 2.** Plasma cortisol measurements were taken on the day of initiation of bilateral STN-DBS and then repeated after 1 and 17 months in twenty patients with advanced Parkinson's disease. After initiation of stimulation, cortisol levels significantly decreased and cortisol changes after 1 and 17 months strongly correlated with the position of active contact in subthalamic area. Patients with at least one contact localized more medially in the STN experienced a significantly greater decrease of cortisol than those with one or both active contacts localized more laterally**.** Furthermore, lower cortisol levels were strongly associated with higher trait anxiety and weight gain, suggesting a negative impact of STN-DBS on limbic system. Thus, medial position of the active contact is associated with weight gain, cortisol and anxiety changes, corresponding to manifestations of chronic stress and suggesting a regional effect of STN-DBS on adjacent limbic structures.

TABLE OF CONTENTS

1 INTRODUCTION

1.1 Deep brain stimulation in Parkinson's disease

Parkinson's disease (PD) is a common neurodegenerative disorder with an approximate prevalence of 1-2% in adults over the age of 60 years. Although Parkinson's disease is multisystem brain disorder, the hallmark of PD is neurodegeneration and the loss of substantia nigra pars compacta dopaminergic neurons, leading to the primary motor manifestations such as bradykinesia, resting tremor, rigidity and flexed posture. In the initial stages of the disease, levodopa and dopamine agonists are the most effective therapy for improving motor manifestations. However, as PD progresses, patients develop fluctuations in motor performance and often severe dyskinesia, progressively compromising quality of life (Olanow, Stern et al. 2009).

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is currently recognized as a standard and highly effective method in treatment of motor manifestations of advanced PD (Fasano, Daniele et al. 2012, deSouza, Moro et al. 2013). The clinical effects of stimulation on motor manifestations have been shown to depend on the position of active electrode contact in the lateral part the STN in a manner that well reflects the functional organization of the subthalamic nucleus and connectivity (Hamel, Fietzek et al. 2003, Herzog, Fietzek et al. 2004). However, in addition to motor improvement, non-motor effects of STN-DBS have been also reported such as various cognitive, emotional and motivational disturbances (Volkmann, Daniels et al. 2010, Serranova, Jech et al. 2011, Castrioto, Lhommee et al. 2014), as well as weight gain, representing the most common seen "adverse" long-term effect of STN DBS (Montaurier, Morio et al. 2007, Novakova, Ruzicka et al. 2007, Kistner, Lhommee et al. 2014). However, the underlying mechanism of weight gain is still not clear.

Some authors have suggested that weight gain may be related to changes in medication, especially to the reduction of dopaminergic drugs (Barichella, Marczewska et al. 2003, Macia, Perlemoine et al. 2004, Novakova, Ruzicka et al. 2007). Others have

emphasized that weight gain may be related to the normalization of energy expenditure due to decreased rigidity and the amelioration of dyskinesia (Perlemoine, Macia et al. 2005, Montaurier, Morio et al. 2007). Additionally, changes in weight have been proposed to reflect the direct influence of STN-DBS on adjacent structures involved in the regulation of eating behavior or energy balance, such as the hypothalamic area (Montaurier, Morio et al. 2007, Novakova, Ruzicka et al. 2007, Bannier, Montaurier et al. 2009).

1.2 Regulation of food intake and stress

Food intake and energy expenditure are controlled by highly complex, interconnected and distributed brain networks (Berthoud and Morrison 2008, Lenard and Berthoud 2008). The “metabolic” network senses the nutritional and metabolic state of the body. The hypothalamus represents a principal structure of this system that provides the basis for the monitoring and integration of relevant information from the internal milieu mediated through peripheral circulating hormones, metabolites, and autonomic neural pathways. Through its widespread connections, the hypothalamus then contributes to the selection of optimal adaptive responses through its influence on endocrine, autonomic, reward and behavioral pathways (Berthoud and Munzberg 2011). The “emotional and cognitive” network is involved in the processing of other aspects of food intake and eating behavior, such as the hedonic and motivational valuation of food and food cues, value-based decision-making, reinforced learning, self-control and the ability to resist temptation, and balancing goal-directed control and habitual behavior (Berthoud 2007, Rangel, Camerer et al. 2008, Berridge, Ho et al. 2010, Volkow, Wang et al. 2012, Volkow, Wang et al. 2013). The second network is comprised of numerous cortical and subcortical brain areas, including the basal ganglia and limbic system (Berthoud 2002, Berridge 2009, Haber and Knutson 2010, Berthoud 2012, Sinha and Jastreboff 2013). It is now increasingly recognized that cognitive, motivational, hedonic and emotional neuronal processes play a decisive role in the obesity epidemic.

The current environment is characterized by abundant food that is inexpensive, high in energy density, well-advertised, highly palatable, flavor-and color-enhanced and easy available; constituting constant background pressure on reward and habitual controllers that promote overeating and weight gain (Peters, Wyatt et al. 2002). This environment has resulted in increased demands on cognitive control making it more likely to fail, especially in the setting of chronic stress (Rangel 2013). Chronic stress has recently been identified as a common and important risk factor for anxiety disorders, weight gain, obesity, and the consumption of palatable food through its detrimental effect on several cortical and limbic structures. A number of studies have provided evidence that chronic stress leads to the incentive salience sensitization (higher desire for food reward), decision-making deficit, impulsivity, hampered self-control and cognitive function, a change in behavior that favors habitual over goal-directed action, and a hypocorticosolemic profile as a result of limbic system dysfunction (Miller, Chen et al. 2007, Berridge, Ho et al. 2010, Dallman 2010, Schwabe and Wolf 2011, Tryon, Carter et al. 2013). The most stress-responsive brain areas include the hippocampus, amygdala, ventral striatum, and medial prefrontal and orbitofrontal areas (Sousa and Almeida 2012, Leuner and Shors 2013). Particularly, the medial prefrontal cortex has received much interest since its implication in value-based decision-making, obesity, addiction and other psychiatric disorders (Shin and Liberzon 2010, Kim, Loucks et al. 2011). The emerging view is that stress induces a "disconnection syndrome" whereby the transmission of information that is critical for orchestrating appropriate behavioral responses is perturbed (Sousa and Almeida 2012).

Thus, considering the widespread connections of the STN to the limbic, cognitive and motor brain structures it seems conceivable that, particularly with the stimulating contact located more medially within the nucleus, STN-DBS may introduce a certain degree of chronic noise into the cognitive and limbic neuronal processing and synchronization, thereby leading to weight gain in a similar manner as chronic stress. Accordingly, STN-DBS has been shown to influence incentive salience attribution processing for both rewarding and aversive stimuli (Serranova, Jech et al. 2011), to

induce worsening executive function and impulse control (Alberts, Voelcker-Rehage et al. 2008, Ballanger, van Eimeren et al. 2009), and to effect decision making with impaired an ability to balance short-term reward against long-term losses (Oyama, Shimo et al. 2011). It has also been demonstrated that initiation of STN-DBS is associated with a persistent decrease of morning plasma cortisol (Novakova, Haluzik et al. 2011).

1.3 Overview of the basic basal ganglia organization

The basal ganglia are highly conservative structures throughout the vertebrate phylum and consist of several interconnected subcortical nuclei that serve in tandem with the cortex and brain stem nuclei to orchestrate and integrate a variety of motor, cognitive and motivational processes (Stephenson-Jones, Samuelsson et al. 2011, Haber, Adler et al. 2012, Grillner, Robertson et al. 2013). The basal ganglia are currently central to theories of behavioural control (Rangel, Camerer et al. 2008, Liljeholm and O'Doherty 2012). There is considerable evidence showing that a large spectrum of multiple neurological and psychiatric diseases, such as movement disorders (Obeso, Rodriguez-Oroz et al. 2008), mood and anxiety disorders (Price and Drevets 2010), addictions, obesity and eating disorders, are associated with differential disruptions of the frontal lobes and basal ganglia circuits (Volkow, Wang et al. 2012, Volkow, Wang et al. 2013). Moreover, the basal ganglia complex network also represents the primary anatomical substrate that is targeted and powerfully modulated by DBS and other stereotactic procedures (Vitek 2008, Collins, Lehmann et al. 2010). Thus, detailed knowledge of functional basal ganglia anatomy is an indispensable prerequisite for understanding the clinical consequences of PD pathology as well the motor and non-motor effects of DBS.

While there is no sharp structural boundary, the basal ganglia are usually subdivided into dorsal and ventral divisions (Haber, Adler et al. 2012). The basic components of the dorsal division include the striatum (STR), which is the largest nucleus, divided into the caudate and putamen by the internal capsule, the external

segment of the globus pallidus (Gpe), the subthalamic nucleus (STN), the internal segment of the globus pallidus (Gpi) and the substantia nigra pars reticulata (SNr). The ventral division of the basal ganglia consists mainly of the ventral striatum (VS) including nucleus accumbens, the ventral pallidum (VP), which exhibits a combination of features of both the internal and external segments of the dorsal pallidum, and the medial parts of STN and SNr (Haber, Adler et al. 2012).

The striatum and the STN are the primary input structures of the basal ganglia, receiving highly topographically- and functionally-organized excitatory projections from the cerebral cortex (Haber 2008, Haynes and Haber 2013). Connection between the cortex and the striatum is directional, in that the cortex projects to the striatum, but the striatum communicates only indirectly to the cortex via polysynaptic downstream pathways. It has been shown that while the striatum receives input from practically the entire cerebral cortex, STN input is more restricted to the frontal lobes. The axons leaving the striatum follow two major pathways. The direct pathway is formed by direct projections from the striatum to the output nuclei, whereas the indirect pathway projects polysynaptically to the Gpi and SNr by way of the Gpe and the STN (Obeso, Marin et al. 2008, Obeso, Rodriguez-Oroz et al. 2008). The hyperdirect pathway refers to the excitatory projections running directly from the cortex to the STN, thus bypassing the striatum and transferring cortical inputs faster to the Gpi/SNr than the direct and indirect pathways (Nambu, Tokuno et al. 2002). The direct, indirect and hyperdirect pathways control the activity of the Gpi, SNr and VP, which represent the primary output nuclei sending inhibitory projections to the thalamic nuclei and several brain stem targets, such as the pedunculpontine nucleus (PPN) and superior colliculus (SC)(Coizet, Graham et al. 2009, Haber, Adler et al. 2012). Thalamic projections to the frontal lobe finally transmit the output of the basal ganglia to the cortex that provides input to the basal ganglia, thus closing the loop of the so-called cortico-basal ganglia-thalamocortical circuit.

As the topographical organization of cortical inputs to the striatum and STN is also, to a large degree, maintained throughout the basal ganglia-thalamocortical circuits

by virtue of highly topographic projections at each synaptic relay, all connections of the basal ganglia are traditionally seen to form multiple parallel loops that have been envisaged to control different aspects of behaviour and different stages of behavioural learning (Alexander and Crutcher 1990, Yin and Knowlton 2006, Graybiel 2008, Redgrave, Rodriguez et al. 2010). The sensorimotor circuit, which is involved in selecting particular movements, learning skills and forming habits, have projections from sensorimotor cortical areas to the dorsolateral striatum. The associative loop, which is responsible for cognitive control, has main projections from the prefrontal cortex to the central and dorsomedial striatum. And the limbic circuit, implicated in motivational and reward processing, includes projections from the orbitofrontal cortex (OFC) and medial prefrontal areas to the ventral striatum and ventromedial parts of both the caudate and the putamen (Haber 2003, Haber 2008, Obeso, Rodriguez-Oroz et al. 2008, Ashby, Turner et al. 2010).

In addition to feed-forward information processing in the basal ganglia, there are also several feedback connections in the basal ganglia network, both reciprocal and non-reciprocal, such as projections from the Gpe to the striatum. In particular, dopaminergic neurons of the SNc and VTA provide massive feedback input to the striatum and to the STN and GPe, influencing the flow of cortical and thalamic projection through the basal ganglia and contributing to action selection, incentive salience attribution, coding of reward-prediction-error and contributing to reward-based learning and habit formation in the basal ganglia circuits (Haber 2003, Montague, Hyman et al. 2004, Berridge 2009, Haber, Adler et al. 2012, Schultz 2013).

There are additionally other nuclei that are also intimately related to the reward function of the basal ganglia, such as the lateral habenula and the tail of the ventral tegmental area, also named the rostromedial tegmental nucleus (RMTg)(Hikosaka 2010, Bourdy and Barrot 2012). These structures have recently been implicated in a novel and specific reward-evaluation circuit of the basal ganglia and are thought to be the key controllers of midbrain dopaminergic neurons (Grillner, Robertson et al. 2013).

1.4 Subthalamic nucleus is the site for limbic, cognitive and motor integration

The STN is the entry nucleus to the basal ganglia circuit and represents the principal target of the deep brain stimulation in PD. It is a small nucleus with an average size of 3 x 5 x 12 mm that takes the shape of a biconvex lens resting on the internal capsule and SNr (Parent and Hazrati 1995, Hamani, Saint-Cyr et al. 2004). The volume of the STN has been estimated at about 240 mm3. The STN is densely populated with medium to large projection cells, with a soma of 35-40 um in diameter and with a dendritic tree extending up to 750 um (Hamani, Saint-Cyr et al. 2004). The dendrites are sparsely covered with spines. Unlike the most of the neurons in the basal ganglia, STN neurons use glutamate as a neurotransmitter and thus exert an excitatory effect on their downstream targets. The STN is reciprocally and massively connected to the GPe and the ventral pallidum (Parent and Hazrati 1995, Karachi, Yelnik et al. 2005, Haber, Adler et al. 2012). Other major inputs to the STN are derived from the cortex (cortico-STN projections are referred as the hyperdirect pathway) (Haynes and Haber 2013), intralaminar thalamic nuclei and the brain stem nuclei including midbrain dopaminergic neurons, serotoninergic neurons from the dorsal raphe nucleus, cholinergic neurons of the PPN, and the superior nucleus (Coizet, Graham et al. 2009, Haber, Adler et al. 2012). The STN neurons can be further distinguished to five groups according to their collateralization to the target structures**:** (i) Gpe, Gpi, SNr (21.3%), (ii) Gpe and SNr (2.7%), (iii) Gpe and Gpi (48%), and (iv) Gpe only (10.7%), (v) striatum (17%) (Parent and Parent 2007). Despite evidence that high-frequency stimulation reduces somatic activity in the stimulated area of the STN, direct neurophysiological studies have demonstrated that subthalamic stimulation leads to an increase in firing rates of these output targets (Vitek 2008). Consistent with the activation of the STN output structures, neuroimaging studies using PET and fMRI in humans undergoing STN-DBS have shown increased of blood flow or BOLD signal in the Gpi (Kringelbach, Jenkinson et al. 2007, Agnesi, Johnson et al. 2013). Moreover, some works further indicate direct or indirect projection of the

STN to the dopaminergic neurons (Watabe-Uchida, Zhu et al. 2012). Accordingly, it has been shown in animal research that the STN-DBS evokes striatal dopamine release(Shimo and Wichmann 2009). However, in humans this issue still remains controversial as positron emission tomography (PET) measures of [^{11}C]-Raclopride uptake during STN-DBS failed to show any changes in striatal dopamine (Hilker, Voges et al. 2003). Conversely, it has been observed that STN-DBS can influence incentive salience attribution, i.e., assigning motivational relevance to a stimulus representation, which is thought to be a process dependent on dopaminergic activity (Serranova, Jech et al. 2011).

The projections from the Gpe are organized in a highly topographical pattern, contributing to the well-known tripartite STN organization comprised of motor, associative and limbic components (Parent and Hazrati 1995). Thus, projections from the limbic part of the Gpe project to the anterior and medioventral portion of the STN, whereas projections from the associative and sensorimotor part of the Gpe target the central and dorsolateral parts of the STN, respectively (Parent and Hazrati 1995, Karachi, Yelnik et al. 2005). However, the concept of distinct and segregated subthalamic subdivision has been recently challenged by several electrophysiological, neuroanatomical and neuroimaging studies (Mallet, Schupbach et al. 2007, Keuken, Uylings et al. 2012, Haynes and Haber 2013). Recent non-human primate work has demonstrated a high degree of convergence between both “dense” and “diffuse” projections from functionally diverse cortical areas including M1, SMA, DLFPC, dACC, OFC and VMPFC, indicating the integrative role of the STN. For example, “dense” projections from the OFC and VMPFC overlap with the terminals from dACC in the medial territory of the STN. Similarly, terminals from dACC, DPFC and SMA converge in the central territory of the STN (Haynes and Haber 2013). Moreover, “diffuse” projections from the cortical areas have been shown to extend over a greater territory and overlap even more extensively. Thus, it has been proposed that the output from each subthalamic neuron, although primarily controlled by the cortical and subcortical inputs matching the territory in which the neurons lies, is more likely the result from the

integration of limbic, cognitive and motor information processing (Haynes and Haber 2013). The complex topographical and functional organization of STN inputs as well as their incomplete anatomical segregation has been further confirmed in human studies using diffusion weighted imaging (DWI) or resting state functional connectivity analysis (Brunenberg, Moeskops et al. 2012, Lambert, Zrinzo et al. 2012). Rather than a sharp separation of different functional territories, a reverse mediolateral gradient of limbic and motor STN connections has been observed in one of these studies (Brunenberg, Moeskops et al. 2012).

The dorsolateral part of the STN has been shown to be related especially to motor function (Hamani, Saint-Cyr et al. 2004, Nambu 2011). Accordingly, there is evidence both from non-human primate research and human perioperative electrophysiology indicating that corticosubthalamic projections from M1 are somatotopically organized with the face region projecting laterally, the arm region centrally, and the leg region medially, whereas inputs from the SMA show inverse somatotopy mirroring those from M1 (Rodriguez-Oroz, Rodriguez et al. 2001, Theodosopoulos, Marks et al. 2003, Nambu 2011).

Consistent with the roles of the limbic prefrontal areas (OFC, dACC, VMPFC) and the related subcortical structures (VS) that project to the STN, several neurophysiological studies exploring reward processing and value-based decision making have observed reward and emotional (valence and arousal) related changes also in the STN neurons (Espinosa-Parrilla, Baunez et al. 2013, Serranova, Sieger et al. 2014). Changes in subthalamic neuron activity have been observed during both instrumental and Pavlovian tasks, in response to unpredicted delivery of reward, and even to the expectation of reward when its delivery is delayed temporally (Espinosa-Parrilla, Baunez et al. 2013)**.** Moreover, a recent human study has further shown two spatially distinct populations of “affective” neurons responding to emotional dimensions of the stimuli: the valence (pleasantness-unpleasantness), and arousal (intensity)(Serranova, Sieger et al. 2014). Several works have further demonstrated that the reward-related neurons as are not strictly limited to the medial limbic part of the STN but are rather scattered

throughout the nucleus, and most neurons also carry signals related to both motor and reward outcomes, thus corroborating the neuroanatomical findings mentioned above (Espinosa-Parrilla, Baunez et al. 2013).

In agreement with the role of the medial prefrontal areas and the DLPFC in cognitive processing, the hyperdirect pathway has been considered to be involved especially as a key component of the brain system underlying behavioural inhibition and increasing the threshold for decision in case of conflict or an ambiguous situation, thus allowing integration of more information before responding properly to the conflict (Frank 2006, Zaghloul, Weidemann et al. 2012, Cavanagh, Sanguinetti et al. 2014). Furthermore, the STN has also been suggested to play a role in the suppression of habitual responses and switch from automatic to controlled goal-directed processing (Hikosaka and Isoda 2010, Anzak, Gaynor et al. 2013).

Finally, huge support for the integrative role of the STN in limbic (reward and aversive), cognitive and motor function comes from animal models, using both lesion and stimulation techniques of the STN as well as from the clinical effects of human DBS in PD, showing a variable degree of motor, cognitive and emotional (for both reward and fear related cues) effects (Balaz, Rektor et al. 2008, Baunez, Yelnik et al. 2011).

Although several models have been proposed, the functional role of the STN in the basal ganglia circuits still remains unclear. However, understanding the neural mechanisms in the subthalamic nucleus as well the non-motor effects of STN-DBS requires delineating the specific functional role for individual neural structures projecting to the STN.

1.5 Major inputs and outputs of the STN

1.5.1 Frontal cortex

Although almost all cortical areas project to striatum, connections from the frontal lobes highly predominate (Haber 2008, Haber, Adler et al. 2012). Importantly, the frontal cortical regions also provide significant direct input to the STN and therefore, in addition to the indirect effect of STN-DBS on cortical function via downstream output nuclei and the thalamus, the function of the frontal cortex may be modulated directly by anterograde propagation of DBS (Walker, Huang et al. 2012, Haynes and Haber 2013). The frontal cortex is composed of several areas that differ in their connection with other cortical areas, the basal ganglia, limbic structures, and the hypothalamus. All frontal regions are heavily interconnected between each other in a hierarchical and organized fashion (Badre and D'Esposito 2009, Petrides and Pandya 2012). A good deal of work has demonstrated that disordered food intake, inability to resist food temptation, loss of self-control, higher craving of food, anxiety and obesity are associated with overlapping changes in the structure and connectivity of the frontal lobes and related basal ganglia nuclei(Volkow, Wang et al. 2012, Volkow, Wang et al. 2013).

Cortical input to the striatum is excitatory and uses glutamate as the principal neurotransmitter. Two major subtypes of cortical neurons projecting to the striatum have been identified (Mathai and Smith 2011, Shepherd 2013). First, the pyramidal tract neurons (PT), which are restricted to the lower cortical layer 5 (B), project to the brainstem and spinal cord with collaterals to the ipsilateral cortex and striatum, bringing to the striatum a copy of the cortical motor signal that directly regulates movement. Importantly, to a variable extent, these neurons also innervate several subcortical structures, such as the Gpe, STN and SNc. Moreover, PT-type neurons of prelimbic areas are thought to account for the cortical input targeting strisomes, which is of interest because striosomes in turn project to the SNc. Thus, it appears that PT-

neurons are in the position to both directly and indirectly control midbrain dopaminergic activity. Second, intratelencephalic neurons (IT), which are primarily found in layer 3 and the upper layer 5 project to the ipsilateral as well as contralateral cortex and striatum, but they do not project out of the telencephalon. It has been shown that PT and IT neurons are clearly dichotomous in several other aspects and they also differ in their size, shape, dendritic arbozation, intracortical connections, instrinsic electrophysiology, neuromodulatory properties, conduction velocities and intrastriatal branching pattern, suggesting that IT-type and PT-type neurons process distinct information from separate cortical networks (Morita, Morishima et al. 2012, Shepherd 2013). Although some studies have indicated that IT-type neurons also preferentially target the direct pathway and PT-type neurons the indirect pathway, this view has been challenged by a recent study showing that direct and indirect MSNs receive a similar amount of input from IT- and PT-type of neurons (Shepherd 2013).

1.5.1.1 Motor and premotor frontal cortex

Cortical projections to the striatum are highly topographically and somatotopically organized as revealed by several experimental works in animals and recently also confirmed by several neuroimaging studies in humans using task based functional MRI (Gerardin, Lehericy et al. 2003), functional resting state MRI (Choi, Yeo et al. 2012) and diffusion imagining methods (Verstynen, Badre et al. 2012).

Motor and premotor areas, constituting the caudal frontal cortex, are responsible for the execution and planning of motor actions and learning skills (Haber, Adler et al. 2012). Moreover, the sensorimotor cortices together with the putamen and dorsolateral striatum are also implicated in automatic and habitual behavior (Ashby, Turner et al. 2010). The motor cortex, M1, sends strong projection to the dorsolateral and central region of the putamen with few terminals extending rostrally, but they generally do not reach rostral of the anterior commissure. The lower extremity, upper extremity and orofacial regions of M1 are arranged from dorsal to ventrally in the

lateral putamen, respectively (Nambu 2011). As the medial parts of the putamen also receive projections from the SMA with similar inverted topography, the putamen has two sets of partially overlapping somatotopic maps. Moreover, this area of the striatum further receives overlapping inputs from somatosensory areas following the same somatotopic organization as motor and caudal premotor areas, suggesting that the putamen also represents an important site for integrating movement-related and sensory-related information. The existence of the somatotopic arrangement of cortical inputs in the putamen has been also supported by numerous electrophysiological studies in experimental animals (Nambu 2011). The rostral premotor areas that are more involved in the cognitive aspects of motor control project in both the caudate and putamen and extend more rostrally than those from the motor and caudal premotor cortex (Haber 2008, Haber, Adler et al. 2012).

1.5.1.2 Dorsolateral prefrontal cortex

Dorsolateral prefrontal cortical regions (DLPFC) are responsible for "cool" cognitive control such as working memory, strategic planning, set-shifting, task-switching and inhibition of inappropriate behaviour and self-control (Hare, Camerer et al. 2009, Hofmann, Schmeichel et al. 2012, Aron, Robbins et al. 2014). These functions permit to flexibly regulate action selection on the basis of internally maintained context, goals and anticipated outcomes. Conversely, dysfunction of the DLFPC and its connection to other cortical regions has been associated with diminished self-control, habitual behaviour, and greater weight gain and obesity (Hare, Camerer et al. 2009, Hofmann, Adriaanse et al. 2013, Volkow, Wang et al. 2013). Accordingly, using positron emission tomography (PET) to measure brain glucose metabolism, an inverse correlation between BMI and prefrontal metabolic activity has been observed in healthy adults (Volkow, Wang et al. 2009). There is convincing evidence that cognitive control is organized systematically along the rostro-caudal axis of the frontal lobes, such as the more rostral regions support cognitive control involving progressively more abstract

representations (Badre 2008, Badre and D'Esposito 2009). Although the mechanisms underlying cognitive function and hierarchical interactions between the prefrontal regions were generally thought to be based primarily on cortico-cortical connections, more recent models of cognitive control have demonstrated that rostro-caudal informational processing is processed via nested corticostriatal circuits in a way that action selection at one corticostriatal level is constrained by inputs from more anterior levels (Badre, Hoffman et al. 2009, Badre and Frank 2012). DLFC innervation is one of the largest to the striatum and extend from the rostral pole of the striatum through its caudal extend (Selemon and Goldman-Rakic 1985, Draganski, Kherif et al. 2008, Verstynen, Badre et al. 2012), however, most projections terminate in the head of the caudate nucleus and in the front of the putamen. As a general rule, fibers from more rostral origins tend to terminate in more rostral regions of the striatum whereas those originating from caudal parts terminate in more caudal striatal regions, and inputs to the striatum form longitudinal fields with patchy clustering of fiber endopoints(Selemon and Goldman-Rakic 1985, Verstynen, Badre et al. 2012). Moreover, it has been shown that there is some degree of asymmetric overlap between different DLFC regions such that more fibers from rostral cortical regions project caudally along the striatum than vice versa, supporting the model of rostro-caudal hierarchy of information processing (Badre 2008, Haber and Calzavara 2009).

1.5.1.3 Anterior cingulate cortex

While the orbitofrontal cortex plays a primary role in linking stimuli to their subjective or expected value, the dorsal anterior cingulate cortex (dACC) has been proposed to play a role in learning the value of actions (Amiez, Joseph et al. 2006), effort-based decision making (Walton, Kennerley et al. 2006), learning and predicting likely outcomes of actions (Rudebeck, Walton et al. 2007, Silvetti, Seurinck et al. 2011), monitoring errors with subsequent adjustment of behavioral performance and detection of conflict when a stimulus or environmental cue evokes two mutually

incompatible motor responses (van Veen, Cohen et al. 2001, Matsumoto, Suzuki et al. 2003). In addition, activation of the dACC has been documented in numerous studies with fear conditioning (Etkin, Egner et al. 2011, Sousa and Almeida 2012) and in response to viewing appetizing foods. Accordingly, dysfunction of the dACC is associated with anxiety disorders (due to altered error processing during decision making) as well as with a propensity to obesity (Paulus, Feinstein et al. 2004, Passamonti, Rowe et al. 2009, Price and Drevets 2010). In agreement with the role of the dACC in action valuation and response selection, the dACC has strong connections to the motor system (Picard and Strick 2001). Striatal projection of this area reaches from the rostral pole of the striatum to the anterior commissure with terminals found in the ventral striatum, the rostral, central caudate nucleus and the central putamen located laterally to the projection from the orbitofrontal cortex (Haber, Kim et al. 2006). Moreover, it has been shown that ACC together with OFC project to the striosomes (Eblen and Graybiel 1995), thus being in the position to modulate midbrain dopaminergic activity, which is thought to reflect reward prediction error underlying reinforcement learning in the basal ganglia.

1.5.1.4 Orbitofrontal cortex

The orbitofrontal cortex (OFC) receives sensory inputs from of all modality-specific pathways, where the identity of the stimuli are encoded, and provides a cortical basis for the stimulus subjective valuation, representation of hedonic pleasure experience and incentive salience of primary reinforces (rewards and punishers) including taste, smell, temperature, touch, food texture stimuli as well as facial attractiveness and expressions, such angry or smiling facial expressions (Kringelbach 2005, Rolls and Grabenhorst 2008, Berridge and Kringelbach 2013).). The orbitofrontal cortex also encodes the expected value and outcome of secondary reinforcers, such as visual or auditory stimuli, as a result of stimulus-reinforcer association (Gottfried, O'Doherty et al. 2003, Rolls 2014, Stalnaker, Cooch et al. 2014). It has been demonstrated that OFC activity and subjective pleasantness of food are significantly

modulated by current motivational states. For example, using magnetic resonance imaging in humans, it has been shown a that distinct region of the orbitofrontal cortex shows decreased activation to a food stimulus when a liquid food is eaten to satiety in close correlation with decreased subjective pleasantness (Kringelbach, O'Doherty et al. 2003). On the other hand, hunger and food deprivation increases activity of the OFC following the presentation of high calorie food (Siep, Roefs et al. 2009). These findings indicate that the OFC plays an important role for food behavior and in influencing whether the a particularly food is selected as a goal for action (Killgore, Weber et al. 2013). Accordingly, many recent studies have shown a close relationship between altered activation of the OFC, self-reported motivational status for foods and greater propensity to obesity (Killgore and Yurgelun-Todd 2005, Dimitropoulos, Tkach et al. 2012, Ho, Kennedy et al. 2012). Furthermore, it has been shown that cognition has a direct, top-down modulatory influence on value representation in the OFC and in determining the pleasantness of a food and how much is to be eaten (Grabenhorst, Rolls et al. 2008). Similarly to the DLFPC, the OFC is functionally and hierarchically organized along a posterior-anterior axis, in that the anterior OFC, a phylogenetically recent structure, process more abstract stimuli, such as monetary gain and loss, and the posterior part OFC processes primary rewards, such as taste or erotic stimuli (Kringelbach 2005, Sescousse, Redoute et al. 2010, Rudebeck and Murray 2011). Non-human primate studies have documented that the OFC projects to the central and lateral parts of the ventral striatum and to both the caudate nucleus and putamen where these projections terminate more medially and centrally to projections from the dACC. Similar findings have also been confirmed in humans using probabilistic tractography on magnetic resonance diffusion weighted imaging (Haber, Kim et al. 2006, Draganski, Kherif et al. 2008, Haber and Knutson 2010).

1.5.1.5 Ventromedial prefrontal cortex

The ventromedial prefrontal cortex (VMPFC) is thought to provide a “hot”

cognitive system for decision making beyond valuation where value representations from the OFC and ACC are transformed into choices between different types of rewards and different of types of decisions (Grabenhorst, Rolls et al. 2008, Grabenhorst and Rolls 2011). Decision-related activity in the VMPFC has been found for choices about primary rewards, such as a pleasant warm or unpleasant cold touch to the hand (Grabenhorst, Rolls et al. 2008). Moreover, neuronal activity in this area also correlates with the expected value of choice options during economic decision-making (Glascher, Hampton et al. 2009). On the basis of numerous neuroeconomic studies, it has been envisaged that the VMPFC represents the subjective value of multiple reward types in a common currency appropriate for guiding choice (Levy and Glimcher 2012). Furthermore, the VMPFC has been long established as a critical region for self-control and the ability to delay immediate gratification and make choices that maximize potential future economic rewards or healthier long-term dietary goals (Bechara 2005, Hare, Camerer et al. 2009, Hare, Hakimi et al. 2014). The importance of this area and ventromedial parts of the striatum for flexible and adaptive goal-directed behavior has been also substantiated both in fMRI studies using an instrumental discrimination task that distinguishes between goal-directed and habit-based response, and in studies on the integrity and white matter track strength between the VMPFC and caudate nucleus (de Wit, Corlett et al. 2009, de Wit, Watson et al. 2012). In agreement with these findings, human behavioral and neuroimaging data have found a close relationship between decision-making deficit, dysfunction of the VMPFC and ventromedial parts of striatum, obesity, addictions and a shift from goal-directed behavior towards maladaptive and inflexible habits (Davis, Levitan et al. 2004, Volkow, Wang et al. 2012, Volkow, Wang et al. 2013). Additionally, the VMPFC is also strongly involved in the regulation of fear-related behavior, stress response and the HPA axis (Dedovic, Duchesne et al. 2009, Price and Drevets 2010, Myers-Schulz and Koenigs 2012, Courtin, Bienvenu et al. 2013). Accordingly, it has been shown that exaggerated reactivity to food cues is closely related to chronic stress, activation of the VMPFC and blunted cortisol response (Tryon, Carter et al. 2013).

Yet furthermore, a considerable body of research over the past several years has identified the human VMPFC as a key region of the default mode system, self-related processing and self-valuation, and autobiographical memory (Buckner, Andrews-Hanna et al. 2008, D'Argembeau 2013). Taken together, it appears that the VMPFC integrates various distinct systems involved in the subjective valuation of rewards, value-based decision making, memory and future projections (Buckner and Carroll 2007, Euston, Gruber et al. 2012, Gerlach, Spreng et al. 2014), self-related processing, goal formation and maintenance, and affective physiological and behavioral response (Euston, Gruber et al. 2012, Roy, Shohamy et al. 2012). As unifying theory, it has recently been suggested that the VMPFC provides a system for the generation of affective meaning, i.e., a sense of the significance of events for an organism's well being and future prospect, flexible goal-directed behaviour mediated by goal anticipation and evaluation (Roy, Shohamy et al. 2012).

1.5.2 Dorsal striatum

The dorsal striatum communicates with the STN mainly via the Gpe, although some projections from the STN to the striatum have been demonstrated (Parent and Parent 2007). The dorsal striatum is the main cortical input to the basal ganglia (Haber 2003, Obeso, Marin et al. 2008, Obeso, Rodriguez-Oroz et al. 2008). There is convincing evidence suggesting the important role of the striatum for food intake regulation (Rothemund, Preuschhof et al. 2007, Rangel 2013, Volkow, Wang et al. 2013). The striatum contains projection neurons and interneurons (Gittis and Kreitzer 2012, Haber, Adler et al. 2012). Projections neurons are referred to as medium spiny neurons (MNS), which form around 90-97% of the striatal neuronal population and represent also major output neurons (Gerfen and Bolam 2010). The remaining striatal neurons are interneurons, which are all aspiny, and whose axons are distributed within the striatum, most of which make synaptic contacts with MSNs (Goldberg and Wilson 2010, Haber, Adler et al. 2012). The cell body of MSNs gives rise to 5-7 primary dendritic processes

that further divide to form secondary or tertiary dendrites, which are typically densely covered with spines representing an important substrate for plasticity and learning in the striatum (Plenz and Wickens 2010). In addition to cortical inputs, MSNs receive afferents from thalamic nuclei and brain stem structures, such as midbrain dopaminergic neurons of the SNc and VTA, and serotoninergic neurons, with a preponderant role for the dorsal raphe nucleus (Gerfen and Bolam 2010, Haber, Adler et al. 2012). The glutamatergic extitatory cortico-striatal fibres make contacts primarily with the head of the dendritic spines, and to a lesser degree with dendritic shafts, whereas thalamo-striatal projections originating from the CM-Pf thalamic complex make contacts primary with dendritic shafts of MSNs (Plenz and Wickens 2010). Massive dopaminergic innervations, which provides key modulatory influence on striatal processing of cortical and thalamic information and plays a fundamental role in reinforcement learning, form strategically placed conventional synapses on the necks of dendritic spines and nearby segments of dendritic shafts as well varicosities near to dendrites and soma of MSNs, releasing DA that mediates its effects through volume transmission (Obeso, Marin et al. 2008, Liljeholm and O'Doherty 2012).

Striatal MSNs are inhibitory neurons that use GABA as the principal neurotransmitter and, although some overlap exists and fewer than 6% of MSNs express both classes of dopamine receptors they are further categorized into two major types based on their axonal projection to output nuclei; DA receptors and neuropeptide expressions (Surmeier, Day et al. 2010). Neurons containing substance P, dynorphin and D1 dopamine receptors have major projection to the output nuclei of the basal ganglia (Gpi and SNr), but also send some collaterals to the Gpe, whereas those containing enkephalin a D2 dopamine receptors project exclusively to the Gpe (Obeso, Marin et al. 2008, Gerfen and Bolam 2010). In addition to these distinct histochemical markers, D1 and D2 MSNs also differ in their dendritic branching pattern, so that D1 MSNs have a significantly greater total dendritic length and more branches than D2 MSNs (Surmeier, Day et al. 2010). Such anatomical dichotomy has been shown to further contribute to electrophysiological differences and the higher excitability of D2 MSNs (Surmeier, Day et

al. 2010). According to the classical model, direct and indirect pathways are viewed as providing counterbalanced regulation of the basal ganglia circuit underlying action selection in the basal ganglia. Activation of the direct striatal output neurons reduces inhibitory basal ganglia output with subsequent disinhibition of excitatory thalamocortical projections, leading to the facilitation of selected actions, whereas activation of the indirect pathway leads to an increase of tonic inhibitory basal ganglia output with resulting attenuation of thalamocortical projections and inhibition of "unwanted" and competing actions (Obeso, Marin et al. 2008, Gerfen and Bolam 2010). Since dopamine exerts a dual effect on MSNs exciting striatal neurons that express D-1 and inhibiting striatal D-2 receptors, it has a general pro-movement effect by simultaneously promoting and disinhibiting actions through the direct and indirect pathways, respectively (Obeso, Rodriguez-Oroz et al. 2008, DeLong and Wichmann 2009). Several studies have also suggested that impairment in striatal dopamine may undermine self-control and is associated with obesity and addiction. For example, obese subjects show a lower baseline level of striatal D2R density, which is further associated with reduced metabolic activity in the DLPFC and ACC (Volkow, Wang et al. 2011).

MSNs are further classified according to their relation to the strisome and matrix compartments of the striatum, defined by expression of number of neurochemical markers, including staining for acetylcholinesterase and mu opiate receptor binding (Crittenden and Graybiel 2011). It has also been shown that local axon collaterals and dendrites of MSNs obey striosome-matrix borders subdividing the striatum into the two functionally distinct compartments, which further differ in their input and output connections. Striosomes make up approximately 10-20% of the volume in the dorsal striatum of humans and form a continuous labyrinth that is embedded in the surrounding matrix (Gerfen and Bolam 2010, Crittenden and Graybiel 2011). Importantly, somatosensory, motor, and association cortices have been shown to preferentially innervate the matrix, targeting the Gpe, Gpi and SNr, whereas projections from limbic areas such as orbitofrontal, anterior cingulate, insular cortices and the amygdala preferentially terminate in the striosomes (and ventral striatum)(Graybiel

2008, Gerfen and Bolam 2010). Furthermore, output from the striosomal compartment in turn projects to the SNc directly as well as indirectly via the border region of the Gpi and the lateral habenula (Haber, Adler et al. 2012(Stephenson-Jones, Kardamakis et al. 2013)). Thus, the ventral striatum and the striosomes are now thought to be in a key position to exert control over dopamine signaling in the dorsal striatum. Interestingly, it has recently been shown that mu opioid stimulation in the striosomal compartment of the dorsal striatum contributes to generating intense motivation to overconsume palatable food rewards (Berridge 2012).

Although striatal interneurons constitute as many as 3-5% of striatal neural populations, it appears that they can produce a strong regulatory effect on striatal functioning and play an important role in, among others, learning and the integration of information processing between the matrix and striosomes (Gittis and Kreitzer 2012).

1.5.3 Ventral striatum

The ventral striatum (VS) is a hub for the integration of reward, motivation, decision-making and behavioral response (Berridge, Ho et al. 2010, Haber and Knutson 2010). It is primarily comprised of the nucleus accumbens and the ventromedial parts of both the caudate and the putamen. There is no sharp boundary between the VS and the dorsal striatum. The ventral striatum is mainly characterized by strong projections from limbic structures such as the hippocampus, amygdala, ventral tegmental areas, thalamic nuclei (midline, medial intralaminar and medial MD) and prefrontal cortical areas including the OFC, vmPFC, and dACC (Haber and Knutson 2010). Using event-related fMRI, several human studies have demonstrated differential VS activation during different phases of reward processing. While VS activation increases proportional to the magnitude of anticipated and obtained reward and with the probability of immediate reward delivery, anticipated reward effort, delay in reward delivery, and omission of expected reward decreases VS activation (Haber and Knutson 2010). Partially, based on these findings, it has been proposed that VS activity tracks a reward prediction error.

Within the nucleus accumbens two major subterritories can be distinguished, the core and the sell, which differ in their input and output organization (Humphries and Prescott 2010).

The projections from the prefrontal cortical region are topographically organized, but there is significant overlap between terminations from distinct cortical inputs, suggesting functional integration of the distinct inputs within the nucleus. In a non-human primate study, it has been shown that the VMPFC projects most medially to the shell and to the medial wall of caudate, the OFC projects to the central and lateral part of the VS, whereas projections from the dACC terminate extensively in rostral, central caudate and central putamen lateral to the projections of the OFC (Haber, Kunishio et al. 1995).

The amygdala is crucial for determining and learning the emotional and motivational significance of environmental stimuli and in the generation of arousal responses reflecting the intensity of activation in the motivational system (Fernando, Murray et al. 2013). These functions are, among others, enabled by the fact that, as in the OFC, the amygdala receives extensive input from all sensory modalities. Basolateral nuclei (BLA) innervate both the shell and the VS region outside the shell (Kim, Loucks et al. 2011). In addition, the shell receives projections from the medial part of central nucleus of the amygdala. The BLA are reciprocally connected with the cortex, thalamus and VS and they are implicated particularly in linking objects with current stimulus value (Baxter and Murray 2002, Gruber and McDonald 2012). Accordingly, it has been shown that computation of expected value of food cues in the orbital and medial prefrontal cortical areas are dependent on amygdala integrity. The BLA are also a part of the mechanism by which emotionally arousing situations influence affective attention and improve memory (Pessoa 2010). The structural and functional connectivity of the amygdala and the vmPFC has also been shown to play a principle role in regulation of negative affect, level of perceived anxiety and diurnal pattern of cortisol secretion (Urry, van Reekum et al. 2006, Kim and Whalen 2009, Kim, Loucks et al. 2011). Conversely, the central nucleus of the amygdala is characterized by extensive reciprocal connections

with the brain stem and the hypothalamus, thus representing the main output station of the amygdala for approach and avoidance responses and regulation of the hypothalamic-pituitary-adrenal axis and autonomic neuronal pathways (Fernando, Murray et al. 2013, Pessoa 2010).

Multiple regions of the hippocampal formation project to the VS, providing the source of spatial and contextual information (Humphries and Prescott 2010, Gruber and McDonald 2012). In contrast to amygdala, the hippocampal formation terminations are directed primary to the shell (Haber and Knutson 2010). Like the amygdala and vmPFC, the hippocampus is also substantially involved in the regulation of the hypothalamic-pituitary-adrenal axis as well as food take (Jankord and Herman 2008, Volkow, Wang et al. 2011). Brain imaging studies have demonstrated activation of the hippocampus with food craving, a state of hunger, food tasting, and in response to food-conditioned stimuli when motivationally-relevant food objects are shown (Volkow, Wang et al. 2011).

The shell region projects to the VTA, and these projections are particularly dense. Further, it projects to the ventral pallidum, lateral hypothalamus, pedunculopontine nucleus and mediodorsal thalamus (Haber, Adler et al. 2012). The direct or indirect (via VP) projections of the shell to the hypothalamus have been suggested to account for the top-down (cognitive and reward) regulation of the hypothalamic “homeostatic” processes (Berthoud 2007). In contrast to the core, the shell does not directly or indirectly project to the SNr or the STN (Humphries and Prescott 2010). The shell is a specific region, in that it is a part of subcortical brain machinery for the generation or initiation of liking reactions (Berridge 2009). “Liking” has been defined as an objective hedonic reaction detected in behavior or neural signals, and generated chiefly by the subcortical brain system. A liking reaction to sweetness produces conscious pleasure by recruiting additional brain systems, such the OFC, but core “liking” can occur independently of consciousness (Berridge 2009, Berridge, Ho et al. 2010). The pleasure generators in the shell and the VP are organized to the “hotspots” in which mu opioid stimulation can substantially enhance the intensity

of liking reactions. In contrast to “linking”, “wanting” is not associated with liking reactions or pleasure. “Wanting” refers to incentive salience or motivation for reward. Attribution of incentive salience makes a cue more attractive, attention grabbing and with a higher motivational value (Berridge, Ho et al. 2010). There is convincing evidence that “wanting” is a mesolimbic-generated process and depends on dopaminergic activity. Like core “liking”, cue-triggered subcortical “wanting” does not require conscious awareness or understanding of the causal relation about hedonic outcome. Unlike “liking”, “wanting” is not restricted to hotspots and can elicited by stimulation throughout the entire shell or even in peripheral structures that include the amygdala or neostriatum. It is hypothesized that distorted “liking” and “wanting” as well as pathological activity in the VS and mesolimbic pathway play an important role in obesity, eating disorders, and addiction. Finally, it has been demonstrated that the shell also contains what was termed “affective keyboards” for the generation of intensive dread versus desire reactions that are controlled by prefrontal projections (Berridge and Kringelbach 2013).

Output of the core is analogous to the dorsal striatal projections, sending fibers to the dorsolateral part of the ventral pallidum, the medial part of the Gpi and SNr, which in turn project to the ventromedial and mediodorsal thalamic nuclei (Humphries and Prescott 2010). These thalamic nuclei are then in reciprocal connection with the medial prefrontal areas. Based on experimental data, it has been suggested that the core is involved in modulation of the vigor of operant response, and in assigning behavioral salience to stimuli during reward-seeking behavior (Gruber, Hussain et al. 2009, Gruber and McDonald 2012).

1.5.4 Ventral pallidum

The ventral pallidum (VS) is considered the “limbic final common pathway” for reward signals, mediating motivational signals to diverse cognitive and motor processes (Smith, Tindell et al. 2009, Berridge, Ho et al. 2010, Haber and Knutson 2010). The VS is

the fundamental site for the coding and enhancement of reward hedonics as well as wanting, i.e., the attribution of motivational value to the stimulus. The VS is thus far the only known region where neuronal death abolishes all liking reactions and replaces them with disliking (Berridge, Ho et al. 2010)(Berridge 2009). In addition to an opioid hedonic hotspot, there is also orexin hotspot in this nucleus, receiving input from the lateral hypothalamus (Ho and Berridge 2013). Activation of the orexin hotspot promotes food intake and hedonic enhancement of sweetness. In line with the findings from rodent and monkey studies, a recent human fMRI study has shown that the ventral pallidum, in addition to the OFC, plays a central role in the moment-to-moment hedonic inferences of visual stimuli that influence food-related decision-making (Tachibana and Hikosaka 2012, Simmons, Rapuano et al. 2014). The VP has strong reciprocal connections with the medial part of the STN. Other descending projections from the VP terminate in the adjacent lateral hypothalamus, the medial part of the SNc, SNr, VTA and PPN. Part of the VP projections innervate the midline and medial MD thalamic nuclei. Moreover, the VP innervates the internal and external segments of dorsal pallidum (Haber and Knutson 2010). Interestingly, this connection is directional, in that the dorsal pallidum does not project ventrally, suggesting the way in which the limbic system exerts an influence on the cognitive or motor systems. Furthermore, the VP also projects to the lateral habenula, which in turn projects to the tail of ventral tegmental area (tVTA). It has been proposed that the tVTA acts as hub, integrating widespread multimodal signals toward the dopamine system and participating in the generation of prediction error and in responses to aversive stimuli (Hikosaka 2010, Bourdy and Barrot 2012).

2 AIMS OF THE STUDY

A. Considering the spatially distributed organization of the STN with limbic connectivity predominately in its medial part, and sensorimotor connectivity in its lateral part, the aim of the first study was to assess whether weight gain and motor improvement observed in PD patients treated by STN-DBS is dependent on the active electrode contact position in the STN, particularly with respect to the mediolateral direction.

B. As we previously observed a persisting decrease of morning cortisol plasma levels with the initiation of chronic stimulation (Novakova, Ruzicka et al. 2007, Ruzicka, Novakova et al. 2012), we further focused on the possible impact of STN-DBS on the endocrine system. Thus, the aim of the second study was to assess whether changes of plasma levels of morning cortisol depend on the position of the active electrode contact in the STN, which would corroborate the heterogeneity of this nucleus and confirm the impact of DBS on the HPA axis.

C. As STN-DBS may also influence the HP axis indirectly via the fear-stress circuits of the limbic system, the secondary aims were to elucidate whether morning plasma cortisol changes after initiation of stimulation are associated with postoperative anxiety and weight gain.

3 HYPOTHESIS

1. We hypothesized that while weight gain would be associated with the medial contact site of STN stimulation, motor improvement would relate to stimulation in the lateral part of the STN.

2. We hypothesized the cortisol decrease would depend on the position of the stimulation contact in the medial (limbic) part of the STN.

3. We hypothesized that DBS-related cortisol decrease would be accompanied by an increase of anxiety and weight gain.

4 WEIGHT GAIN IS ASSOCIATED WITH MEDIAL CONTACT SITE OF SUBTHALAMIC STIMULATION IN PARKINSON'S DISEASE

4.1 Material and Methods

Patients and weight measurement

Regular body weight measurements were made on the day of surgery and one, two, four, six, twelve and eighteen months after electrode implantation in 20 patients with advanced PD (6 women, 14 men; mean age 56.6±(SD)5.8 years; disease duration 13.2±4.5 years). Demographic data of the patients that participated in the study are summarized in table 1. A maximum change in weight during the study period and weight change at the 18th month were considered in each patient. Weight changes were expressed in absolute values as well as in percentage of initial body weight. Eating related questionnaires were administered at each visit. Food intake, hunger, general appetite and preference for sweet food were rated by patients as (0) without any change, (-1) lower or (+1) higher than at the previous visit. 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.

	gender	age at surgery (yrs)	PD duration before surg. (yrs)	UPDRSIII s-OFF	UPDRSIII s-ON	initial BMI (kg/m^2)	initial body weight (kg)	maximum weight gain (kg)
1	F	53	20	30	17	19.9	53.3	18.3
2	F	63	18	32	17	17.8	50.1	14.9
3	M	65	22	44	24	23.2	84.2	12.3
4	F	61	12	43	28	24.4	65.6	12.0
5	M	53	15	62	22	22.0	69.6	9.4
6	F	58	10	37	17	26.6	64.1	7.5
7	M	56	12	41	23	30.9	100.0	7.2
8	M	57	14	30	26	20.6	71.3	7.2
9	M	55	7	25	18	27.5	86.0	7.0
10	M	67	11	32	16	28.2	86.4	6.5
11	F	58	7	37	18	22.4	61.6	6.4
12	F	42	23	53	19	33.3	80.0	6.0
13	M	48	14	36	17	21.6	70.0	5.3
14	M	56	13	39	16	27.7	95.2	4.5
15	M	49	11	25	12	25.1	67.5	4.1
16	M	57	15	44	11	26.8	84.8	3.9
17	M	63	10	35	14	25.8	72.9	3.6
18	M	58	9	36	24	25.0	76.6	2.1
19	M	57	10	35	12	28.3	86.8	0.2
20	M	55	10	18	5	29.8	112.3	-0.3

Table 1

Clinical description of PD patients treated with subthalamic deep brain stimulation
F – female, M – male; PD – Parkinson's disease; UPDRS-III – motor subscore of the Unified Parkinson's Disease Rating Scale; sOFF – postoperative off-neurostimulation state; sON – postoperative on-neurostimulation state; BMI – body mass index; initial body weight – body weight assessed before implantation; maximum weight gain – maximum weight change over the whole study period.

Surgical procedure and stimulation settings

Bilateral DBS electrode implantation (model 3389, Medtronic, Minneapolis, MN, USA) was guided by MRI-based stereotaxy, microelectrode recordings and the test stimulation procedure as described elsewhere (Machado, Rezai et al. 2006). Within three days the electrodes were connected to a subcutaneously implanted pulse generator (Kinetra, Medtronic). Stimulation was initiated one month following implantation when each patient underwent standard screening of all electrode contacts in an off-medication state. Finally, one contact on each side and stimulation settings using a monopolar or bipolar (in one patient) setting were selected to obtain the best motor outcome. In the following month, the stimulation intensity was gradually increased (Figure 1) while dopaminergic medication was in most cases reduced to further optimize the motor outcome. For the purpose of our study, stimulation intensity was calculated as the mean of arithmetic products of all the parameters from both neurostimulators (I-intensity, u-voltage, d-pulse duration, f-frequency): $I= (u_L.d_L.f_L + u_R.d_R.f_R)/2$ [25]. At month 18, the stimulation parameters were 2.8±0.5 V, 60-120 µs and 130 Hz and the mean stimulation intensity was $2.8±0.8 . 10^4$ VµsHz.

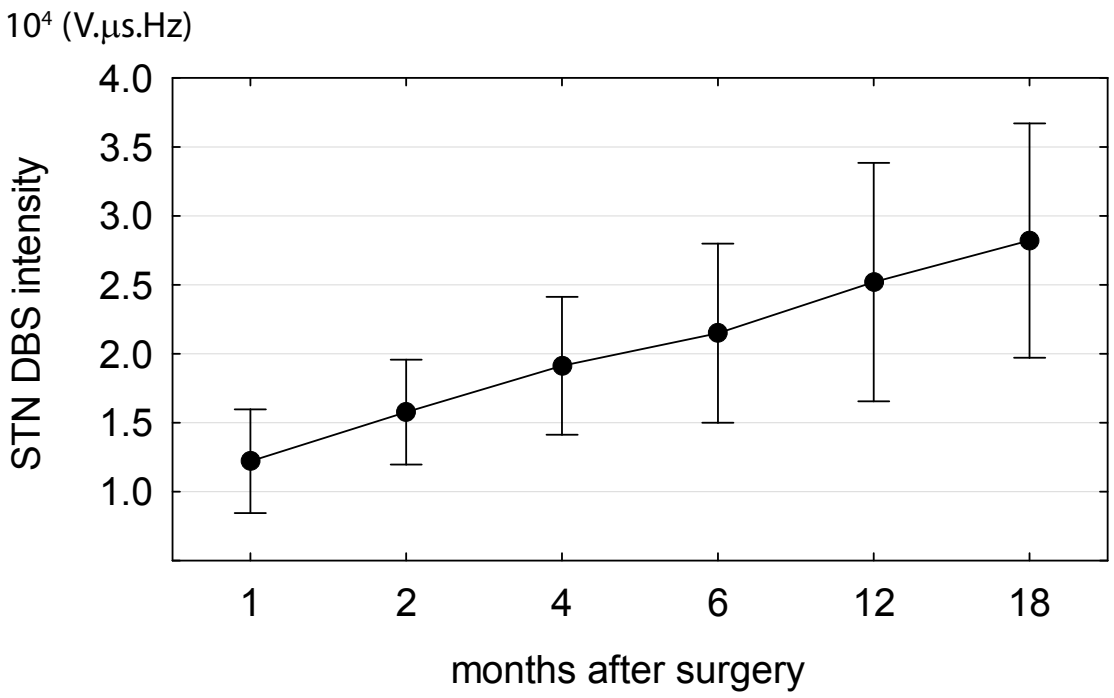

FIGURE 1

Mean stimulation intensity (±SD) of the STN-DBS at 1, 2, 4, 6, 12 and 18 months after implantation in 20 patients with Parkinson's disease. The stimulation intensity was calculated as the arithmetic product of the I-intensity, u-voltage, d-pulse duration and f-frequency from both hemispheres (uL.dL.fL + uR.dR.fR)/2. The stimulation intensity was gradually increasing during the study to optimize the motor outcome.

Motor outcome assessment of STN-DBS

Motor status was evaluated using the motor subscore of the Unified Parkinson's Disease Rating Scale (UPDRS-III). Each subject was examined postoperatively under two conditions at least 12 hours after discontinuing all antiparkinsonian drugs: (1) in the off-neurostimulation state (sOFF) and (2) in the on-neurostimulation state (sON). The change of motor status induced by stimulation was expressed as the percentage of UPDRS-III (100-100sON/sOFF). Additionally, hemi-body subscores derived from the UPDRS-III (items 20-26) were calculated as the sum of limb ratings of ridigity, akinesia and tremor, separately for the left and right extremities.

Assessment of active contact position

Magnetic resonance images were acquired at 1.5 T on a Siemens Avanto system (Siemens, Erlangen, Germany) in each patient approximately one year after DBS implantation. To obtain better image resolution, sagittal (0.9 mm isotropic) and axial (1x1x1.6 mm) T1-weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) images were automatically co-registered and averaged using SPM5 software (Wellcome Trust Centre for Neuroimaging, London, UK).

All four contacts (0,1,2,3) of the DBS electrode produced well-defined susceptibility artifacts on the T1-MPRAGE image in each patient (Yelnik, Damier et al. 2003). While the coordinates of contacts 0 and 3 were established directly from the center of the distal and proximal artifacts using MRIcro 1.40 software (www.cabiatl.com/mricro), the coordinates of contacts 1 and 2 were calculated. The x-coordinate of each contact was measured from the wall of the third ventricle, whereas the y- and z-coordinates were measured from the midcommisural point. Two coordinate systems, native and normalized, were used in the study. During linear normalization, all dimensions were manually adjusted with respect to the standardized AC-PC length, to the distance of the midcommissural point from the lateral edge of the putamen, and to

the distance of the optic tract from the dorsal edge of the putamen. Finally, the active contacts in both hemispheres were plotted on axial (xy), coronal (xz) and sagittal (yz) planes covering the whole subthalamic area.

Analysis

Statistical analysis was performed using SPSS 14.0.1 software (SPSS Inc, Chicago, IL, USA). For parameters with normal distribution, parametric tests (one sample t-test, paried t-test, Pearson correlation analysis) were used. The others were assessed with the non-parametric tests (Friedman test, Spearman rank correlation analysis).

Primary outcomes of the study were based on the maximum weight gain throughout the study and on the hemibody UPDRS-III in the sON state after initiation of neurostimulation. Their dependence on active contact position was analyzed for each x, y and z-axis separately by Pearson correlation analysis when considering the left and right hemispheres independently, as well as for all active contacts pooled bilaterally taking into account only one active contact (more medial or lateral contact from both hemispheres) in each patient.

In addition, we systematically sought a border dividing the subthalamic area into regions with higher and lower risk of weight gain. To do so, we compared weight gain relative to the active contact position in the subthalamic area divided into two regions of interest (ROI) by a movable yz-plane in the mediolateral direction (x-axis). The iterative general linear model (GLM) was used to compare weight gain in patients with at least one contact within one ROI and patients with both contacts in the other ROI. The factor GENDER and covariates AGE and TIME of postoperative maximum weight gain were included to control for possible confounding effects. The division yz-plane was then successively moved along the x-axis by 0.5-1 mm steps to define a BORDER with lowest p-value. A similar approach was used to compare weight gain considering active contacts in two subthalamic ROIs separated by a movable xz-plane in the

anteroposterior direction (y-axis) and by the xy-plane in the ventrodorsal direction (z-axis).

Relationships between body weight, motor performance, eating behavior and intensity of stimulation were assessed separately as secondary outcomes. As they were based on multiple comparisons, the Bonferroni correction was applied whenever appropriate.

4.2 Results

After initiation of STN DBS, the UPDRS-III score dropped on average from 36.7±(SD)9.6 (sOFF) to 17.8±5.5 (sON) ($T=7.3$, $p<10^{-7}$) showing good efficacy of neurostimulation treatment. The maximum change in body weight in the eighteen-month period after implantation was on average +6.9kg±4.5kg (–0.3 to +18.3kg) and was strongly significant ($T=6.6$, $p<10^{-5}$). Despite gradually increasing weight during the entire study period (Figure 2), nine patients reached the maximum body weight within the first 6 months after surgery, five patients in months 6-12 and six patients in months 12-18 after surgery.

As the analyses of active contact coordinates derived from native and normalized approaches yielded similar results, only statistics based on coordinates in native space are reported. In individual patients, the maximum weight gain correlated inversely along the x-axis with the distance of the active contact from the wall of the third ventricle in the left hemisphere ($r=-0.48$, $p<0.05$), right hemisphere ($r=-0.50$, $p<0.05$), and in pooled data ($r=-0.55$, $p<0.01$) if only more medial active contact regardless to hemisphere was considered (Figure 3). Similar results were obtained for maximum weight gain expressed in percentage of initial body weight as well as when considering weight gain at the end of the 18th month. In addition, the hemi-body UPDRS-III subscores in sON condition inversely correlated with the distance of the contralateral active contact from the wall of the third ventricle in the mediolateral direction ($r=-0.42$, $p<0.01$) (Figure 4). However, none of these parameters showed any relation to the active contact position along the y-axis or z-axis.

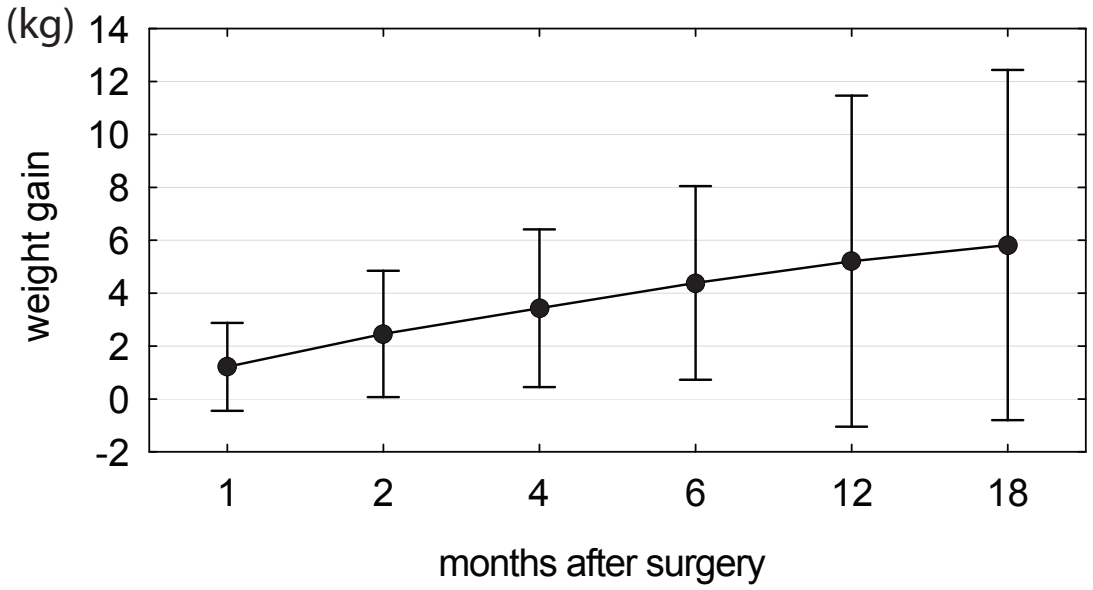

FIGURE 2

Mean changes in weight after implantation in 20 patients with Parkinson's disease. Body weight gradually increased during the study period. Weight gain represents the difference in weight (±SD) compared to the preoperative state.

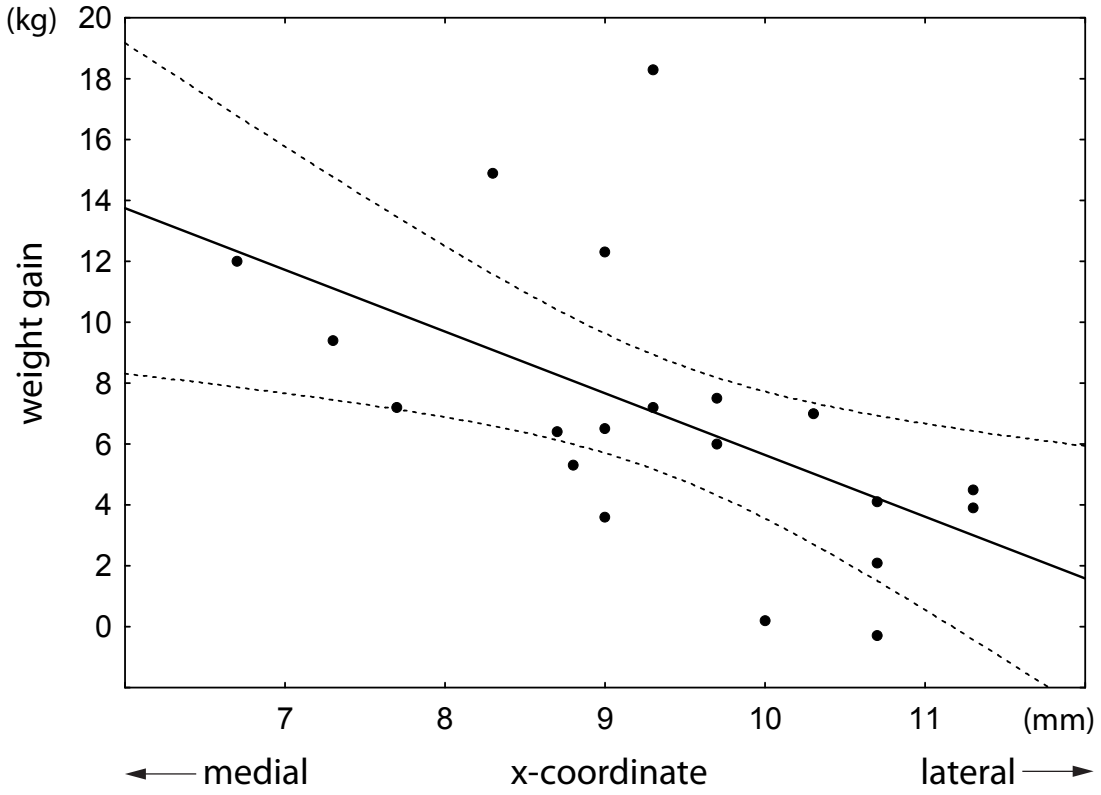

FIGURE 3

Weight gain in 20 patients with Parkinson's disease in relation to the mediolateral position of the active contact with bilateral STN-DBS ($r=-0.55$, $p<0.01$). Only one active contact (more medial contact from both hemispheres) was used in each patient. The x-coordinate represents the distance of the active contact from the wall of the third ventricle. Each millimeter in the medial direction was associated on average with a 1.6-kg increase in body weight. Dotted lines denote the 95% confidence interval of the regression line.

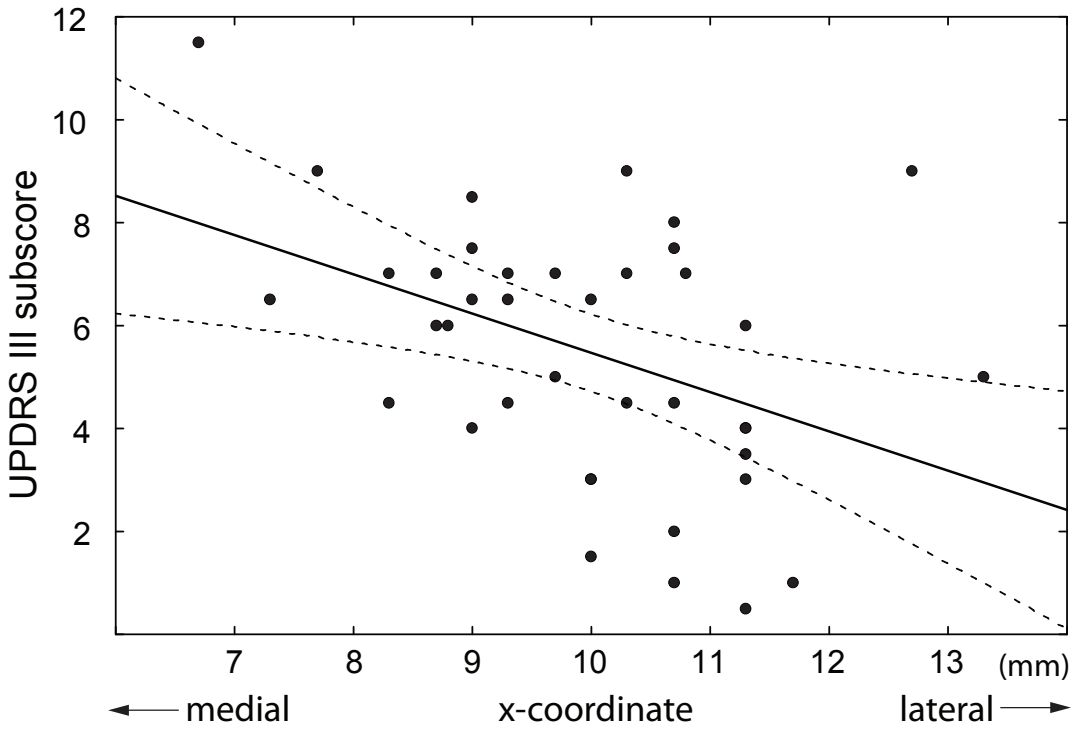

FIGURE 4

Hemi-body UPDRS-III subscores in the sON condition after overnight withdrawal of dopaminergic therapy in relation to the mediolateral position of the contralateral active contact. After initiation of STN-DBS, the hemi-body side with the lowest motor score (best motor condition) had the contralateral contacts located more laterally from the wall of the third ventricle ($r=-0.42$, $p<0.01$). Dotted lines denote the 95% confidence interval of the regression line.

With the iterative moving plane approach, we found a border orthogonal to the x-axis dividing the subthalamic area into two ROIs that differed in postoperative weight gain. Patients with at least one active contact within 9.3 mm of the wall of the third ventricle demonstrated significantly greater weight gain (9.4±4.4 kg, N=11) than those patients with both contacts located more laterally from the wall (3.9±2.7 kg, N=9) (GLM, factor BORDER: $F=16.1$, $p<0.001$)(Figure 5). The postoperative maximum weight gain significantly differed between genders, with a greater increase in women (N=6, 10.9±(SD)4.8kg) than in men (N=14, 5.2±3.4kg) (GLM, factor: GENDER, $F=10.7$, $p<0.01$). However, no other covariates (factor AGE: $F=0.001$, $p=0.99$; factor TIME: $F=0.002$, $p=0.96$) nor interactions between BORDER, GENDER, AGE and TIME were significant.

In addition, the postoperative maximum weight gain in all patients inversely correlated with preoperative body weight ($r=-0.62$, $p<0.05$ corrected). Maximum weight gain did not significantly depend on UPDRS-III improvement after switching the stimulation on ($r=-38$, $p=0.1$), and no correlation between weight gain at the 18th month and stimulation intensity was found. Analysis of eating behavior failed to demonstrate any change in hunger, appetite, preference for sweet food or food intake in our patients. However, there was a positive correlation between food intake and body-weight gain at the 18th month ($rho=0.66$, $P<0.05$ corrected).

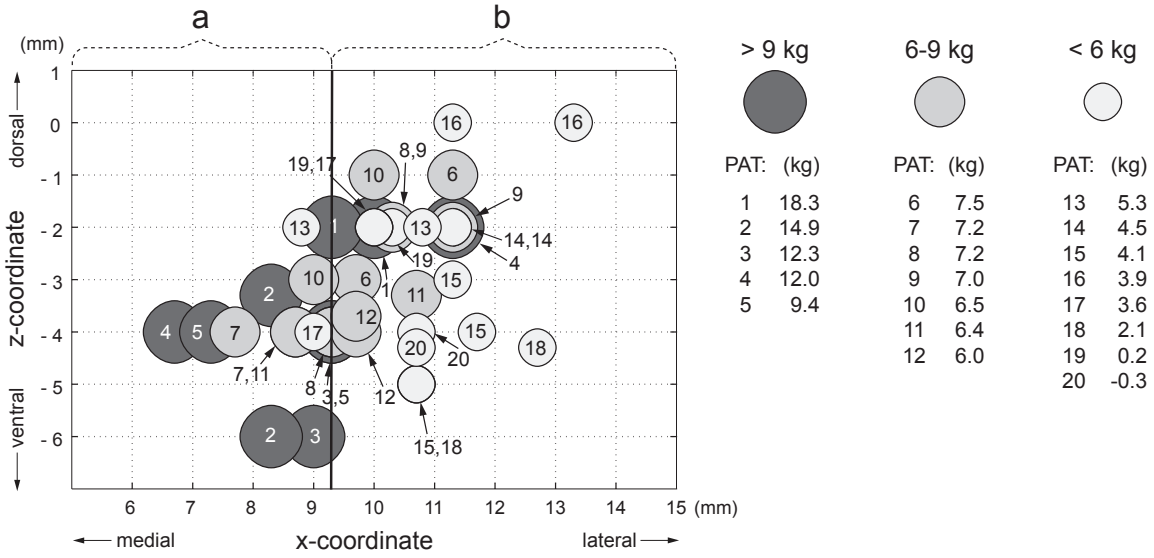

FIGURE 5

Bilateral STN-DBS active contact positions of 20 patients with Parkinson's disease plotted in the coronal plane with respect to weight gain. Patients (N=11) with at least one active contact (a) placed within 9.3-mm of the wall of the third ventricle gained significantly more weight than patients (N=9) with both contacts (b) located more laterally ($p<0.001$).

4.3 Discussion

We observed weight gain inversely related to the distance of the contacts from the wall of the third ventricle (Figure 3), and patients with at least one contact located medially in the STN experienced significantly greater weight gain than those with both active contacts located laterally (Figure 5). Thus, our results are consistent with the hypothesis that STN-DBS exerts a regional effect on adjacent structures involved in energy balance. In addition, our findings are also in agreement with reports of weight gain observed after unilateral STN-DBS (Walker, Lyerly et al. 2009, Lee, Kurundkar et al. 2011). As the position of each implanted electrode was verified by intraoperative microrecording and DBS caused clear motor improvement, we believe that our observations are not affected by electrode misplacement outside the STN. However, no correlation between stimulation intensity (Figure 1) and weight gain (Figure 2) was found in our study. This may be partly explained by low variability of stimulation parameters between patients or limited size of the patient group.

The maximum weight gain in our study was significantly larger in women than in men. Although women may be more susceptible to weight gain (Mueller, Anwander et al. 2011), previous studies have proven no significant sex-related differences in weight gain after unilateral or bilateral STN-DBS (Barichella, Marczewska et al. 2003, Macia, Perlemoine et al. 2004, Walker 2006, Montaurier, Morio et al. 2007, Bannier, Montaurier et al. 2009, Lee, Kurundkar et al. 2011). These findings are in agreement with our observation that weight gain in all six women of our study was associated with the medial contact site and that no interaction between active contact position and gender was found.

Similar to other studies (Hamel, Fietzek et al. 2003, Herzog, Fietzek et al. 2004, Godinho, Thobois et al. 2006), we found an inverse correlation between unilateral motor outcome (measured for rigidity, akinesia and tremor using hemi-body UPDRS-III subscore) and contralateral position of the active contact (Figure 4). Thus, patients with the lowest motor score (best motor condition) had contacts located more laterally from

the wall of the third ventricle. Such results most likely reflect the internal organization of the STN with the sensorimotor part located dorsolaterally in the nucleus (Hamani, Saint-Cyr et al. 2004).

However, we did not observe any significant correlation between weight gain and change in UPDRS-III score. This finding is consistent with those published previously (Barichella, Marczewska et al. 2003, Macia, Perlemoine et al. 2004, Sauleau, Leray et al. 2009) and may indicate that the connection between changes in weight and motor outcomes is not as straightforward as has been proposed (Gironell, Pascual-Sedano et al. 2002). Unrelated weight gain to motor outcome was also shown in another study in which weight gain was more pronounced in patients with subthalamic stimulation than in patients with pallidal stimulation, despite similar motor improvement in both groups(Sauleau, Leray et al. 2009). Thus, additional factors likely contribute to greater weight gain in subthalamic stimulation.

The central mechanism by which STN-DBS might cause weight gain remains unclear. It could be hypothesized that the spread of stimulation current beyond the borders of the STN may influence the hypothalamic regulation of energy metabolism or the homeostatic pathway of food intake. However, there are so far only a few studies on the effects of long-term STN-DBS on autonomic (Priori, Cinnante et al. 2001, Holmberg, Corneliusson et al. 2005, Ludwig, Remien et al. 2007) or hormonal systems (Novakova, Haluzik et al. 2011), and they have provided no clear explanation for weight gain.

Conversely, increased food intake by non-homeostatic or reward mechanisms may also provide a compelling hypothesis. The medial tip of the STN is involved in basal ganglia limbic and motivational functions (Temel, Blokland et al. 2005, Morel 2007, Haegelen, Rouaud et al. 2009, Rouaud, Lardeux et al. 2010). It is connected to key structures of the reward system such as the ventral pallidum and the ventral tegmental area (Groenewegen and Berendse 1990, Groenewegen, Berendse et al. 1993, Parent and Hazrati 1995). It has been shown that STN-DBS can affect the neural activity of these structures, as well as increase dopaminergic transmission in the striatum (Turner, Lavin et al. 2001, Winter, Lemke et al. 2008, Shon, Lee et al. 2010). Moreover, the medial part

of the STN is adjacent to the medial forebrain bundle which contains essential projections underlying reward functions (Wise 2005). Extensive research has demonstrated a close relationship between the mesolimbic system, medial forebrain bundle and ventral pallidum in motivational desire for food rewards, increase in food intake and obesity (Beaver, Lawrence et al. 2006, Davis, Patte et al. 2007, Berridge 2009, Smith, Tindell et al. 2009). Therefore, it seems plausible that an active electrode in the proximity of the medial STN could be ideally positioned to stimulate the reward system, thereby contributing to changes in motivational behaviors related to food intake and weight gain. Our previous study supports this hypothesis, as it revealed that postoperative weight gain correlated with arousal ratings from food pictures in the STN-DBS ON condition, suggesting an altered attribution of incentive salience (i.e., emotional relevance) to rewarding stimuli(Serranova, Jech et al. 2011).

Although most of the subjects did not report any changes in food intake, hunger or appetite in our study, the inaccuracy of self-reported intake (Hill and Davies 2001, Jakes, Day et al. 2004, Anagnostis, Athyros et al. 2009) should prompt caution in the interpretation of these results. Food intake depends largely on reward or homeostatic systems and is only partly under cognitive control (Peters, Wyatt et al. 2002, Davis, Patte et al. 2007, Berridge, Ho et al. 2010). We can hypothesize that slight individual changes in motivational behavior and reward system induced by DBS of subcortical structures need not be reflected in subjective feelings such as hunger or appetite (Winkielman, Berridge et al. 2005, Serranova, Jech et al. 2011). Further prospective studies taking into account changes in sensitivity to reward (Davis, Patte et al. 2007) and actual food intake would be necessary to clarify this question.

In agreement with another study (Bannier, Montaurier et al. 2009), we found a significant inverse correlation between preoperative body weight and postoperative weight gain. Since weight has been reported to decrease with PD progression (Bachmann and Trenkwalder 2006), it has been suggested that patients treated with DBS normalize their weight compared to their premorbid status because of motor improvement (Macia, Perlemoine et al. 2004, Montaurier, Morio et al. 2007). However,

this hypothesis cannot fully account for the fact that although most patients indicated for DBS are normal weight or overweight, the majority of them experience continuous weight gain after surgery (Barichella, Marczewska et al. 2003, Bannier, Montaurier et al. 2009). Yet it seems that changes in motor manifestations and energy expenditure can only partly explain both the weight loss in PD and weight gain after initiation of DBS (Bachmann and Trenkwalder 2006, Delikanaki-Skaribas, Trail et al. 2009, Sauleau, Leray et al. 2009). It has been shown that overweight and obese individuals have higher sensitivity to reward which predicts the tendency for overeating and strengthens preferences for sweet and fatty foods (Davis, Patte et al. 2007). We speculate that if STN-DBS increases sensitivity to reward in relation to the medial contact site in the subthalamic area, thereby modulating eating behavior, this effect would be more pronounced especially in patients with preoperatively lower body weight, lower sensitivity to reward and without previous, excessive caloric intake.

Some limitations have to be taken into account when interpreting our results. Since 0body weight may be reflected in local white matter changes (Mueller, Anwander et al. 2011) and the size and position of the STN varies (Richter, Hoque et al. 2004, Daniluk, K et al. 2010) to some extent relative to the midcommisural point, the influence of anatomic variability cannot be excluded from our measurements. However, we compensated for the variable width of the third ventricle, which significantly affects the mediolateral position of the STN (Zhu, Hamel et al. 2002, Daniluk, K et al. 2010), by measuring the x-coordinate from the wall of the third ventricle.

In conclusion, our findings support the hypothesis that weight gain in PD patients treated by STN-DBS may, at least in part, result from the regional effect of stimulation on adjacent structures involved in the central regulation of energy balance or reward**.**

5 A CHRONIC STRESS-LIKE SYNDROME AS CONSEQUENCE OF MEDIAL SITE OF SUBTHALAMIC STIMULATION IN PARKINSON'S DISEASE

5.1 Material and Methods

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) indicated 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, Daniel et al. 2002). Patient demographic and clinical data are summarized in Table 2 and in our previous publication (Ruzicka, Jech et al. 2012). Patients with dementia and/or severe depression were excluded on the basis of psychiatric examination and neuropsychological testing (Mattis Dementia Rating Scale score ≤ 123, Beck Depression Inventory score of ≥ 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.

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, Rezai et al. 2006). Stimulation was initiated one month following implantation 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 with the stimulator on (sON). The change of motor status was calculated as the percentage of UPDRS-III (100 - 100sON/sOFF) at each visit, 1, 3, 5, 11 and 17 months after STN-DBS initiation. 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. At month 17 after initiation of stimulation, 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 the parameters from DBS in both hemispheres (I-intensity, u-voltage, d-pulse duration, f-frequency, L-left electrode, R-right electrode): $I=(u_L.d_L.f_L+u_R.d_R.f_R)/2$ (Jech, Ruzicka et al. 2006). Daily doses of dopaminergic medication preoperatively and 12 months following surgery were converted to Levodopa Equivalent Daily Dose (LEDD: 100 mg of standard levodopa equals 150 mg of CR levodopa, 1 mg pramipexole, or 6 mg ropinirole). Changes in dopaminergic medication at 12 months after surgery were calculated in percentage of preoperative doses.

Assessment of active contact position

Magnetic resonance images were acquired at 1.5 T on a Siemens Symphony scanner (Siemens, Erlangen, Germany) in each patient approximately one year after DBS implantation using T1-weighted magnetization-prepared rapid acquisition gradient-echo sequences acquired in axial (1x1x1.6 mm) and sagittal (0.9x0.9x0.9 mm) planes, with a re-sampled resolution of 0.9 mm^3. The positions of active electrode contacts were determined by x, y and z-coordinates as described previously (Ruzicka, Jech et al. 2012). Briefly, the x- coordinate of each contact was measured manually from the wall of the third ventricle, whereas the y- and z-coordinates were measured from the mid-commisural point. Mean contact positions are shown in Table 3.

Plasma cortisol

The first plasma cortisol sample was taken in the morning on day of bilateral STN-DBS initiation (TIME 0). Further samples were taken at one month (TIME 1) and at 17 months (TIME 17) after STN-DBS initiation. On testing days, 5 ml of blood was withdrawn between 7–8 AM always in the off medication and fasting state (no dopaminergic mediation or food from previous evening). Blood samples were immediately spun, refrigerated at 2-8° C and analyzed within several hours. Plasma cortisol (nmol/l) was measured using a commercially available automated immunoassay, with intra-assay and inter-assay coefficients of variation of 4.8% and 5.2% (ADVIA Centaur CP System, Siemens Diagnostic, Germany).

gender	age at surgery (yrs)	PD duration before surg. (yrs)	Cortisol (nmol/l): TIME 0	Cortisol (nmol/l): TIME 1	Cortisol (nmol/l): TIME 17	weight gain (kg): TIME 17	STAI-2 before surg.	STAI-2 after surg.
F	53	20	786	670	544	12,1	-	-
F	63	18	665	468	290	13	48	46
M	65	22	630	372	412	13,4	37	62
F	61	12	711	445	320	9,6	39	45
M	53	15	586	290	372	10,3	44	68
F	58	10	844	371	528	7,5	-	-
M	56	12	806	252	483	1,6	-	-
M	57	14	615	494	572	7,5	41	50
M	55	7	814	803	639	9,9	39	48
M	67	11	790	950	583	1,6	-	-
F	58	7	494	556	571	8	34	47
F	42	23	381	441	373	6	58	66
M	48	14	767	588	861	-0,5	23	37
M	56	13	479	391	459	-1,3	41	44
M	49	11	328	740	586	2,3	47	44
M	57	15	429	692	634	4,1	33	42
M	63	10	655	246	565	3,4	-	-
M	58	9	513	472	750	-3,7	51	42
M	57	10	729	737	926	0,5	32	29
M	55	10	489	397	517	-9,2	31	45

Table 2
F – female, M – male; PD – Parkinson's disease; TIME 0- before initiation of stimulation; TIME 1- 1 month after initiation of stimulation; TIME 17- 17 months after initiation of stimulation; STAI-2- trait anxiety score

Average position of the active electrode contacts in the subthalamic region	
Right hemisphere (mm)	
x	10.3±1.4
y	-0.3±1.9
z	-2.8±1.5
Left hemisphere (mm)	
x	-9.6±1.2
y	-0.7±1.3
z	-3.4±1.4

Table 3: The x-coordinate of each contact was measured from the wall of the third ventricle (+ toward right; - toward left), the y-coordinate (+ toward anterior, - toward posterior) and z-coordinate (+ toward vertex, - toward brain-stem) were measured from the mid-commissural point. Values are expressed as mean (SD).

Neuropsychological assessment

Two neuropsychological tests were fully performed in a subgroup of 15 patients (see Table 2) prior to implantation and more than one year following implantation (15.7 ± 2.6 months). The State-Trait Anxiety Inventory (STAI) was used to assess the severity of anxiety preoperatively and approximately one year after surgery. The STAI is a self-administrated questionnaire based on two 20-item scales designed to measure state and trait anxiety. While state anxiety refers to a transitory emotional state, trait anxiety refers to an individual's predisposition to anxiety (Mondolo, Jahanshahi et al. 2007). The Beck Depression Inventory (BDI), a 21-item self-reported instrument, was used to measure the severity of depressive symptoms in the previous two weeks.

Body weight measurements

Body weight measurements were made on the day chronic STN-DBS (TIME 0) was initiated and longitudinally during each routine visit after 1, 3, 5, 11 a 17 months.

Analysis

Since normality was met for each parameter distribution (Shapiro–Wilk W Test), parametric tests were used in all analyses. The mean position of the active contact was calculated in each patient by averaging coordinates in the right and left hemispheres along each axis (x, y, z). The Repeated measures general linear model (RM-GLM) was used to assess

changes of cortisol over time, with TIME as the intra-subject factor (TIME 0, 1, 17), GENDER and POSITION (for x, y and z-axis) as inter-subject factors; and AGE, PD duration, LEDD change, UPDRS-III change and initial STIM intensity as confounding covariates. Pearson correlation analysis was used in the evaluation of cortisol plasma levels throughout the study (TIME 1-0 vs. TIME 17-0), with the x-coordinate of each active contact i) calculated as the mean of left and right hemispheres, ii) calculated for each hemisphere separately or iii) calculated with more medial or lateral contact in any of the two hemispheres.

In addition, two RM-GLM analyses were used to assess cortisol and weight with TIME (0, 1, 17 or 0, 1, 3, 5, 17 months) as the intra-subject factor and the trait ANXIETY as the inter-subject factor. Fisher analysis was used for post-hoc pairwise comparisons. Results were considered significant at $p<0.05$ after Bonferroni correction. Statistical analyses were performed using STATISTICA software, version 10 (StatSoft Inc., 2011).

5.2 Results

Using RM-GLM analysis, the change in *cortisol* over TIME in response to STN-DBS was significant ($F= 6.81$, $p=0.004$). The only significant interaction was between POSITION (x-axis) and TIME ($F= 6.28$, $p=0.005$). With the additional RM-GLM analysis adjusted for the confounding effects (AGE, PD duration, LEDD change, UPDRS change, stimulation intensity STIM), the interaction of POSITION (x-axis) and TIME remained significant ($F=6.5$ $p=0.007$). None of other factors or interactions were significant in either of the two analyses. *Cortisol* changes (TIME 0-1, TIME 0-17) correlated inversely with the distance of the active contact from the wall of the third ventricle in the mediolateral direction (x-axis), calculated as the mean of the x-coordinates of the left and right hemispheres (TIME 0-1: $r=0.59$, $p=0.006$; TIME 0-17: $r=0.71$, $p=0.0004$; Figure 6). The correlation remained significant regardless of calculation method of the x-coordinate.

While *state-anxiety* and *BDI* scores did not change throughout the study, *trait anxiety* became significantly worse one year after surgery compared to the pre-operative state, increasing from 39 ± 8.8 to 47 ± 10.5 ($T=3.13$, $p=0.01$). When patients were divided by *trait anxiety* median into two groups, patients with higher postoperative scores had active contacts localized more medially than those with lower postoperative scores ($T=3.4$, $p=0.002$; Figure 7).

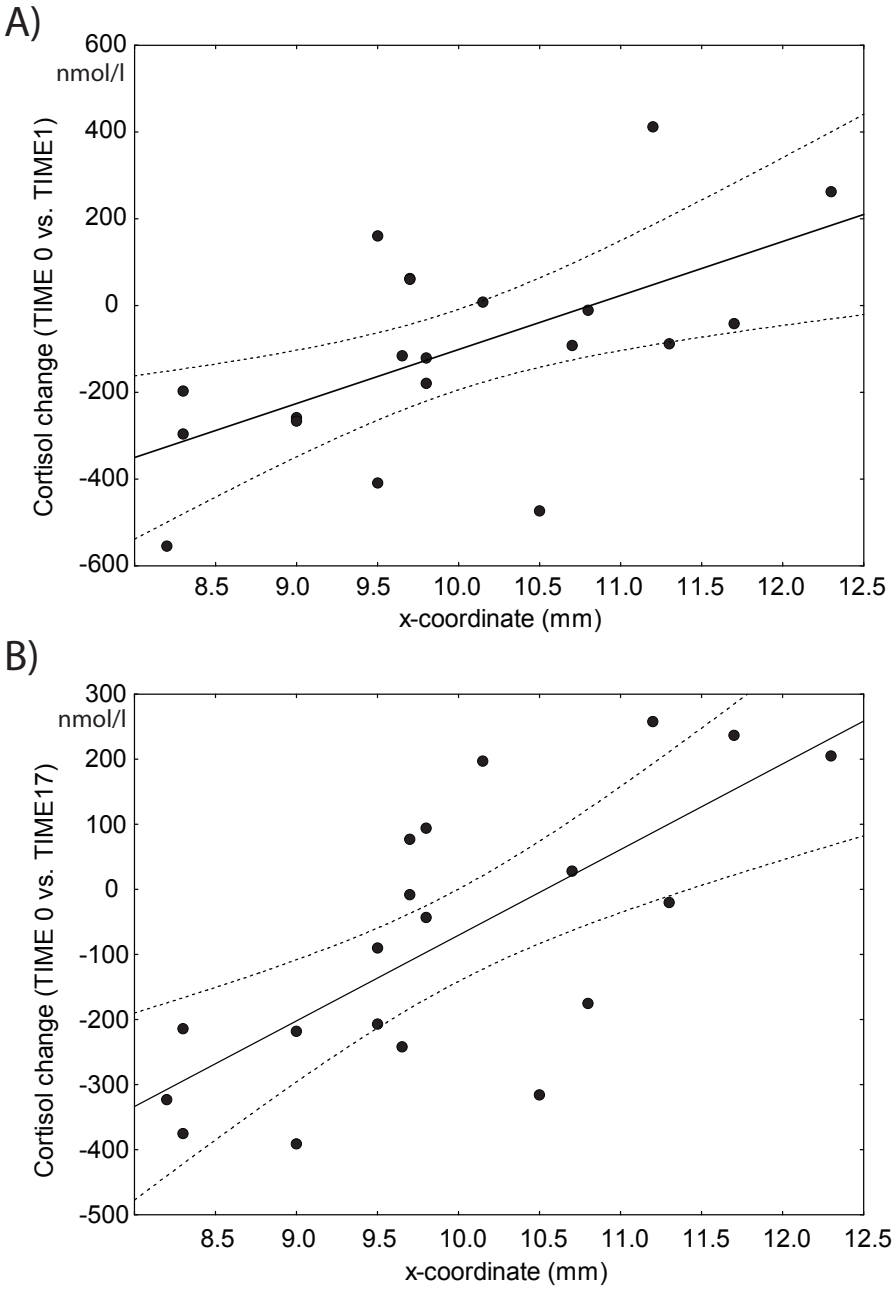

FIGURE 6

Morning plasma cortisol changes in the 1st (A) and 17th (B) month of stimulation relative to prestimulation state in relation to the mediolateral position of the active contact in bilateral STN-DBS (A - 1st month: p=0.006, r=0.59; B - 17th month: p=0.0004, r=0.71). The x-coordinate represents the distance of the active contact from the wall of the third ventricle. Dotted lines denote the 95% confidence interval of the regression line.

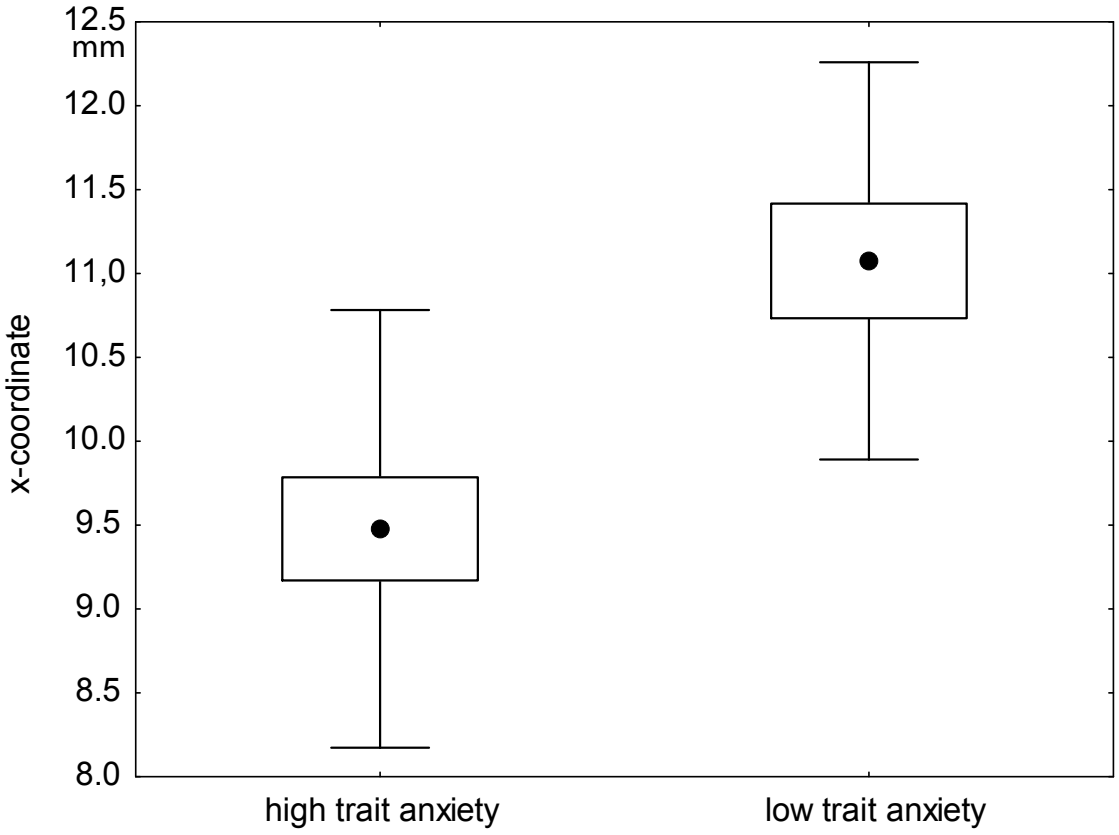

FIGURE 7

Patients with higher postoperative trait anxiety scores had active contacts localized more medially than those with lower postoperative scores (T=-3.4, p=0.002). The x-coordinate represents the distance of the active contact from the wall of the third ventricle.

When modeling the cortisol level with the RM-GLM restricted to the group of patients in which anxiety was assessed, we observed a significant trait ANXIETY versus TIME interaction effect (F=7.03, p=0.004; Figure 8-A). Post hoc analyses revealed significant differences in cortisol levels in TIME 17 only (p= 0.003). Using Pearson analysis, postoperative trait-anxiety inversely correlated with cortisol levels in TIME 17 (r=-0.70, p=0.004; Figure 8-B).

Finally, for weight gain the RM-GLM showed a significant effect of ANXIETY (F=5.87, p =0.03) and ANXIETY versus TIME interaction (F=5.03, p=0.002; Figure 9). Differences in weight gain assessed with Fisher post hoc tests were significant in TIME 5 (p=0.02), TIME 11 (p=0.009) and TIME 17 (p=0.001).

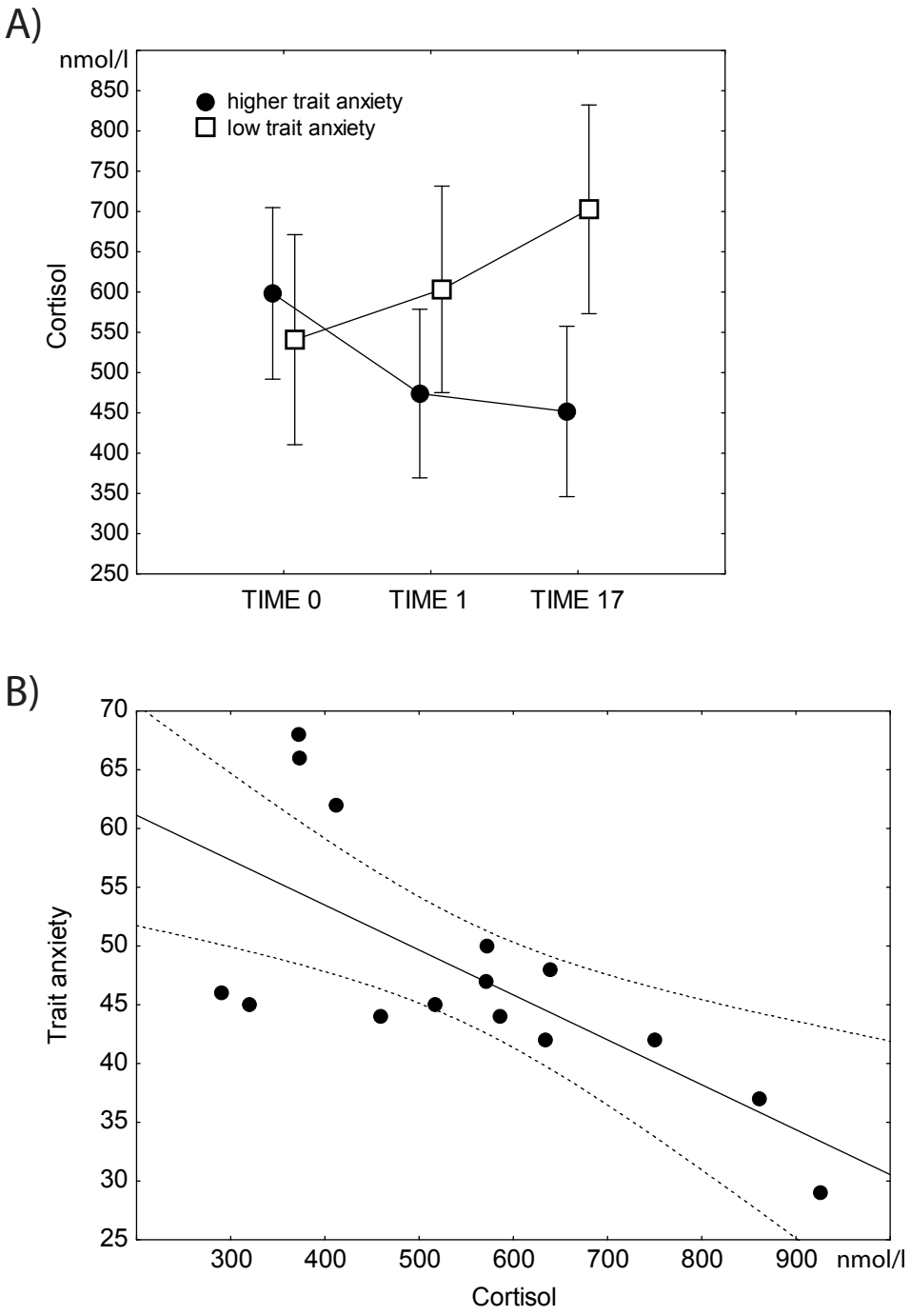

FIGURE 8

A - Association of plasma cortisol levels with anxiety. Patients with higher postoperative trait anxiety at 12th month had significantly lower cortisol levels at 17th month after initiation of the STN-DBS (Fisher post-hoc test p= 0.003). B- trait anxiety at 12th month inversely correlated with cortisol levels at 17th month after initiation of the STN-DBS (r=-0.70, p=0.004).

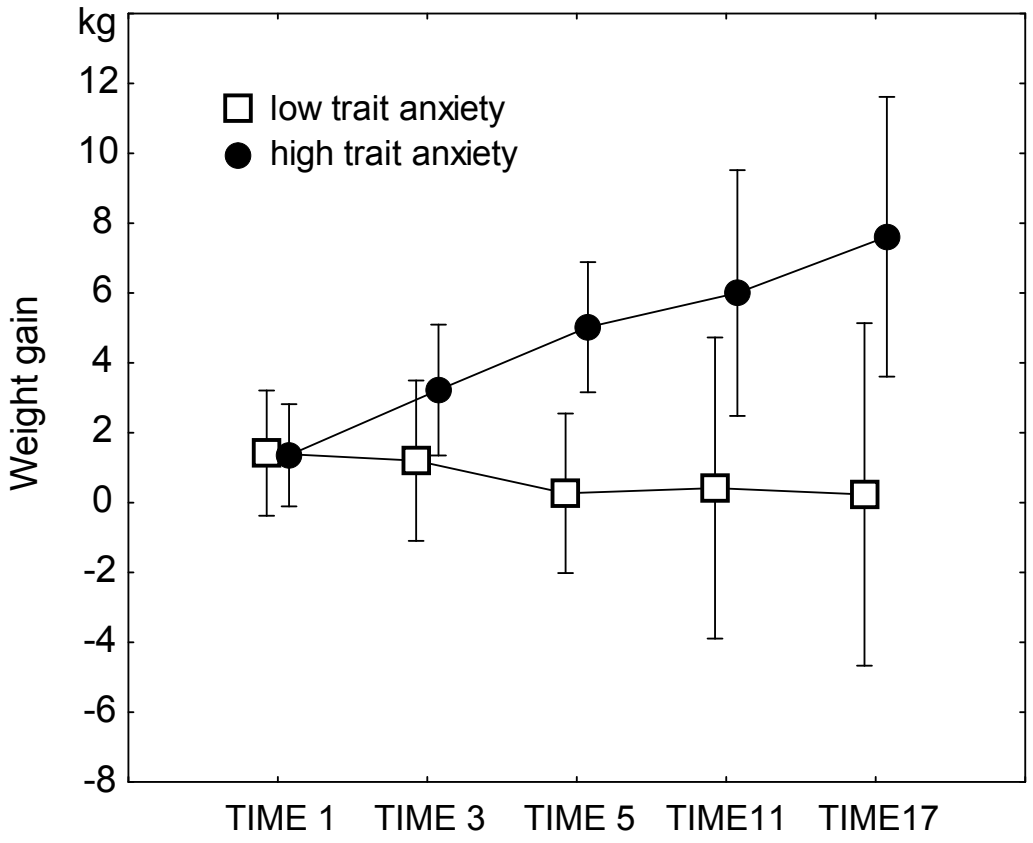

FIGURE 9

Weight gain over the period of the study in relation to anxiety. From 5th month after initiation of the STN-DBS, patients with higher trait anxiety experienced significant greater weight gain than patients with lower anxiety (Fisher post hoc test: at 5th month, p=0.02; 11th month, p=0.009; 17th month, p=0.001).

5.3 Discussion

We observed that the initiation of STN-DBS was associated with morning cortisol changes in close relation to the mediolateral position of the active electrode in the STN (Figure 6). Patients with at least one contact localized more medially in the STN experienced significantly greater decrease of cortisol than those with one or both active contacts localized more laterally.

This result is robust, as it remained significant after compensation for possible confounding variables such as gender, duration of PD, change in dopaminergic therapy, motor outcome and stimulation intensity. Thus, the present findings are consistent with the hypothesis that STN-DBS exerts influence on the HPA axis in relation to the mediolateral position of the stimulating contact.

In contrast to our findings, a previous study examining the entire profile of cortisol failed to find any cortisol changes in relation to STN-DBS (Seifried, Boehncke et al. 2012). However, smaller sample size, cortisol testing while undergoing dopaminergic treatment, disregarding the active contact position and different measurement intervals (3^{rd} and 6^{th} month after stimulation onset) may account for the reported negative findings.

Decreased morning cortisol levels have been documented in several neuropsychiatric conditions particularly associated with chronic stress (Miller, Chen et al. 2007), such as posttraumatic stress disorder (Wessa, Rohleder et al. 2006), general anxiety (Hek, Direk et al. 2013) and chronic fatigue syndrome (Van Den Eede, Moorkens et al. 2007). Lower cortisol output has been further reported in chronically stressed non-psychiatric populations (O'Connor, Hendrickx et al. 2009). In addition, individuals high in trait anxiety, who encounter a greater number of stressors and react more negatively to stress, have been also shown to secrete less cortisol at awakening compared to those low in trait anxiety (Therrien, Drapeau et al. 2008). Therefore, we hypothesized that cortisol changes induced by stimulation may be accompanied by altered postoperative anxiety. Accordingly, and in agreement with previously published work (Chang, Li et al. 2012) postoperative trait anxiety significantly worsened in our study. Furthermore, we observed that patients with higher postoperative trait anxiety had one of two active contacts located more medially in the STN (Figure 7) and showed significantly lower morning cortisol than those with lower anxiety (Figure 8). Thus, we may speculate that stimulation of medial areas of the STN acts on the HPA axis analogously to chronic stress.

Our hypothesis is supported by several lines of evidence indicating a close link between the STN and structures of the fear-stress network, most notably the ventromedial prefrontal cortex (vmPFC). It has been well established that medial territories of the STN are directly targeted by limbic prefrontal areas including the vmPFC and further bidirectionally linked with the ventral pallidum, representing the main output of the medial prefrontal basal ganglia circuitry (Haynes and Haber 2013). In addition, close functional connectivity of the STN with this cortical region has been confirmed by PET neuroimaging studies of PD patients with STN-DBS (Le

Jeune, Peron et al. 2008, Gjedde and Geday 2009). Extensive research over the past decade has particularly identified the vmPFC as one of the key regions for stress response regulation with an influence on the HPA axis (Jankord and Herman 2008), on fear conditioning and extinction (Etkin, Egner et al. 2011), and on decision-making (Bechara 2005, Grabenhorst and Rolls 2011). Conversely, dysfunction of the vmPFC has been shown to be associated with both HPA axis dysregulation and the pathogenesis of higher trait anxiety (Kim and Whalen 2009), anxiety disorders (Myers-Schulz and Koenigs 2012), impulsivity, addictions and obesity (Bechara 2005, Volkow, Wang et al. 2012). Therefore, it is conceivable that even in the absence of acute adverse effects of stimulation, a more medial STN-DBS contact site may introduce a certain degree of chronic noise projecting to the vmPFC, thereby leading to cortisol and trait-anxiety changes found in our study.

Finally, we observed that weight gain was closely associated with anxiety as well as with cortisol levels in the present study. Thus, patients with higher anxiety and lower cortisol increased body weight more than those with lower anxiety (Figure 9). Our findings are broadly consistent with a number of studies highlighting the role of anxiety and chronic stress with overeating, enhanced reward processing and obesity (Dallman 2010). Moreover, our results are also consistent with other studies showing decreased cortisol in overweight and obese individuals (Travison, O'Donnell et al. 2007, Champaneri, Xu et al. 2013). However, human overeating is not just a passive response to salient food triggers, but it is also about making choices (Davis, Levitan et al. 2004). Since the STN is thought to be involved in decision making (Zaghloul, Weidemann et al. 2012), and that neural systems implicated in fear and anxiety overlap in the vmPFC with those involved in the decision-making processes, we may speculate that decision making deficits may be an important factor contributing to weight gain and trait anxiety following STN-DBS. It should also be noted that several other disorders associated with decision-making deficits and vmPFC dysfunction, such as addiction (Lovallo 2006) impulsivity (Djamshidian, O'Sullivan et al. 2011) and psychopathy (van Honk, Schutter et al. 2003) have also been shown to be accompanied by lower morning cortisol.

In conclusion, we observed a higher chance for decreased plasma cortisol, increased anxiety and weight gain in PD patients with STN-DBS when the active DBS electrode is located more medially in the STN. Therefore, we speculate that our findings may reflect modulation of the fear-stress network, notably the vmPFC, through limbic circuits to the STN in a way that mimics the effects of chronic stress. In addition, our results provide further support to the

hypothesis that changes in the regulation of emotional or motivational processing play an important role in weight gain following STN-DBS. Our findings may also be of clinical relevance (Lovallo 2006, Vreeburg, Hoogendijk et al. 2013), as patients with higher postoperative trait anxiety and lower cortisol levels following STN-DBS are at increased future risk of developing mood and behavioral disorders, chronic fatigue and obesity.

6 CONCLUSIONS

1. We observed that weight gain inversely related to the distance of the contacts from the wall of the third ventricle (Figure 3), and patients with at least one contact localized medially in the STN experienced significantly greater weight gain than those with both active contacts localized laterally (Figure 5). Thus, our results are consistent with the hypothesis that STN-DBS exerts a regional effect on adjacent structures involved in food intake or energy balance.
2. We found inverse correlation between the unilateral motor outcome (measured for rigidity, akinesia and tremor using the hemi-body UPDRS-III subscore) and the contralateral position of the active contact (Figure 4). Thus, patients with the lowest motor score (best motor condition) had contacts localized more laterally from the wall of the third ventricle. Such results most likely reflect the internal organization of the STN with the sensorimotor part localized dorsolaterally in the nucleus.
3. We observed that the initiation of STN-DBS was associated with morning cortisol changes in close relation to the medio-lateral position of the active electrode contact in the subthalamic nucleus. Patients with at least one contact localized more medially in the STN experienced a significantly greater decrease of cortisol than those with one or both active contacts more laterally. Thus, the present findings are consistent with the hypothesis that the STN-DBS exerts influence on the HP axis in relation to the mediol-lateral position of the stimulating contact.
4. We observed that patients with higher postoperative trait anxiety had one of two active contacts localized more medially in the STN (Figure 7) and showed significantly lower morning cortisol than those with lower anxiety (Figure 8). Thus, we may speculate that the stimulation of medial areas of the STN acts on the HP axis in a similar manner as chronic stress.
5. We found that patients with higher anxiety and lower cortisol increased their body weight more than those with lower anxiety (Figure 9). Our findings are broadly consistent with a number of studies highlighting the role of anxiety and chronic stress in overeating, enhanced reward processing and obesity.

7 REFERENCES

Agnesi, F., M. D. Johnson and J. L. Vitek (2013). "Deep brain stimulation: how does it work?" Handb Clin Neurol **116**: 39-54.

Alberts, J. L., C. Voelcker-Rehage, K. Hallahan, M. Vitek, R. Bamzai and J. L. Vitek (2008). "Bilateral subthalamic stimulation impairs cognitive-motor performance in Parkinson's disease patients." Brain **131**(Pt 12): 3348-3360.

Alexander, G. E. and M. D. Crutcher (1990). "Functional architecture of basal ganglia circuits: neural substrates of parallel processing." Trends in neurosciences **13**(7): 266-271.

Amiez, C., J. P. Joseph and E. Procyk (2006). "Reward encoding in the monkey anterior cingulate cortex." Cereb Cortex **16**(7): 1040-1055.

Anagnostis, P., V. G. Athyros, K. Tziomalos, A. Karagiannis and D. P. Mikhailidis (2009). "Clinical review: The pathogenetic role of cortisol in the metabolic syndrome: a hypothesis." J Clin Endocrinol Metab **94**(8): 2692-2701.

Anzak, A., L. Gaynor, M. Beigi, T. Foltynie, P. Limousin, L. Zrinzo, P. Brown and M. Jahanshahi (2013). "Subthalamic nucleus gamma oscillations mediate a switch from automatic to controlled processing: a study of random number generation in Parkinson's disease." Neuroimage **64**: 284-289.

Aron, A. R., T. W. Robbins and R. A. Poldrack (2014). "Inhibition and the right inferior frontal cortex: one decade on." Trends Cogn Sci **18**(4): 177-185.

Ashby, F. G., B. O. Turner and J. C. Horvitz (2010). "Cortical and basal ganglia contributions to habit learning and automaticity." Trends Cogn Sci **14**(5): 208-215.

Bachmann, C. G. and C. Trenkwalder (2006). "Body weight in patients with Parkinson's disease." Mov Disord **21**(11): 1824-1830.

Badre, D. (2008). "Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes." Trends Cogn Sci **12**(5): 193-200.

Badre, D. and M. D'Esposito (2009). "Is the rostro-caudal axis of the frontal lobe hierarchical?" Nat Rev Neurosci **10**(9): 659-669.

Badre, D. and M. J. Frank (2012). "Mechanisms of hierarchical reinforcement learning in cortico-striatal circuits 2: evidence from fMRI." Cereb Cortex **22**(3): 527-536.

Badre, D., J. Hoffman, J. W. Cooney and M. D'Esposito (2009). "Hierarchical cognitive control deficits following damage to the human frontal lobe." Nat Neurosci **12**(4): 515-522.

Balaz, M., I. Rektor and J. Pulkrabek (2008). "Participation of the subthalamic nucleus in executive functions: An intracerebral recording study." Mov Disord **23**(4): 553-557.

Ballanger, B., T. van Eimeren, E. Moro, A. M. Lozano, C. Hamani, P. Boulinguez, G. Pellecchia, S. Houle, Y. Y. Poon, A. E. Lang and A. P. Strafella (2009). "Stimulation of the subthalamic nucleus and impulsivity: release your horses." Ann Neurol **66**(6): 817-824.

Bannier, S., C. Montaurier, P. P. Derost, M. Ulla, J. J. Lemaire, Y. Boirie, B. Morio and F. Durif (2009). "Overweight after deep brain stimulation of the subthalamic nucleus

in Parkinson disease: long term follow-up." J Neurol Neurosurg Psychiatry **80**(5): 484-488.
Barichella, M., A. M. Marczewska, C. Mariani, A. Landi, A. Vairo and G. Pezzoli (2003). "Body weight gain rate in patients with Parkinson's disease and deep brain stimulation." Mov Disord **18**(11): 1337-1340.
Baunez, C., J. Yelnik and L. Mallet (2011). "Six questions on the subthalamic nucleus: lessons from animal models and from stimulated patients." Neuroscience **198**: 193-204.
Baxter, M. G. and E. A. Murray (2002). "The amygdala and reward." Nat Rev Neurosci **3**(7): 563-573.
Beaver, J. D., A. D. Lawrence, J. van Ditzhuijzen, M. H. Davis, A. Woods and A. J. Calder (2006). "Individual differences in reward drive predict neural responses to images of food." J Neurosci **26**(19): 5160-5166.
Bechara, A. (2005). "Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective." Nat Neurosci **8**(11): 1458-1463.
Berridge, K. C. (2009). "'Liking' and 'wanting' food rewards: brain substrates and roles in eating disorders." Physiol Behav **97**(5): 537-550.
Berridge, K. C., C. Y. Ho, J. M. Richard and A. G. DiFeliceantonio (2010). "The tempted brain eats: pleasure and desire circuits in obesity and eating disorders." Brain Res **1350**: 43-64.
Berridge, K. C. and M. L. Kringelbach (2013). "Neuroscience of affect: brain mechanisms of pleasure and displeasure." Curr Opin Neurobiol **23**(3): 294-303.
Berthoud, H. R. (2002). "Multiple neural systems controlling food intake and body weight." Neurosci Biobehav Rev **26**(4): 393-428.
Berthoud, H. R. (2007). "Interactions between the "cognitive" and "metabolic" brain in the control of food intake." Physiol Behav **91**(5): 486-498.
Berthoud, H. R. (2012). "The neurobiology of food intake in an obesogenic environment." Proc Nutr Soc **71**(4): 478-487.
Berthoud, H. R. and C. Morrison (2008). "The brain, appetite, and obesity." Annu Rev Psychol **59**: 55-92.
Berthoud, H. R. and H. Munzberg (2011). "The lateral hypothalamus as integrator of metabolic and environmental needs: from electrical self-stimulation to opto-genetics." Physiol Behav **104**(1): 29-39.
Bourdy, R. and M. Barrot (2012). "A new control center for dopaminergic systems: pulling the VTA by the tail." Trends Neurosci **35**(11): 681-690.
Brunenberg, E. J., P. Moeskops, W. H. Backes, C. Pollo, L. Cammoun, A. Vilanova, M. L. Janssen, V. E. Visser-Vandewalle, B. M. ter Haar Romeny, J. P. Thiran and B. Platel (2012). "Structural and resting state functional connectivity of the subthalamic nucleus: identification of motor STN parts and the hyperdirect pathway." PLoS One **7**(6): e39061.
Buckner, R. L., J. R. Andrews-Hanna and D. L. Schacter (2008). "The brain's default network: anatomy, function, and relevance to disease." Ann N Y Acad Sci **1124**: 1-38.
Buckner, R. L. and D. C. Carroll (2007). "Self-projection and the brain." Trends Cogn Sci **11**(2): 49-57.

Castrioto, A., E. Lhommee, E. Moro and P. Krack (2014). "Mood and behavioural effects of subthalamic stimulation in Parkinson's disease." Lancet Neurol **13**(3): 287-305.
Cavanagh, J. F., J. L. Sanguinetti, J. J. Allen, S. J. Sherman and M. J. Frank (2014). "The Subthalamic Nucleus Contributes to Post-error Slowing." J Cogn Neurosci.
Champaneri, S., X. Xu, M. R. Carnethon, A. G. Bertoni, T. Seeman, A. S. DeSantis, A. Diez Roux, S. Shrager and S. H. Golden (2013). "Diurnal salivary cortisol is associated with body mass index and waist circumference: the multiethnic study of atherosclerosis." Obesity (Silver Spring) **21**(1): E56-63.
Chang, C., N. Li, Y. Wu, N. Geng, S. Ge, J. Wang, X. Wang and X. Wang (2012). "Associations between bilateral subthalamic nucleus deep brain stimulation (STN-DBS) and anxiety in Parkinson's disease patients: a controlled study." J Neuropsychiatry Clin Neurosci **24**(3): 316-325.
Choi, E. Y., B. T. Yeo and R. L. Buckner (2012). "The organization of the human striatum estimated by intrinsic functional connectivity." J Neurophysiol **108**(8): 2242-2263.
Coizet, V., J. H. Graham, J. Moss, J. P. Bolam, M. Savasta, J. G. McHaffie, P. Redgrave and P. G. Overton (2009). "Short-latency visual input to the subthalamic nucleus is provided by the midbrain superior colliculus." J Neurosci **29**(17): 5701-5709.
Collins, K. L., E. M. Lehmann and P. G. Patil (2010). "Deep brain stimulation for movement disorders." Neurobiol Dis **38**(3): 338-345.
Courtin, J., T. C. Bienvenu, E. O. Einarsson and C. Herry (2013). "Medial prefrontal cortex neuronal circuits in fear behavior." Neuroscience **240**: 219-242.
Crittenden, J. R. and A. M. Graybiel (2011). "Basal Ganglia disorders associated with imbalances in the striatal striosome and matrix compartments." Front Neuroanat **5**: 59.
D'Argembeau, A. (2013). "On the role of the ventromedial prefrontal cortex in self-processing: the valuation hypothesis." Front Hum Neurosci **7**: 372.
Dallman, M. F. (2010). "Stress-induced obesity and the emotional nervous system." Trends Endocrinol Metab **21**(3): 159-165.
Daniluk, S., G. D. K, S. A. Ellias, P. Novak and J. M. Nazzaro (2010). "Assessment of the variability in the anatomical position and size of the subthalamic nucleus among patients with advanced Parkinson's disease using magnetic resonance imaging." Acta Neurochir (Wien) **152**(2): 201-210; discussion 210.
Davis, C., R. D. Levitan, P. Muglia, C. Bewell and J. L. Kennedy (2004). "Decision-making deficits and overeating: a risk model for obesity." Obes Res **12**(6): 929-935.
Davis, C., R. D. Levitan, P. Muglia, C. Bewell and J. L. Kennedy (2004). "Decision‐making deficits and overeating: A risk model for obesity." Obesity research **12**(6): 929-935.
Davis, C., K. Patte, R. Levitan, C. Reid, S. Tweed and C. Curtis (2007). "From motivation to behaviour: a model of reward sensitivity, overeating, and food preferences in the risk profile for obesity." Appetite **48**(1): 12-19.
de Wit, S., P. R. Corlett, M. R. Aitken, A. Dickinson and P. C. Fletcher (2009). "Differential engagement of the ventromedial prefrontal cortex by goal-directed and

habitual behavior toward food pictures in humans." J Neurosci **29**(36): 11330-11338.
de Wit, S., P. Watson, H. A. Harsay, M. X. Cohen, I. van de Vijver and K. R. Ridderinkhof (2012). "Corticostriatal connectivity underlies individual differences in the balance between habitual and goal-directed action control." J Neurosci **32**(35): 12066-12075.
Dedovic, K., A. Duchesne, J. Andrews, V. Engert and J. C. Pruessner (2009). "The brain and the stress axis: the neural correlates of cortisol regulation in response to stress." Neuroimage **47**(3): 864-871.
Delikanaki-Skaribas, E., M. Trail, W. W. Wong and E. C. Lai (2009). "Daily energy expenditure, physical activity, and weight loss in Parkinson's disease patients." Mov Disord **24**(5): 667-671.
DeLong, M. and T. Wichmann (2009). "Update on models of basal ganglia function and dysfunction." Parkinsonism Relat Disord **15 Suppl 3**: S237-240.
deSouza, R. M., E. Moro, A. E. Lang and A. H. Schapira (2013). "Timing of deep brain stimulation in Parkinson disease: a need for reappraisal?" Ann Neurol **73**(5): 565-575.
Dimitropoulos, A., J. Tkach, A. Ho and J. Kennedy (2012). "Greater corticolimbic activation to high-calorie food cues after eating in obese vs. normal-weight adults." Appetite **58**(1): 303-312.
Djamshidian, A., S. S. O'Sullivan, A. Papadopoulos, P. Bassett, K. Shaw, B. B. Averbeck and A. Lees (2011). "Salivary cortisol levels in Parkinson's disease and its correlation to risk behaviour." J Neurol Neurosurg Psychiatry **82**(10): 1107-1111.
Draganski, B., F. Kherif, S. Kloppel, P. A. Cook, D. C. Alexander, G. J. Parker, R. Deichmann, J. Ashburner and R. S. Frackowiak (2008). "Evidence for segregated and integrative connectivity patterns in the human Basal Ganglia." J Neurosci **28**(28): 7143-7152.
Eblen, F. and A. M. Graybiel (1995). "Highly restricted origin of prefrontal cortical inputs to striosomes in the macaque monkey." J Neurosci **15**(9): 5999-6013.
Espinosa-Parrilla, J. F., C. Baunez and P. Apicella (2013). "Linking reward processing to behavioral output: motor and motivational integration in the primate subthalamic nucleus." Front Comput Neurosci **7**: 175.
Etkin, A., T. Egner and R. Kalisch (2011). "Emotional processing in anterior cingulate and medial prefrontal cortex." Trends Cogn Sci **15**(2): 85-93.
Euston, D. R., A. J. Gruber and B. L. McNaughton (2012). "The role of medial prefrontal cortex in memory and decision making." Neuron **76**(6): 1057-1070.
Fasano, A., A. Daniele and A. Albanese (2012). "Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation." Lancet Neurol **11**(5): 429-442.
Frank, M. J. (2006). "Hold your horses: a dynamic computational role for the subthalamic nucleus in decision making." Neural Netw **19**(8): 1120-1136.
Gerardin, E., S. Lehericy, J. B. Pochon, S. Tezenas du Montcel, J. F. Mangin, F. Poupon, Y. Agid, D. Le Bihan and C. Marsault (2003). "Foot, hand, face and eye representation in the human striatum." Cereb Cortex **13**(2): 162-169.

Gerfen, C. R. and J. P. Bolam (2010). Chapter 1 - The Neuroanatomical Organization of the Basal Ganglia. Handbook of Behavioral Neuroscience. S. Heinz and Y. T. Kuei, Elsevier. **Volume 20:** 3-28.
Gerlach, K. D., R. N. Spreng, K. P. Madore and D. L. Schacter (2014). "Future planning: default network activity couples with frontoparietal control network and reward-processing regions during process and outcome simulations." Soc Cogn Affect Neurosci.
Gironell, A., B. Pascual-Sedano, P. Otermin and J. Kulisevsky (2002). "[Weight gain after functional surgery for Parkinsons disease]." Neurologia **17**(6): 310-316.
Gittis, A. H. and A. C. Kreitzer (2012). "Striatal microcircuitry and movement disorders." Trends Neurosci **35**(9): 557-564.
Gjedde, A. and J. Geday (2009). "Deep brain stimulation reveals emotional impact processing in ventromedial prefrontal cortex." PLoS One **4**(12): e8120.
Glascher, J., A. N. Hampton and J. P. O'Doherty (2009). "Determining a role for ventromedial prefrontal cortex in encoding action-based value signals during reward-related decision making." Cereb Cortex **19**(2): 483-495.
Godinho, F., S. Thobois, M. Magnin, M. Guenot, G. Polo, I. Benatru, J. Xie, A. Salvetti, L. Garcia-Larrea, E. Broussolle and P. Mertens (2006). "Subthalamic nucleus stimulation in Parkinson's disease : anatomical and electrophysiological localization of active contacts." J Neurol **253**(10): 1347-1355.
Goldberg, J. A. and C. J. Wilson (2010). Chapter 7 - The Cholinergic Interneurons of the Striatum: Intrinsic Properties Underlie Multiple Discharge Patterns. Handbook of Behavioral Neuroscience. S. Heinz and Y. T. Kuei, Elsevier. **Volume 20:** 133-149.
Gottfried, J. A., J. O'Doherty and R. J. Dolan (2003). "Encoding predictive reward value in human amygdala and orbitofrontal cortex." Science **301**(5636): 1104-1107.
Grabenhorst, F. and E. T. Rolls (2011). "Value, pleasure and choice in the ventral prefrontal cortex." Trends Cogn Sci **15**(2): 56-67.
Grabenhorst, F., E. T. Rolls and A. Bilderbeck (2008). "How cognition modulates affective responses to taste and flavor: top-down influences on the orbitofrontal and pregenual cingulate cortices." Cereb Cortex **18**(7): 1549-1559.
Grabenhorst, F., E. T. Rolls and B. A. Parris (2008). "From affective value to decision-making in the prefrontal cortex." Eur J Neurosci **28**(9): 1930-1939.
Graybiel, A. M. (2008). "Habits, rituals, and the evaluative brain." Annu Rev Neurosci **31**: 359-387.
Grillner, S., B. Robertson and M. Stephenson-Jones (2013). "The evolutionary origin of the vertebrate basal ganglia and its role in action selection." J Physiol **591**(Pt 22): 5425-5431.
Groenewegen, H. J. and H. W. Berendse (1990). "Connections of the subthalamic nucleus with ventral striatopallidal parts of the basal ganglia in the rat." J Comp Neurol **294**(4): 607-622.
Groenewegen, H. J., H. W. Berendse and S. N. Haber (1993). "Organization of the output of the ventral striatopallidal system in the rat: ventral pallidal efferents." Neuroscience **57**(1): 113-142.
Gruber, A. J., R. J. Hussain and P. O'Donnell (2009). "The nucleus accumbens: a switchboard for goal-directed behaviors." PLoS One **4**(4): e5062.

Gruber, A. J. and R. J. McDonald (2012). "Context, emotion, and the strategic pursuit of goals: interactions among multiple brain systems controlling motivated behavior." Front Behav Neurosci **6**: 50.
Haber, S. (2008). "Parallel and integrative processing through the Basal Ganglia reward circuit: lessons from addiction." Biol Psychiatry **64**(3): 173-174.
Haber, S. N. (2003). "The primate basal ganglia: parallel and integrative networks." J Chem Neuroanat **26**(4): 317-330.
Haber, S. N., A. Adler and H. Bergman (2012). Chapter 20 - The Basal Ganglia. The Human Nervous System (Third Edition). J. K. Mai and G. Paxinos. San Diego, Academic Press**:** 678-738.
Haber, S. N. and R. Calzavara (2009). "The cortico-basal ganglia integrative network: the role of the thalamus." Brain Res Bull **78**(2-3): 69-74.
Haber, S. N., K. S. Kim, P. Mailly and R. Calzavara (2006). "Reward-related cortical inputs define a large striatal region in primates that interface with associative cortical connections, providing a substrate for incentive-based learning." J Neurosci **26**(32): 8368-8376.
Haber, S. N. and B. Knutson (2010). "The reward circuit: linking primate anatomy and human imaging." Neuropsychopharmacology **35**(1): 4-26.
Haegelen, C., T. Rouaud, P. Darnault and X. Morandi (2009). "The subthalamic nucleus is a key-structure of limbic basal ganglia functions." Med Hypotheses **72**(4): 421-426.
Hamani, C., J. A. Saint-Cyr, J. Fraser, M. Kaplitt and A. M. Lozano (2004). "The subthalamic nucleus in the context of movement disorders." Brain **127**(Pt 1): 4-20.
Hamel, W., U. Fietzek, A. Morsnowski, B. Schrader, J. Herzog, D. Weinert, G. Pfister, D. Muller, J. Volkmann, G. Deuschl and H. M. Mehdorn (2003). "Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: evaluation of active electrode contacts." J Neurol Neurosurg Psychiatry **74**(8): 1036-1046.
Hare, T. A., C. F. Camerer and A. Rangel (2009). "Self-control in decision-making involves modulation of the vmPFC valuation system." Science **324**(5927): 646-648.
Hare, T. A., S. Hakimi and A. Rangel (2014). "Activity in dlPFC and its effective connectivity to vmPFC are associated with temporal discounting." Front Neurosci **8**: 50.
Haynes, W. I. and S. N. Haber (2013). "The organization of prefrontal-subthalamic inputs in primates provides an anatomical substrate for both functional specificity and integration: implications for Basal Ganglia models and deep brain stimulation." J Neurosci **33**(11): 4804-4814.
Hek, K., N. Direk, R. S. Newson, A. Hofman, W. J. Hoogendijk, C. L. Mulder and H. Tiemeier (2013). "Anxiety disorders and salivary cortisol levels in older adults: a population-based study." Psychoneuroendocrinology **38**(2): 300-305.
Herzog, J., U. Fietzek, W. Hamel, A. Morsnowski, F. Steigerwald, B. Schrader, D. Weinert, G. Pfister, D. Muller, H. M. Mehdorn, G. Deuschl and J. Volkmann (2004). "Most effective stimulation site in subthalamic deep brain stimulation for Parkinson's disease." Mov Disord **19**(9): 1050-1054.
Hikosaka, O. (2010). "The habenula: from stress evasion to value-based decision-making." Nat Rev Neurosci **11**(7): 503-513.

Hikosaka, O. and M. Isoda (2010). "Switching from automatic to controlled behavior: cortico-basal ganglia mechanisms." Trends Cogn Sci **14**(4): 154-161.
Hilker, R., J. Voges, M. Ghaemi, R. Lehrke, J. Rudolf, A. Koulousakis, K. Herholz, K. Wienhard, V. Sturm and W. D. Heiss (2003). "Deep brain stimulation of the subthalamic nucleus does not increase the striatal dopamine concentration in parkinsonian humans." Mov Disord **18**(1): 41-48.
Hill, R. J. and P. S. Davies (2001). "The validity of self-reported energy intake as determined using the doubly labelled water technique." Br J Nutr **85**(4): 415-430.
Ho, A., J. Kennedy and A. Dimitropoulos (2012). "Neural correlates to food-related behavior in normal-weight and overweight/obese participants." PLoS One **7**(9): e45403.
Ho, C. Y. and K. C. Berridge (2013). "An orexin hotspot in ventral pallidum amplifies hedonic 'liking' for sweetness." Neuropsychopharmacology **38**(9): 1655-1664.
Hofmann, W., M. Adriaanse, K. D. Vohs and R. F. Baumeister (2013). "Dieting and the self-control of eating in everyday environments: An experience sampling study." Br J Health Psychol.
Hofmann, W., B. J. Schmeichel and A. D. Baddeley (2012). "Executive functions and self-regulation." Trends Cogn Sci **16**(3): 174-180.
Holmberg, B., O. Corneliusson and M. Elam (2005). "Bilateral stimulation of nucleus subthalamicus in advanced Parkinson's disease: no effects on, and of, autonomic dysfunction." Mov Disord **20**(8): 976-981.
Hughes, A. J., S. E. Daniel, Y. Ben-Shlomo and A. J. Lees (2002). "The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service." Brain **125**(Pt 4): 861-870.
Humphries, M. D. and T. J. Prescott (2010). "The ventral basal ganglia, a selection mechanism at the crossroads of space, strategy, and reward." Prog Neurobiol **90**(4): 385-417.
Jakes, R. W., N. E. Day, R. Luben, A. Welch, S. Bingham, J. Mitchell, S. Hennings, K. Rennie and N. J. Wareham (2004). "Adjusting for energy intake--what measure to use in nutritional epidemiological studies?" Int J Epidemiol **33**(6): 1382-1386.
Jankord, R. and J. P. Herman (2008). "Limbic regulation of hypothalamo-pituitary-adrenocortical function during acute and chronic stress." Ann N Y Acad Sci **1148**: 64-73.
Jech, R., E. Ruzicka, D. Urgosik, T. Serranova, M. Volfova, O. Novakova, J. Roth, P. Dusek and P. Mecir (2006). "Deep brain stimulation of the subthalamic nucleus affects resting EEG and visual evoked potentials in Parkinson's disease." Clin Neurophysiol **117**(5): 1017-1028.
Karachi, C., J. Yelnik, D. Tande, L. Tremblay, E. C. Hirsch and C. Francois (2005). "The pallidosubthalamic projection: an anatomical substrate for nonmotor functions of the subthalamic nucleus in primates." Mov Disord **20**(2): 172-180.
Keuken, M. C., H. B. Uylings, S. Geyer, A. Schafer, R. Turner and B. U. Forstmann (2012). "Are there three subdivisions in the primate subthalamic nucleus?" Front Neuroanat **6**: 14.
Killgore, W. D., M. Weber, Z. J. Schwab, M. Kipman, S. R. DelDonno, C. A. Webb and S. L. Rauch (2013). "Cortico-limbic responsiveness to high-calorie food images predicts weight status among women." Int J Obes (Lond) **37**(11): 1435-1442.

Killgore, W. D. and D. A. Yurgelun-Todd (2005). "Body mass predicts orbitofrontal activity during visual presentations of high-calorie foods." Neuroreport **16**(8): 859-863.
Kim, M. J., R. A. Loucks, A. L. Palmer, A. C. Brown, K. M. Solomon, A. N. Marchante and P. J. Whalen (2011). "The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety." Behav Brain Res **223**(2): 403-410.
Kim, M. J. and P. J. Whalen (2009). "The structural integrity of an amygdala-prefrontal pathway predicts trait anxiety." J Neurosci **29**(37): 11614-11618.
Kistner, A., E. Lhommee and P. Krack (2014). "Mechanisms of Body Weight Fluctuations in Parkinson's Disease." Front Neurol **5**: 84.
Kringelbach, M. L. (2005). "The human orbitofrontal cortex: linking reward to hedonic experience." Nat Rev Neurosci **6**(9): 691-702.
Kringelbach, M. L., N. Jenkinson, S. L. Owen and T. Z. Aziz (2007). "Translational principles of deep brain stimulation." Nat Rev Neurosci **8**(8): 623-635.
Kringelbach, M. L., J. O'Doherty, E. T. Rolls and C. Andrews (2003). "Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness." Cereb Cortex **13**(10): 1064-1071.
Lambert, C., L. Zrinzo, Z. Nagy, A. Lutti, M. Hariz, T. Foltynie, B. Draganski, J. Ashburner and R. Frackowiak (2012). "Confirmation of functional zones within the human subthalamic nucleus: patterns of connectivity and sub-parcellation using diffusion weighted imaging." Neuroimage **60**(1): 83-94.
Le Jeune, F., J. Peron, I. Biseul, S. Fournier, P. Sauleau, S. Drapier, C. Haegelen, D. Drapier, B. Millet, E. Garin, J. Y. Herry, C. H. Malbert and M. Verin (2008). "Subthalamic nucleus stimulation affects orbitofrontal cortex in facial emotion recognition: a PET study." Brain **131**(Pt 6): 1599-1608.
Lee, E. M., A. Kurundkar, G. R. Cutter, H. Huang, B. L. Guthrie, R. L. Watts and H. C. Walker (2011). "Comparison of weight changes following unilateral and staged bilateral STN DBS for advanced PD." Brain Behav **1**(1): 12-18.
Lenard, N. R. and H. R. Berthoud (2008). "Central and peripheral regulation of food intake and physical activity: pathways and genes." Obesity (Silver Spring) **16 Suppl 3**: S11-22.
Leuner, B. and T. J. Shors (2013). "Stress, anxiety, and dendritic spines: what are the connections?" Neuroscience **251**: 108-119.
Levy, D. J. and P. W. Glimcher (2012). "The root of all value: a neural common currency for choice." Curr Opin Neurobiol **22**(6): 1027-1038.
Liljeholm, M. and J. P. O'Doherty (2012). "Contributions of the striatum to learning, motivation, and performance: an associative account." Trends Cogn Sci **16**(9): 467-475.
Lovallo, W. R. (2006). "Cortisol secretion patterns in addiction and addiction risk." Int J Psychophysiol **59**(3): 195-202.
Ludwig, J., P. Remien, C. Guballa, A. Binder, S. Binder, J. Schattschneider, J. Herzog, J. Volkmann, G. Deuschl, G. Wasner and R. Baron (2007). "Effects of subthalamic nucleus stimulation and levodopa on the autonomic nervous system in Parkinson's disease." J Neurol Neurosurg Psychiatry **78**(7): 742-745.

Machado, A., A. R. Rezai, B. H. Kopell, R. E. Gross, A. D. Sharan and A. L. Benabid (2006). "Deep brain stimulation for Parkinson's disease: surgical technique and perioperative management." Mov Disord **21 Suppl 14**: S247-258.
Macia, F., C. Perlemoine, I. Coman, D. Guehl, P. Burbaud, E. Cuny, H. Gin, V. Rigalleau and F. Tison (2004). "Parkinson's disease patients with bilateral subthalamic deep brain stimulation gain weight." Mov Disord **19**(2): 206-212.
Mallet, L., M. Schupbach, K. N'Diaye, P. Remy, E. Bardinet, V. Czernecki, M. L. Welter, A. Pelissolo, M. Ruberg, Y. Agid and J. Yelnik (2007). "Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behavior." Proc Natl Acad Sci U S A **104**(25): 10661-10666.
Mathai, A. and Y. Smith (2011). "The corticostriatal and corticosubthalamic pathways: two entries, one target. So what?" Front Syst Neurosci **5**: 64.
Matsumoto, K., W. Suzuki and K. Tanaka (2003). "Neuronal correlates of goal-based motor selection in the prefrontal cortex." Science **301**(5630): 229-232.
Miller, G. E., E. Chen and E. S. Zhou (2007). "If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans." Psychol Bull **133**(1): 25-45.
Mondolo, F., M. Jahanshahi, A. Grana, E. Biasutti, E. Cacciatori and P. Di Benedetto (2007). "Evaluation of anxiety in Parkinson's disease with some commonly used rating scales." Neurol Sci **28**(5): 270-275.
Montague, P. R., S. E. Hyman and J. D. Cohen (2004). "Computational roles for dopamine in behavioural control." Nature **431**(7010): 760-767.
Montaurier, C., B. Morio, S. Bannier, P. Derost, P. Arnaud, M. Brandolini-Bunlon, C. Giraudet, Y. Boirie and F. Durif (2007). "Mechanisms of body weight gain in patients with Parkinson's disease after subthalamic stimulation." Brain **130**(Pt 7): 1808-1818.
Morel, A. (2007). Atlas of the Human Thalamus and Basal Ganglia. New York, Informa Helthcare**:** 160.
Morita, K., M. Morishima, K. Sakai and Y. Kawaguchi (2012). "Reinforcement learning: computing the temporal difference of values via distinct corticostriatal pathways." Trends Neurosci **35**(8): 457-467.
Mueller, K., A. Anwander, H. E. Moller, A. Horstmann, J. Lepsien, F. Busse, S. Mohammadi, M. L. Schroeter, M. Stumvoll, A. Villringer and B. Pleger (2011). "Sex-dependent influences of obesity on cerebral white matter investigated by diffusion-tensor imaging." PLoS One **6**(4): e18544.
Myers-Schulz, B. and M. Koenigs (2012). "Functional anatomy of ventromedial prefrontal cortex: implications for mood and anxiety disorders." Mol Psychiatry **17**(2): 132-141.
Nambu, A. (2011). "Somatotopic organization of the primate Basal Ganglia." Front Neuroanat **5**: 26.
Nambu, A., H. Tokuno and M. Takada (2002). "Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway." Neurosci Res **43**(2): 111-117.
Novakova, L., M. Haluzik, R. Jech, D. Urgosik, F. Ruzicka and E. Ruzicka (2011). "Hormonal regulators of food intake and weight gain in Parkinson's disease after subthalamic nucleus stimulation." Neuro Endocrinol Lett **32**(4): 437-441.

Novakova, L., E. Ruzicka, R. Jech, T. Serranova, P. Dusek and D. Urgosik (2007). "Increase in body weight is a non-motor side effect of deep brain stimulation of the subthalamic nucleus in Parkinson's disease." Neuro Endocrinol Lett **28**(1): 21-25.
O'Connor, D. B., H. Hendrickx, T. Dadd, T. D. Elliman, T. A. Willis, D. Talbot, A. E. Mayes, K. Thethi, J. Powell and L. Dye (2009). "Cortisol awakening rise in middle-aged women in relation to psychological stress." Psychoneuroendocrinology **34**(10): 1486-1494.
Obeso, J. A., C. Marin, C. Rodriguez-Oroz, J. Blesa, B. Benitez-Temino, J. Mena-Segovia, M. Rodriguez and C. W. Olanow (2008). "The basal ganglia in Parkinson's disease: current concepts and unexplained observations." Ann Neurol **64 Suppl 2**: S30-46.
Obeso, J. A., M. C. Rodriguez-Oroz, B. Benitez-Temino, F. J. Blesa, J. Guridi, C. Marin and M. Rodriguez (2008). "Functional organization of the basal ganglia: therapeutic implications for Parkinson's disease." Mov Disord **23 Suppl 3**: S548-559.
Olanow, C. W., M. B. Stern and K. Sethi (2009). "The scientific and clinical basis for the treatment of Parkinson disease (2009)." Neurology **72**(21 Suppl 4): S1-136.
Oyama, G., Y. Shimo, S. Natori, M. Nakajima, H. Ishii, H. Arai and N. Hattori (2011). "Acute effects of bilateral subthalamic stimulation on decision-making in Parkinson's disease." Parkinsonism Relat Disord **17**(3): 189-193.
Parent, A. and L. N. Hazrati (1995). "Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry." Brain Res Brain Res Rev **20**(1): 128-154.
Parent, M. and A. Parent (2007). "The microcircuitry of primate subthalamic nucleus." Parkinsonism & Related Disorders **13, Supplement 3**(0): S292-S295.
Passamonti, L., J. B. Rowe, C. Schwarzbauer, M. P. Ewbank, E. von dem Hagen and A. J. Calder (2009). "Personality predicts the brain's response to viewing appetizing foods: the neural basis of a risk factor for overeating." J Neurosci **29**(1): 43-51.
Paulus, M. P., J. S. Feinstein, A. Simmons and M. B. Stein (2004). "Anterior cingulate activation in high trait anxious subjects is related to altered error processing during decision making." Biol Psychiatry **55**(12): 1179-1187.
Perlemoine, C., F. Macia, F. Tison, I. Coman, D. Guehl, P. Burbaud, E. Cuny, L. Baillet, H. Gin and V. Rigalleau (2005). "Effects of subthalamic nucleus deep brain stimulation and levodopa on energy production rate and substrate oxidation in Parkinson's disease." Br J Nutr **93**(2): 191-198.
Pessoa, L. (2010). "Emotion and cognition and the amygdala: from "what is it?" to "what's to be done?"." Neuropsychologia **48**(12): 3416-3429.
Peters, J. C., H. R. Wyatt, W. T. Donahoo and J. O. Hill (2002). "From instinct to intellect: the challenge of maintaining healthy weight in the modern world." Obes Rev **3**(2): 69-74.
Petrides, M. and D. N. Pandya (2012). Chapter 26 - The Frontal Cortex. The Human Nervous System (Third Edition). J. K. Mai and G. Paxinos. San Diego, Academic Press**:** 988-1011.
Picard, N. and P. L. Strick (2001). "Imaging the premotor areas." Curr Opin Neurobiol **11**(6): 663-672.
Plenz, D. and J. R. Wickens (2010). Chapter 5 - The Striatal Skeleton: Medium Spiny Projection Neurons and their Lateral Connections. Handbook of Behavioral Neuroscience. S. Heinz and Y. T. Kuei, Elsevier. **Volume 20:** 99-112.

Price, J. L. and W. C. Drevets (2010). "Neurocircuitry of mood disorders." Neuropsychopharmacology **35**(1): 192-216.
Priori, A., C. Cinnante, S. Genitrini, A. Pesenti, G. Tortora, C. Bencini, M. V. Barelli, V. Buonamici, F. Carella, F. Girotti, P. Soliveri, F. Magrini, A. Morganti, A. Albanese, S. Broggi, G. Scarlato and S. Barbieri (2001). "Non-motor effects of deep brain stimulation of the subthalamic nucleus in Parkinson's disease: preliminary physiological results." Neurol Sci **22**(1): 85-86.
Rangel, A. (2013). "Regulation of dietary choice by the decision-making circuitry." Nat Neurosci **16**(12): 1717-1724.
Rangel, A., C. Camerer and P. R. Montague (2008). "A framework for studying the neurobiology of value-based decision making." Nat Rev Neurosci **9**(7): 545-556.
Redgrave, P., M. Rodriguez, Y. Smith, M. C. Rodriguez-Oroz, S. Lehericy, H. Bergman, Y. Agid, M. R. DeLong and J. A. Obeso (2010). "Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease." Nat Rev Neurosci **11**(11): 760-772.
Richter, E. O., T. Hoque, W. Halliday, A. M. Lozano and J. A. Saint-Cyr (2004). "Determining the position and size of the subthalamic nucleus based on magnetic resonance imaging results in patients with advanced Parkinson disease." J Neurosurg **100**(3): 541-546.
Rodriguez-Oroz, M. C., M. Rodriguez, J. Guridi, K. Mewes, V. Chockkman, J. Vitek, M. R. DeLong and J. A. Obeso (2001). "The subthalamic nucleus in Parkinson's disease: somatotopic organization and physiological characteristics." Brain **124**(Pt 9): 1777-1790.
Rolls, E. T. (2014). "Emotion and decision-making explained: Precis: Synopsis of book published by Oxford University Press 2014." Cortex.
Rolls, E. T. and F. Grabenhorst (2008). "The orbitofrontal cortex and beyond: from affect to decision-making." Prog Neurobiol **86**(3): 216-244.
Rothemund, Y., C. Preuschhof, G. Bohner, H. C. Bauknecht, R. Klingebiel, H. Flor and B. F. Klapp (2007). "Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals." Neuroimage **37**(2): 410-421.
Rouaud, T., S. Lardeux, N. Panayotis, D. Paleressompoulle, M. Cador and C. Baunez (2010). "Reducing the desire for cocaine with subthalamic nucleus deep brain stimulation." Proc Natl Acad Sci U S A **107**(3): 1196-1200.
Roy, M., D. Shohamy and T. D. Wager (2012). "Ventromedial prefrontal-subcortical systems and the generation of affective meaning." Trends Cogn Sci **16**(3): 147-156.
Rudebeck, P. H. and E. A. Murray (2011). "Balkanizing the primate orbitofrontal cortex: distinct subregions for comparing and contrasting values." Ann N Y Acad Sci **1239**: 1-13.
Rudebeck, P. H., M. E. Walton, B. H. Millette, E. Shirley, M. F. Rushworth and D. M. Bannerman (2007). "Distinct contributions of frontal areas to emotion and social behaviour in the rat." Eur J Neurosci **26**(8): 2315-2326.
Ruzicka, E., L. Novakova, R. Jech, D. Urgosik, F. Ruzicka and M. Haluzik (2012). "Decrease in blood cortisol corresponds to weight gain following deep brain stimulation of the subthalamic nucleus in Parkinson's disease." Stereotact Funct Neurosurg **90**(6): 410-411.

Ruzicka, F., R. Jech, L. Novakova, D. Urgosik, J. Vymazal and E. Ruzicka (2012). "Weight gain is associated with medial contact site of subthalamic stimulation in Parkinson's disease." PLoS One **7**(5): e38020.
Sauleau, P., E. Leray, T. Rouaud, S. Drapier, D. Drapier, S. Blanchard, G. Drillet, J. Peron and M. Verin (2009). "Comparison of weight gain and energy intake after subthalamic versus pallidal stimulation in Parkinson's disease." Mov Disord **24**(14): 2149-2155.
Schultz, W. (2013). "Updating dopamine reward signals." Curr Opin Neurobiol **23**(2): 229-238.
Schwabe, L. and O. T. Wolf (2011). "Stress-induced modulation of instrumental behavior: from goal-directed to habitual control of action." Behav Brain Res **219**(2): 321-328.
Seifried, C., S. Boehncke, J. Heinzmann, S. Baudrexel, L. Weise, T. Gasser, K. Eggert, W. Fogel, H. Baas, K. Badenhoop, H. Steinmetz and R. Hilker (2012). "Diurnal Variation of Hypothalamic Function and Chronic Subthalamic Nucleus Stimulation in Parkinson's Disease." Neuroendocrinology.
Selemon, L. D. and P. S. Goldman-Rakic (1985). "Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey." J Neurosci **5**(3): 776-794.
Serranova, T., R. Jech, P. Dusek, T. Sieger, F. Ruzicka, D. Urgosik and E. Ruzicka (2011). "Subthalamic nucleus stimulation affects incentive salience attribution in Parkinson's disease." Mov Disord **26**(12): 2260-2266.
Serranova, T., T. Sieger, F. Růžička, P. Vostatek, J. Wild, D. Štastná, C. Bonnet, D. Novák, E. Růžička, D. Urgosik and R. Jech (2014). "Distinct Populations of Neurons Respond to Emotional Valence and Arousal in the Human Subthalamic Nucleus." Submitted to Proceedings of the National Academy of Sciences of the United States of America.
Sescousse, G., J. Redoute and J. C. Dreher (2010). "The architecture of reward value coding in the human orbitofrontal cortex." J Neurosci **30**(39): 13095-13104.
Shepherd, G. M. (2013). "Corticostriatal connectivity and its role in disease." Nat Rev Neurosci **14**(4): 278-291.
Shimo, Y. and T. Wichmann (2009). "Neuronal activity in the subthalamic nucleus modulates the release of dopamine in the monkey striatum." Eur J Neurosci **29**(1): 104-113.
Shin, L. M. and I. Liberzon (2010). "The neurocircuitry of fear, stress, and anxiety disorders." Neuropsychopharmacology **35**(1): 169-191.
Shon, Y. M., K. H. Lee, S. J. Goerss, I. Y. Kim, C. Kimble, J. J. Van Gompel, K. Bennet, C. D. Blaha and S. Y. Chang (2010). "High frequency stimulation of the subthalamic nucleus evokes striatal dopamine release in a large animal model of human DBS neurosurgery." Neurosci Lett **475**(3): 136-140.
Siep, N., A. Roefs, A. Roebroeck, R. Havermans, M. L. Bonte and A. Jansen (2009). "Hunger is the best spice: an fMRI study of the effects of attention, hunger and calorie content on food reward processing in the amygdala and orbitofrontal cortex." Behav Brain Res **198**(1): 149-158.

Silvetti, M., R. Seurinck and T. Verguts (2011). "Value and prediction error in medial frontal cortex: integrating the single-unit and systems levels of analysis." Front Hum Neurosci **5**: 75.
Simmons, W. K., K. M. Rapuano, J. E. Ingeholm, J. Avery, S. Kallman, K. D. Hall and A. Martin (2014). "The ventral pallidum and orbitofrontal cortex support food pleasantness inferences." Brain Struct Funct **219**(2): 473-483.
Sinha, R. and A. M. Jastreboff (2013). "Stress as a common risk factor for obesity and addiction." Biol Psychiatry **73**(9): 827-835.
Smith, K. S., A. J. Tindell, J. W. Aldridge and K. C. Berridge (2009). "Ventral pallidum roles in reward and motivation." Behav Brain Res **196**(2): 155-167.
Sousa, N. and O. F. Almeida (2012). "Disconnection and reconnection: the morphological basis of (mal)adaptation to stress." Trends Neurosci **35**(12): 742-751.
Stalnaker, T. A., N. K. Cooch, M. A. McDannald, T. L. Liu, H. Wied and G. Schoenbaum (2014). "Orbitofrontal neurons infer the value and identity of predicted outcomes." Nat Commun **5**: 3926.
Stephenson-Jones, M., A. A. Kardamakis, B. Robertson and S. Grillner (2013). "Independent circuits in the basal ganglia for the evaluation and selection of actions." Proc Natl Acad Sci U S A **110**(38): E3670-3679.
Stephenson-Jones, M., E. Samuelsson, J. Ericsson, B. Robertson and S. Grillner (2011). "Evolutionary conservation of the basal ganglia as a common vertebrate mechanism for action selection." Curr Biol **21**(13): 1081-1091.
Surmeier, D. J., M. Day, T. Gertler, S. Chan and W. Shen (2010). Chapter 6 - D1 and D2 Dopamine Receptor Modulation of Glutamatergic Signaling in Striatal Medium Spiny Neurons. Handbook of Behavioral Neuroscience. S. Heinz and Y. T. Kuei, Elsevier. **Volume 20:** 113-132.
Tachibana, Y. and O. Hikosaka (2012). "The primate ventral pallidum encodes expected reward value and regulates motor action." Neuron **76**(4): 826-837.
Temel, Y., A. Blokland, H. W. Steinbusch and V. Visser-Vandewalle (2005). "The functional role of the subthalamic nucleus in cognitive and limbic circuits." Prog Neurobiol **76**(6): 393-413.
Theodosopoulos, P. V., W. J. Marks, Jr., C. Christine and P. A. Starr (2003). "Locations of movement-related cells in the human subthalamic nucleus in Parkinson's disease." Mov Disord **18**(7): 791-798.
Therrien, F., V. Drapeau, S. J. Lupien, S. Beaulieu, J. Dore, A. Tremblay and D. Richard (2008). "Awakening cortisol response in relation to psychosocial profiles and eating behaviors." Physiol Behav **93**(1-2): 282-288.
Travison, T. G., A. B. O'Donnell, A. B. Araujo, A. M. Matsumoto and J. B. McKinlay (2007). "Cortisol levels and measures of body composition in middle-aged and older men." Clin Endocrinol (Oxf) **67**(1): 71-77.
Tryon, M. S., C. S. Carter, R. Decant and K. D. Laugero (2013). "Chronic stress exposure may affect the brain's response to high calorie food cues and predispose to obesogenic eating habits." Physiol Behav **120**: 233-242.
Turner, M. S., A. Lavin, A. A. Grace and T. C. Napier (2001). "Regulation of limbic information outflow by the subthalamic nucleus: excitatory amino acid projections to the ventral pallidum." J Neurosci **21**(8): 2820-2832.

Urry, H. L., C. M. van Reekum, T. Johnstone, N. H. Kalin, M. E. Thurow, H. S. Schaefer, C. A. Jackson, C. J. Frye, L. L. Greischar, A. L. Alexander and R. J. Davidson (2006). "Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults." J Neurosci **26**(16): 4415-4425.
Van Den Eede, F., G. Moorkens, B. Van Houdenhove, P. Cosyns and S. J. Claes (2007). "Hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome." Neuropsychobiology **55**(2): 112-120.
van Honk, J., D. J. Schutter, E. J. Hermans and P. Putman (2003). "Low cortisol levels and the balance between punishment sensitivity and reward dependency." Neuroreport **14**(15): 1993-1996.
van Veen, V., J. D. Cohen, M. M. Botvinick, V. A. Stenger and C. S. Carter (2001). "Anterior cingulate cortex, conflict monitoring, and levels of processing." Neuroimage **14**(6): 1302-1308.
Verstynen, T. D., D. Badre, K. Jarbo and W. Schneider (2012). "Microstructural organizational patterns in the human corticostriatal system." J Neurophysiol **107**(11): 2984-2995.
Vitek, J. L. (2008). "Deep brain stimulation: how does it work?" Cleve Clin J Med **75 Suppl 2**: S59-65.
Volkmann, J., C. Daniels and K. Witt (2010). "Neuropsychiatric effects of subthalamic neurostimulation in Parkinson disease." Nat Rev Neurol **6**(9): 487-498.
Volkow, N. D., G. J. Wang and R. D. Baler (2011). "Reward, dopamine and the control of food intake: implications for obesity." Trends Cogn Sci **15**(1): 37-46.
Volkow, N. D., G. J. Wang, J. S. Fowler, D. Tomasi and R. Baler (2012). "Food and drug reward: overlapping circuits in human obesity and addiction." Curr Top Behav Neurosci **11**: 1-24.
Volkow, N. D., G. J. Wang, F. Telang, J. S. Fowler, R. Z. Goldstein, N. Alia-Klein, J. Logan, C. Wong, P. K. Thanos, Y. Ma and K. Pradhan (2009). "Inverse association between BMI and prefrontal metabolic activity in healthy adults." Obesity (Silver Spring) **17**(1): 60-65.
Volkow, N. D., G. J. Wang, D. Tomasi and R. D. Baler (2013). "Obesity and addiction: neurobiological overlaps." Obes Rev **14**(1): 2-18.
Volkow, N. D., G. J. Wang, D. Tomasi and R. D. Baler (2013). "Unbalanced neuronal circuits in addiction." Curr Opin Neurobiol **23**(4): 639-648.
Vreeburg, S. A., W. J. Hoogendijk, R. H. Derijk, R. van Dyck, J. H. Smit, F. G. Zitman and B. W. Penninx (2013). "Salivary cortisol levels and the 2-year course of depressive and anxiety disorders." Psychoneuroendocrinology.
Walker, B. R. (2006). "Cortisol--cause and cure for metabolic syndrome?" Diabet Med **23**(12): 1281-1288.
Walker, H. C., H. Huang, C. L. Gonzalez, J. E. Bryant, J. Killen, R. C. Knowlton, E. B. Montgomery, Jr., G. C. Cutter, A. Yildirim, B. L. Guthrie and R. L. Watts (2012). "Short latency activation of cortex by clinically effective thalamic brain stimulation for tremor." Mov Disord **27**(11): 1404-1412.
Walker, H. C., M. Lyerly, G. Cutter, J. Hagood, N. P. Stover, S. L. Guthrie, B. L. Guthrie and R. L. Watts (2009). "Weight changes associated with unilateral STN DBS and advanced PD." Parkinsonism Relat Disord **15**(9): 709-711.

Walton, M. E., S. W. Kennerley, D. M. Bannerman, P. E. Phillips and M. F. Rushworth (2006). "Weighing up the benefits of work: behavioral and neural analyses of effort-related decision making." Neural Netw **19**(8): 1302-1314.
Watabe-Uchida, M., L. Zhu, S. K. Ogawa, A. Vamanrao and N. Uchida (2012). "Whole-brain mapping of direct inputs to midbrain dopamine neurons." Neuron **74**(5): 858-873.
Wessa, M., N. Rohleder, C. Kirschbaum and H. Flor (2006). "Altered cortisol awakening response in posttraumatic stress disorder." Psychoneuroendocrinology **31**(2): 209-215.
Winkielman, P., K. C. Berridge and J. L. Wilbarger (2005). "Unconscious affective reactions to masked happy versus angry faces influence consumption behavior and judgments of value." Pers Soc Psychol Bull **31**(1): 121-135.
Winter, C., C. Lemke, R. Sohr, W. Meissner, D. Harnack, G. Juckel, R. Morgenstern and A. Kupsch (2008). "High frequency stimulation of the subthalamic nucleus modulates neurotransmission in limbic brain regions of the rat." Exp Brain Res **185**(3): 497-507.
Wise, R. A. (2005). "Forebrain substrates of reward and motivation." J Comp Neurol **493**(1): 115-121.
Yelnik, J., P. Damier, S. Demeret, D. Gervais, E. Bardinet, B. P. Bejjani, C. Francois, J. L. Houeto, I. Arnule, D. Dormont, D. Galanaud, B. Pidoux, P. Cornu and Y. Agid (2003). "Localization of stimulating electrodes in patients with Parkinson disease by using a three-dimensional atlas-magnetic resonance imaging coregistration method." J Neurosurg **99**(1): 89-99.
Yin, H. H. and B. J. Knowlton (2006). "The role of the basal ganglia in habit formation." Nat Rev Neurosci **7**(6): 464-476.
Zaghloul, K. A., C. T. Weidemann, B. C. Lega, J. L. Jaggi, G. H. Baltuch and M. J. Kahana (2012). "Neuronal activity in the human subthalamic nucleus encodes decision conflict during action selection." J Neurosci **32**(7): 2453-2460.
Zhu, X. L., W. Hamel, B. Schrader, D. Weinert, J. Hedderich, J. Herzog, J. Volkmann, G. Deuschl, D. Muller and H. M. Mehdorn (2002). "Magnetic resonance imaging-based morphometry and landmark correlation of basal ganglia nuclei." Acta Neurochir (Wien) **144**(10): 959-969; discussion 968-959.

8 SUPLEMENT I- PUBLICATIONS

Original articles related to the Thesis:

Serranova, T., Sieger, T., **Růžička, F.**, Vostatek, P., Wild, J., Šťastná, D., Bonnet, C., Novák, D., Růžička, E., Urgosik, D., Jech, R., 2014. Distinct Populations of Neurons Respond to Emotional Valence and Arousal in the Human Subthalamic Nucleus. Submitted to Proceedings of the National Academy of Sciences of the United States of America.

Serranova, T., Sieger, T., Dusek, P., **Ruzicka, F**., Urgosik, D., Ruzicka, E., Valls-Sole, J., Jech, R., 2013. Sex, food and threat: startling changes after subthalamic stimulation in Parkinson's disease. Brain stimulation 6, 740-745. **IF- 4.538**

Ruzicka, F., Jech, R., Novakova, L., Urgosik, D., Vymazal, J., Ruzicka, E., 2012. Weight gain is associated with medial contact site of subthalamic stimulation in Parkinson's disease. PloS one 7, e38020. **IF- 3.73**

Ruzicka, E., Novakova, L., Jech, R., Urgosik, D., **Ruzicka, F**., Haluzik, M., 2012. Decrease in blood cortisol corresponds to weight gain following deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Stereotactic and functional neurosurgery 90, 410-411. **IF- 1.458**

Serranova, T., Jech, R., Dusek, P., Sieger, T., **Ruzicka, F.**, Urgosik, D., Ruzicka, E., 2011. Subthalamic nucleus stimulation affects incentive salience attribution in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 26, 2260-2266. **IF- 4.558**

Novakova, L., Haluzik, M., Jech, R., Urgosik, D., **Ruzicka, F**., Ruzicka, E., 2011. Hormonal regulators of food intake and weight gain in Parkinson's disease after subthalamic nucleus stimulation. Neuro endocrinology letters 32, 437-441. **IF 1,62**

Other original articles:

Sieger, T., Bonnet, C., Serranova, T., Wild, J., Novak, D**., Ruzicka, F**., Urgosik, D., Ruzicka, E., Gaymard, B., Jech, R., 2013. Basal ganglia neuronal activity during scanning eye movements in Parkinson's disease. PloS one 8, e78581.**IF- 3.73**

Jech, R., Mueller, K., Urgosik, D., Sieger, T., Holiga, S., **Ruzicka, F**., Dusek, P., Havrankova, P., Vymazal, J., Ruzicka, E., 2012. The subthalamic microlesion story in Parkinson's disease: electrode insertion-related motor improvement with relative cortico-subcortical hypoactivation in fMRI. PloS one 7, e49056. **IF- 3.73**

9 SUPLEMENT II- PUBLICATIONS IN EXTENSO

Novakova, L., Haluzik, M., Jech, R., Urgosik, D., **Ruzicka, F**., Ruzicka, E., 2011. Hormonal regulators of food intake and weight gain in Parkinson's disease after subthalamic nucleus stimulation. Neuro endocrinology letters 32, 437-441. **IF 1,62**

Serranova, T., Jech, R., Dusek, P., Sieger, T., **Ruzicka, F.**, Urgosik, D., Ruzicka, E., 2011. Subthalamic nucleus stimulation affects incentive salience attribution in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 26, 2260-2266. **IF- 4.558**

Ruzicka, E., Novakova, L., Jech, R., Urgosik, D., **Ruzicka, F**., Haluzik, M., 2012. Decrease in blood cortisol corresponds to weight gain following deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Stereotactic and functional neurosurgery 90, 410-411. **IF- 1.458**

Ruzicka, F., Jech, R., Novakova, L., Urgosik, D., Vymazal, J., Ruzicka, E., 2012. Weight gain is associated with medial contact site of subthalamic stimulation in Parkinson's disease. PloS one 7, e38020. **IF- 3.73**

Serranova, T., Sieger, T., Dusek, P., **Ruzicka, F**., Urgosik, D., Ruzicka, E., Valls-Sole, J., Jech, R., 2013. Sex, food and threat: startling changes after subthalamic stimulation in Parkinson's disease. Brain stimulation 6, 740-745. **IF- 4.538**

Serranova, T., Sieger, T., **Růžička, F.**, Vostatek, P., Wild, J., Šťastná, D., Bonnet, C., Novák, D., Růžička, E., Urgosik, D., Jech, R., 2014. Distinct Populations of Neurons Respond to Emotional Valence and Arousal in the Human Subthalamic Nucleus. Submitted to Proceedings of the National Academy of Sciences of the United States of America.

Hormonal regulators of food intake and weight gain in Parkinson's disease after subthalamic nucleus stimulation

Lucie Nováková [1], Martin Haluzík [2], Robert Jech [1], Dušan Urgošík [3], Filip Růžička [4], Evžen Růžička [1]

1 Department of Neurology and Centre of Clinical Neuroscience, Charles University in Prague, First Faculty of Medicine and General University Hospital in Prague, Czech Republic
2 Department of Internal Medicine, Charles University in Prague, First Faculty of Medicine and General University Hospital in Prague, Czech Republic
3 Department of Stereotactic and Radiation Neurosurgery, Na Homolce Hospital, Prague, Czech Republic
4 Department of Neurosurgery, Na Homolce Hospital, Prague, Czech Republic

Correspondence to: Prof. Evžen Růžička, MD., DSc.
Department of Neurology, First Medical Faculty, Charles University in Prague, Kateřinská 30, 120 00, Praha 2, Czech Republic.
TEL: +420 224965550; FAX: +420 224 922678; E-MAIL: eruzi@lf1.cuni.cz

Submitted: 2011-07-04 Accepted: 2011-07-19 Published online: 2011-08-29

Key words: **deep brain stimulation; subthalamic nucleus; weight gain; leptin; cortisol**

Neuroendocrinol Lett 2011; **32**(4):437–441 **PMID:** 21876505 NEL320411A18

Abstract

OBJECTIVES: Weight gain has been reported in patients with Parkinson's disease (PD) treated with deep brain stimulation of the subthalamic nucleus (STN-DBS). To evaluate the influence of STN-DBS on weight changes, we studied food-related hormones.

DESIGN: Anthropometric parameters and food-related hormones (leptin, adiponectin, resistin, ghrelin, cortisol, insulin, and thyroid stimulating hormone) were measured in 27 patients with STN-DBS during a 12 month period following electrode implantation.

RESULTS: Besides marked motor improvements on STN-DBS, PD patients significantly gained weight. The mean weight gain at 12 months was 5.2±(SD)5.8 kg. A significant decrease in cortisol levels compared to baseline appeared at month 2 and persisted at 12 months (p<0.01, corrected), with no significant changes in other hormones tested.

CONCLUSIONS: Changes in peripheral food-related hormones do not appear to cause weight gain in PD patients. Direct effects of STN-DBS on hypothalamic catabolic/anabolic peptide balance remain hypothetical and necessitate further elucidation.

Abbreviations:

STN-DBS	- Deep brain stimulation of the subthalamic nucleus
PD	- Parkinson's disease
CRF	- Corticotropin-releasing factor
BMI	- Body mass index
UPDRS	- Unified Parkinson disease rating scale
IGF-1	- Insulin-like growth factor 1
TSH	- Thyroid stimulating hormone
LEDD	- Levodopa equivalent daily dose

ORIGINAL ARTICLE

INTRODUCTION

Weight gain has been repeatedly reported following subthalamic nucleus deep brain stimulation (STN-DBS) in patients with advanced Parkinson's disease (PD) (Barichella *et al.* 2003; Gironell *et al.* 2002; Macia *et al.* 2004; Novakova *et al.* 2007; Strowd *et al.* 2010). Improved mobility, the resolution of dyskinesias, as well as increased appetite or restoration of hormonal balance have been suggested as contributing factors (Barichella *et al.* 2009). However, little is known about hormones involved in the regulation of energy homeostasis in PD patients treated by STN-DBS.

The food-related hormones leptin, adiponectin, and resistin are produced by adipocytes. If the amount of body fat increases, leptin elevates and acts on the brain, in particular the hypothalamus, reducing food intake and stimulating energy expenditure (Anubhuti &

Arora 2008; Arora & Anubhuti 2006). Adiponectin and resistin primarily target peripheral organs (Fruebis *et al.* 2001; Qi *et al.* 2004). In obese patients, adiponectin is decreased and resistin increased (Arita *et al.* 1999). Ghrelin is an appetite inducing hormone mainly secreted by gastric cells in the empty stomach (Cummings *et al.* 2001). The hypothalamus plays a crucial role in the regulation of energy and food metabolism. In an obese individual, elevated leptin and decreased ghrelin incite hypothalamic neurons to produce anorexigenic peptides, such as proopiomelanocortin and hypothalamic corticotropin-releasing factor (CRF), in order to reduce food intake (Leibowitz & Wortley 2004). Glucocorticoids act as key modulators of body weight and food intake, promoting leptin secretion and limiting central leptin induced effects (Leal-Cerro *et al.* 2001). Several reports have been published regarding food-related hormones in PD (Aziz *et al.* 2011; Evidente *et al.* 2001; Fiszer *et al.* 2010; Lorefalt *et al.* 2009), however only scarce data are available for PD patients treated by STN-DBS (Corcuff *et al.* 2006).

The aim of this study was to explore whether weight gain in STN-DBS treated patients is associated with changes of hormones involved in the regulation of energy homeostasis and food intake.

MATERIAL AND METHODS

Twenty-seven PD patients that received STN-DBS were enrolled in the study (21 men, 6 women; age at time of intervention: mean 56.8±(SD)7 years, range 42–68; disease duration: mean 12.5±4 years, range 7–23. All subjects suffered from severe motor fluctuations that were not improved by adjustments in antiparkinsonian medication. The study was approved by the local Ethics Committee, and all participants provided signed, informed consent prior to enrollment.

Stimulation was initiated four weeks after implantation of the electrodes. DBS settings and medication were subsequently adapted to achieve the best possible compensation. Each subject was evaluated on the day of intervention (baseline, pre-surgery) after at least 12 hours of discontinuing all antiparkinsonian drugs (MED-OFF), then at one month, before the setting-up (MED-OFF/DBS-OFF), and after the initiation of stimulation (MED-OFF/DBS-ON). Further assessments were completed at 2, 4, 6 and 12 months after surgery. The sum of total electrical energy delivered by DBS in 12 months was calculated using the formula proposed by Koss *et al.* (Koss *et al.* 2005).

Motor status was evaluated using the Unified Parkinson Disease Rating Scale motor subscale (UPDRS III). Eating related questionnaires (food intake, hunger, appetite) were administered at each visit. Anthropometric examination included body weight and height, body mass index (BMI=weight in kg/height in m^2), and waist circumference. At each visit, 5 ml of blood was withdrawn between 7–8 AM following an overnight fast, and serum biochemical parameters (total protein, albumin, prealbumin, cholesterol, triglycerides, insulin, glycemia, glycated hemoglobin and insulin-like growth factor 1 (IGF-1), thyroid stimulating hormone (TSH), cortisol, leptin, adiponectin, resistin and ghrelin were assessed by standard laboratory methods using commercial kits:

Serum insulin concentrations were measured by RIA kit (Cis Bio International, Gif-sur-Yvette, France). Sensitivity was 2.0 μIU/ml, and the intra- and inter-assay variability was 4.2 and 8.8%, respectively. IGF-1: IRMA kit (Immunotech, Prague, Czech Republic), 2 ng/ml, 6.3 and 6.8%. Leptin: ELISA kit (BioVendor, Brno, Czech Republic), 0.12 ng/ml, 1.7 and 8.0%. Adiponectin: RIA kit (Linco Research, St. Charles, MO), 1.0 ng/ml, 1.8 and 9.3%. Resistin: ELISA kit (BioVendor, Brno, Czech Republic), 0.2 ng/ml, 3.1 and 6.5%. Ghrelin: RIA kit (Linko research, Saint Charles, MO), 93 pg/ml, 10 and 14.7%, respectively. The other biochemical parameters were measured by standard laboratory methods using commercial kits.

Daily doses of dopaminergic medication at baseline, 1 month, and 12 months following surgery were converted to Levodopa Equivalent Daily Dose (LEDD; 100 mg of standard levodopa equals 150 mg of CR levodopa, 1 mg pramipexole, or 6 mg ropinirole). Statistical analyses were performed using Statgraphics software (Warrenton, VA). Non-parametric tests were used as a substantial portion of the data did not fit a normal distribution (Mann-Whitney test, Kruskal-Wallis test, paired signed-rank test, Spearman's rank correlation). Wherever appropriate, results were corrected for multiple comparisons by Bonferroni correction.

RESULTS

Motor and Pharmacological Outcomes

Comparison of the MED-OFF state at baseline to the MED-OFF/DBS-OFF condition at one month after surgery did not reveal any significant change, with

mean UPDRS III scores of 33.0 ±(SD)11 and 34.7 ±10, respectively (p<0.8). In the MED-OFF/DBS-ON condition at one month after surgery, the mean UPDRS III score significantly decreased to 17.2±6 (p<0.001). The MED-OFF/DBS-ON UPDRS III score at 12 months did not significantly change (14.5±7, p<0.14) in comparison to one month after surgery.

The LEDD significantly decreased from 1330±538 mg at baseline to 1196±401 mg (p<0.001) at one month, and to 704±429 mg (p<0.001) at 12 months after surgery.

DBS Parameters

The average sum of stimulation energy delivered over the 12 month study period was 3412±1280 J. No correlation between change in body weight and the energy of stimulation was found (12 month vs baseline, r_s = 0.1844, p<0.3).

Anthropometric Parameters

On average, we found increases in body weight, BMI, waist circumference and body fat percentage during the entire study period (Table 1). Notably, a significant change in body weight was observed already at one month following surgery, i.e., before stimulation was started, in comparison to baseline: +1.1±2 kg, range –2.6 to 5.0, (p<0.05). Change in mean weight from baseline to 12 months following STN-DBS implantation was +5.18±5.8 kg, range –6.30 to +19.80, (p<0.001) (Figure 1). At month one, taken individually, 17 patients gained weight compared to baseline while weight loss was noted in 10 patients. At month twelve, 24 patients gained weight and 3 patients had lower weight compared to baseline. In examining gender differences, body weight increased at 12 months after STN-DBS implantation by 9.0±5 kg in women (range 5.0 to 18.3) and 4.1±6 kg in men (range –6.3 to 19.8). Body weight and BMI differed significantly between the genders, with a greater increase in women (p<0.05, p<0.01, respectively). A borderline correlation between weight gain following STN-DBS and PD duration was observed (r_s = 0.418, p<0.05), but not with age at PD onset. No significant correlation was found between the change in LEDD and change in weight. Most of the subjects did not report any changes in food intake, hunger or appetite.

Laboratory Parameters

A significant decrease in cortisol levels compared to baseline appeared at month 2 and persisted at 12 months (p<0.01, corrected), with no significant changes in other tested hormones or biochemical parameters (Table 1, Figure 1). A positive correlation between leptin levels and body weight (r_s = 0.299, p<0.001) and body fat percentage (r_s =0.343, p<0.05) was found. Body weight negatively correlated with adiponectin (r_s = –0.604, p<0.001), positively with ghrelin (r_s = 0.253, p<0.01) and did not significantly correlate with cortisol (r_s = –0.114, p<0.2).

DISCUSSION

In this prospective study, we tested the hypothesis that weight changes in PD patients treated with STN-DBS are connected with abnormalities in the hormonal regulation of food intake. In concordance with previous

Tab. 1. Patient anthropometric parameters and select hormonal levels pre-surgery (baseline), 1 month, and 12 months after STN-DBS.

Hormonal and Anthropometric parameters	Pre-surgery DBS	1 month after DBS		12 months after DBS	
	mean±SD	mean±SD	*p*-value	mean±SD	*p*-value
Body weight [kg]	78.7±16	79.8±16	0.0185*	83.9±15	0.0001***
BMI [kg/m2]	25.8±4.0	26.11±3.8	0.0251*	27.51±3.7	0.0001***
Waist circum. [cm]	94.0±13.0	94.95±12.6	0.08	98.76±11.7	0.001**
Body fat [%]	21.6±7.4	21.9±7.4	0.20	25.8±5.9	0.003*
Leptin [ng/ml]	7.6±8.7	6.8±6.7	1.0	9.5±9.0	0.09
Adiponectin [ng/ml]	21.3±12.3	23.13±12.5	0.30	19.8±9.6	0.36
Resistin [ng/ml]	7.2±3.0	6.4±2.8	0.08	6.9±2.7	0.74
Ghrelin [ng/l]	1.3±0.7	1.2±0.4	0.78	1.1±0.4	0.34
Insulin [IU/ml]	7.8±4.6	11.5±12.3	0.34	8.0±3.8	0.56
Cortisol [nmol/l]	689±149	619±160	0.09	531±180	0.0008**
IGF-1 [ng/ml]	181±76	185±67	0.84	170±53	0.21
TSH [mIU/l]	2.3±2.3	1.8±1.2	0.43	1.9±1.5	0.97

DBS, deep brain stimulation; BMI, body mass index; TSH, thyroid stimulating hormone; IGF-1, insulin-like growth factor 1.
Statistical significance of differences in parameters measured at baseline and at months one and twelve, tested by paired signed-rank test; after Bonferroni correction at levels p<0.05 (*), p<0.01 (**), p<0.001(***)

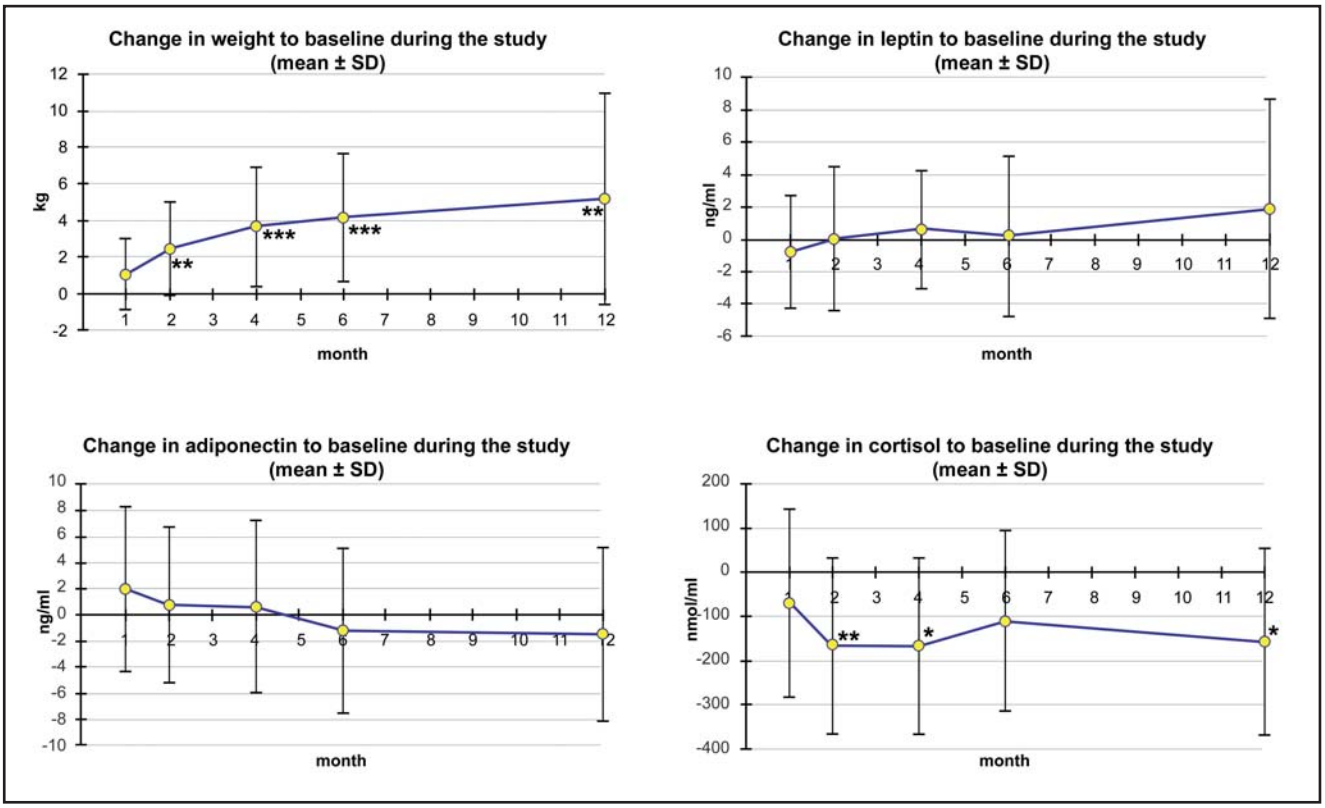

Fig. 1. Mean changes in weight, leptin, adiponectin, and cortisol during the study. X axis: individual measurements at 1, 2, 4, 6, and 12 months after surgery. Y axis: difference from baseline, measured parameter.

studies (Barichella *et al.* 2003; Macia *et al.* 2004; Montaurier *et al.* 2007; Perlemoine *et al.* 2005; Tuite *et al.* 2005), body weight increased in most of our patients, together with increasing BMI, waist circumference and body fat percentage within one year on STN-DBS. Body weight correlated positively with serum levels of leptin and inversely with adiponectin, which correspond to the physiological regulatory mechanisms of food related processes (Meier & Gressner 2004). In addition, ghrelin positively correlated with weight in our patients. This corroborates previous findings that were considered paradoxical in PD patients where weight loss usually occurs with the disease progression – the lower BMI was, the lower ghrelin levels were found (Fiszer *et al.* 2010). However, in accordance with Corcuff *et al.*, we did not observe any increase in ghrelin following STN-DBS (Corcuff *et al.* 2006).. In fact, since the peripheral ghrelin was measured, the results may not reflect possible changes in centrally released ghrelin that mainly participates in the regulation of food intake and body weight.

As the most prominent hormonal change, serum levels of cortisol were found to significantly decrease on STN-DBS, although cortisol should typically increase in the course of truncal fat accumulation and increasing body weight (Reynolds 2010). Hence, direct effects of STN stimulation on adjacent nerve fibers and nuclei must be considered. STN-DBS may hypothetically act on the hypothalamus by suppressing the secretion of CRF with a subsequent decrease in the production of cortisol, leading to a predominance of anabolic reactions. Indeed, in rats exposed to high-frequency electrical stimulation of the lateral hypothalamus, body weight changes occurred even if no difference was observed in food intake between stimulated and unstimulated animals (Sani *et al.* 2007). Accordingly, no consistent changes in food-related behavior were recorded in our patients. This is in agreement with previous studies indicating no changes in food related behavior connected to STN-DBS weight gain (Bannier *et al.* 2009; Macia *et al.* 2004; Montaurier *et al.* 2007; Perlemoine *et al.* 2005). Alternatively, body weight gain could be attributed to indirect factors such as decreased energy expenditure after DBS (Barichella *et al.* 2003; Gironell *et al.* 2002; Montaurier *et al.* 2007). However, in a study comparing weight gain and energy intake after STN-DBS versus pallidal DBS, changes in BMI were correlated with reduction of dyskinesias in the pallidal but not in the STN-DBS group (Sauleau *et al.* 2009). This supports a direct or indirect effect of subthalamic stimulation on the hypothalamic homeostatic centers regulating energy balance, resulting in hormonal dysregulation and weight gain. Finally, for the sake of completeness, we must consider that decreased serum

cortisol following DBS may simply be a non-specific observation, representing the reversal of a temporary perioperative increase in cortisol levels due to surgical stress (Desborough 2000).

In conclusion, our findings did not reveal the cause of weight gain in patients with PD treated by STN-DBS. We found only physiological changes in peripheral food-related hormones corresponding to prevalent weight gain. Even if decreased cortisol production might be connected with STN-DBS and lead to subsequent weight gain, direct effects of STN-DBS on hypothalamic catabolic/anabolic peptide balance remain hypothetical and necessitate further elucidation.

ACKNOWLEDGMENTS

Study support by grants from the Czech Ministry of Health, IGA NT/11331-6, Czech Science Foundation, 309/09/1145, and Czech Ministry of Education, Research Program MSM0021620849.

REFERENCES

1 Anubhuti, Arora S (2008) Leptin and its metabolic interactions: an update. Diabetes Obes Metab. **10**: 973–993.
2 Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al (1999) Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun. **257**: 79–83.
3 Arora S, Anubhuti (2006) Role of neuropeptides in appetite regulation and obesity–a review. Neuropeptides. **40**: 375–401.
4 Aziz NA, Pijl H, Frolich M, Roelfsema F, Roos RA (2011) Leptin, adiponectin, and resistin secretion and diurnal rhythmicity are unaltered in Parkinson's disease. Mov Disord. **26**: 760–761.
5 Bannier S, Montaurier C, Derost PP, Ulla M, Lemaire JJ, Boirie Y, et al (2009) Overweight after deep brain stimulation of the subthalamic nucleus in Parkinson disease: long term follow-up. J Neurol Neurosurg Psychiatry. **80**: 484–488.
6 Barichella M, Cereda E, Pezzoli G (2009) Major nutritional issues in the management of Parkinson's disease. Mov Disord. **24**: 1881–1892.
7 Barichella M, Marczewska AM, Mariani C, Landi A, Vairo A, Pezzoli G (2003) Body weight gain rate in patients with Parkinson's disease and deep brain stimulation. Mov Disord. **18**: 1337–1340.
8 Corcuff JB, Krim E, Tison F, Foubert-Sanier A, Guehl D, Burbaud P, et al (2006) Subthalamic nucleus stimulation in patients with Parkinson's disease does not increase serum ghrelin levels. Br J Nutr. **95**: 1028–1029.
9 Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS (2001) A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes. **50**: 1714–1719.
10 Desborough JP (2000) The stress response to trauma and surgery. Br J Anaesth. **85**: 109–117.
11 Evidente VG, Caviness JN, Adler CH, Gwinn-Hardy KA, Pratley RE (2001) Serum leptin concentrations and satiety in Parkinson's disease patients with and without weight loss. Mov Disord. **16**: 924–927.
12 Fiszer U, Michalowska M, Baranowska B, Wolinska-Witort E, Jeske W, Jethon M, et al (2010) Leptin and ghrelin concentrations and weight loss in Parkinson's disease. Acta Neurol Scand. **121**: 230–236.
13 Fruebis J, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MR, Yen FT, et al (2001) Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. Proc Natl Acad Sci U S A. **98**: 2005–2010.
14 Gironell A, Pascual-Sedano B, Otermin P, Kulisevsky J (2002) Weight gain after functional surgery for Parkinsons disease. Neurologia. **17**: 310–316.
15 Koss AM, Alterman RL, Tagliati M, Shils JL (2005) Calculating total electrical energy delivered by deep brain stimulation systems. Ann Neurol. **58**: 168–169.
16 Leal-Cerro A, Soto A, Martinez MA, Dieguez C, Casanueva FF (2001) Influence of cortisol status on leptin secretion. Pituitary. **4**: 111–116.
17 Leibowitz SF, Wortley KE (2004) Hypothalamic control of energy balance: different peptides, different functions. Peptides. **25**: 473–504.
18 Lorefalt B, Toss G, Granerus AK (2009) Weight loss, body fat mass, and leptin in Parkinson's disease. Mov Disord. **24**: 885–890.
19 Macia F, Perlemoine C, Coman I, Guehl D, Burbaud P, Cuny E, et al (2004) Parkinson's disease patients with bilateral subthalamic deep brain stimulation gain weight. Mov Disord. **19**: 206–212.
20 Meier U, Gressner AM (2004) Endocrine regulation of energy metabolism: review of pathobiochemical and clinical chemical aspects of leptin, ghrelin, adiponectin, and resistin. Clin Chem. **50**: 1511–1525.
21 Montaurier C, Morio B, Bannier S, Derost P, Arnaud P, Brandolini-Bunlon M, et al (2007) Mechanisms of body weight gain in patients with Parkinson's disease after subthalamic stimulation. Brain. **130**: 1808–1818.
22 Novakova L, Ruzicka E, Jech R, Serranova T, Dusek P, Urgosik D (2007) Increase in body weight is a non-motor side effect of deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Neuro Endocrinol Lett. **28**: 21–25.
23 Perlemoine C, Macia F, Tison F, Coman I, Guehl D, Burbaud P, et al (2005) Effects of subthalamic nucleus deep brain stimulation and levodopa on energy production rate and substrate oxidation in Parkinson's disease. Br J Nutr. **93**: 191–198.
24 Qi Y, Takahashi N, Hileman SM, Patel HR, Berg AH, Pajvani UB, et al (2004) Adiponectin acts in the brain to decrease body weight. Nat Med. **10**: 524–529.
25 Reynolds RM (2010) Corticosteroid-mediated programming and the pathogenesis of obesity and diabetes. J Steroid Biochem Mol Biol. **122**: 3–9.
26 Sani S, Jobe K, Smith A, Kordower JH, Bakay RA (2007) Deep brain stimulation for treatment of obesity in rats. J Neurosurg. **107**: 809–813.
27 Sauleau P, Leray E, Rouaud T, Drapier S, Drapier D, Blanchard S, et al (2009) Comparison of weight gain and energy intake after subthalamic versus pallidal stimulation in Parkinson's disease. Mov Disord. **24**: 2149–2155.
28 Strowd RE, Cartwright MS, Passmore LV, Ellis TL, Tatter SB, Siddiqui MS (2010) Weight change following deep brain stimulation for movement disorders. J Neurol. **257:** 1293–1297.
29 Tuite PJ, Maxwell RE, Ikramuddin S, Kotz CM, Billington CJ, Laseski MA, et al (2005).Weight and body mass index in Parkinson's disease patients after deep brain stimulation surgery. Parkinsonism Relat Disord. **11**: 247–252.

RESEARCH ARTICLE

Subthalamic Nucleus Stimulation Affects Incentive Salience Attribution in Parkinson's Disease

Tereza Serranová, MD,[1]* Robert Jech, MD,[1] Petr Dušek, MD,[1] Tomáš Sieger,[1,2] Filip Růžička, MD,[1,3] Dušan Urgošík, MD,[1,4] and Evžen Růžička, MD[1]

[1]*Department of Neurology and Center of Clinical Neuroscience, Charles University in Prague, 1st Faculty of Medicine and General University Hospital, Prague, Czech Republic*
[2]*Department of Cybernetics, Faculty of Electrical Engineering, Czech Technical University in Prague, Prague, Czech Republic*
[3]*Department of Neurosurgery, Na Homolce Hospital, Prague, Czech Republic*
[4]*Department of Stereotactic and Radiation Neurosurgery, Na Homolce Hospital, Prague, Czech Republic*

ABSTRACT: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) can induce nonmotor side effects such as behavioral and mood disturbances or body weight gain in Parkinson's disease (PD) patients. We hypothesized that some of these problems could be related to an altered attribution of incentive salience (ie, emotional relevance) to rewarding and aversive stimuli. Twenty PD patients (all men; mean age ± SD, 58.3 ± 6 years) in bilateral STN DBS switched ON and OFF conditions and 18 matched controls rated pictures selected from the International Affective Picture System according to emotional valence (unpleasantness/pleasantness) and arousal on 2 independent visual scales ranging from 1 to 9. Eighty-four pictures depicting primary rewarding (erotica and food) and aversive fearful (victims and threat) and neutral stimuli were selected for this study. In the STN DBS ON condition, the PD patients attributed lower valence scores to the aversive pictures compared with the OFF condition ($P < .01$) and compared with controls ($P < .01$). The difference between the OFF condition and controls was less pronounced ($P < .05$). Furthermore, postoperative weight gain correlated with arousal ratings from the food pictures in the STN DBS ON condition ($P < .05$ compensated for OFF condition). Our results suggest that STN DBS increases activation of the aversive motivational system so that more relevance is attributed to aversive fearful stimuli. In addition, STN DBS–related sensitivity to food reward stimuli cues might drive DBS-treated patients to higher food intake and subsequent weight gain.

Key Words: STN DBS; emotion; affective; IAPS; weight gain; motivation

Deep brain stimulation of the subthalamic nucleus (STN DBS) has become a standard and highly effective treatment in advanced Parkinson's disease (PD).[1] In addition to motor symptom improvement, STN DBS–treated patients can develop behavioral and mood disturbances (impulsivity, irritability, mania, depression).[2,3] In addition, weight gain has also been reported as a common nonmotor side effect.[4,5] However, the mechanisms of these complications still remain unclear.

Changes in emotional and motivational processes may be part of the side effects of STN DBS in PD. Although 1 study using a mood-induction procedure found that STN DBS may enhance emotional processing,[6] other studies reported that STN DBS induced impaired facial expression recognition selective for negative emotions,[7–10] and reduced differentiation and self-reported intensity of negative feelings induced by film excerpts.[11] Emotion recognition and differentiation are adaptive skills important for social interactions.[12] However, a disturbance in these abilities can only explain part of the emotional and behavioral complications seen in STN DBS–treated patients.

***Correspondence to:** Tereza Serranová, Department of Neurology, First Medical Faculty, Charles University in Prague, Kateřinská 30, 120 00, Praha 2, Czech Republic; tereza.serranova@gmail.com

Funding agencies: This work was supported by the Czech Science Foundation (grant project 309/09/1145) and by the Czech Ministry of Education (research project MŠM 0021620849).
Relevant conflicts of interest/financial disclosures: All authors received grant support from the Czech Science Foundation (309/09/1145) and the Czech Ministry of Education (MŠM 0021620849). Robert Jech, Dušan Urgošík, and Evžen Růžička received consulting fees from Medtronic.
Full financial disclosures and author roles may be found in the online version of this article.

Received: 7 November 2010; **Revised:** 4 April 2011; **Accepted:** 9 May 2011
Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/mds.23880

Moreover, appropriate decision making and adaptive behavior are promoted by motivational processes. The motivational process that assigns behavioral or emotional relevance to a stimulus representation is referred to as incentive salience attribution.[13] It has been demonstrated that incentive salience attribution to both appetitive and aversive stimuli depends largely on the mesolimbic dopaminergic system,[13–15] and there is ample evidence showing the close relationship between activation of the mesolimbic dopaminergic neurotransmission, motivational "wanting" for food rewards, increase in food intake, and obesity.[16–18] This dopamine-mediated behavior also seems to be modulated by the control of the STN, as both the subthalamotomy and the STN DBS increased motivation for food in experimental animals.[19–24] The role of STN in emotional and motivational processing was also demonstrated in neurophysiological studies in monkeys and in PD patients.[25,26]

We used a computer-based visual test containing a series of images chosen from the International Affective Picture System (IAPS), which has been proven to activate either appetitive or aversive motivational functions.[27] At a conscious level, these activations can be expressed in subjective ratings along the dimension of emotional valence (qualitative measure of emotion from pleasant to unpleasant, with neutral stimuli in the middle) and emotional arousal or intensity (quantitative measure of emotional intensity from calm to excited) as personal relevance appraisal (incentive salience attribution).[28,29] To test our hypothesis, we compared ratings of IAPS pictures in a group of PD patients with DBS switched ON and OFF and in healthy controls. To examine changes in activation of the appetitive motivational system, we focused on the possible STN DBS–related effects on incentive salience of pictures containing food or erotic material, as they represent the 2 primary rewards and high sensitivity to rewards was found to be related to eating behaviors that contribute to excess body weight.[17] Similarly, changes in activation of the aversive motivational system were analyzed from the perspective of 2 categories of aversive fearful stimuli—pictures of threats of aggression and pictures of victims of destructive or injurious actions.

Patients and Methods

Subjects

The study was approved by the local ethics committee, and all participants gave their informed consent prior to inclusion in the study. Twenty PD patients treated with bilateral STN DBS for motor fluctuations and/or dyskinesias and 18 matched controls, all men, were included in the study. All the patients fulfilled the UK Brain Bank criteria for diagnosis of PD.[30]

TABLE 1. Parkinson's disease patients and control group—demographic and disease characteristics

		PD patients	Controls
Age (y)		58.3 ± 6	56.1 ± 7
Education duration (y)		13.8 ± 3	16.9 ± 3
MMSE		28.6 ± 1	29,4 ± 1
BDI		11.8 ± 7	8.4 ± 6
Disease duration (y)		15.7 ± 4	
Time interval after surgery (y)		2.8 ± 2	
DBS STN parameters	Frequency (Hz)	130.8 ± 3	
	Pulse width (μs)	76.3 ± 23	
	Amplitude (V)	2.8 ± 0.4	

Values are expressed as means ± SD.
MMSE, Mini Mental State Examination; BDI, Beck Depression Inventory; DBS STN, deep brain stimulation of the subthalamic nucleus.

On the day of the study all participants were screened for cognitive and mood status using the Mini Mental State Examination (MMSE)[31] and the Beck Depression inventory (BDI; Beck et al, 1996).[32] The demographic variables of the patients and controls and disease characteristics are summarized in Table 1. No differences were found for age, MMSE, BDI, or education duration between the patients and the control group. In the PD group, the mean daily dose of dopaminergic medications (in levodopa equivalents)[33] was 550.3 ± 479 mg. Fourteen patients were on levodopa only, 2 were taking a combination of levodopa with dopamine agonists, 2 were on dopamine agonist therapy only, and 2 patients were free of dopaminergic medication. Five of the patients were on antidepressant therapy (3 on citalopram, 1 on mirtazapine, 1 on sertraline). One of the control subjects was on anxiolytic therapy with buspiron. No other psychotropic medication was taken. In addition, the preoperative and postoperative body weights were recorded in the PD group. Sixteen patients were chronically stimulated by bilateral monopolar STN DBS, 4 patients by bipolar on 1 side and monopolar on the other.

The possible presence of impulse control disorder or repetitive behaviors in PD patients was screened using a modified version of the Minnesota Impulsive Disorders Interview (MIDI),[34] and all patients who scored in the MIDI were examined by a psychiatrist. Only 1 patient, who presented signs of binge eating and punding, met the criteria for obsessive–compulsive disorder.[35]

Visual Task and Procedure

Visual stimuli were selected from the International Affective Picture system (IAPS) in order to represent specific thematic appetitive and aversive contents.[27] Eighty-four pictures were selected consisting of: (1) 21 with erotica content (erotic women and couples), (2) 21 with food content, (3) 21 with aversive content—victims (mutilations) and threat (human or animal

attacks, aimed guns), and (4) 21 with neutral content (household objects, buildings, plants). Erotic and aversive pictures were valence- and arousal-matched according to their normative ratings. Three sets of pictures in different orders were compiled so that maximally 2 pictures with the same content followed.[#]

Patients were tested after overnight withdrawal from dopaminergic medication. On the day of testing their stimulators were switched off for 2 hours starting at 8 AM. Then they were tested in 2 conditions with STN DBS switched ON and OFF in counterbalanced orders. There was a 1-hour break between when the stimulators were switched into the particular condition and affective testing (thus, stimulators had been switched OFF for 3 hours in patients who were tested in the OFF condition first). For each patient a different set of pictures was used for DBS ON and DBS OFF conditions. In each condition prior to affective testing, the UPDRS III rating was performed by a rater who was unaware of the DBS condition.

The participants were comfortably seated in front of a touch-sensitive screen. Each picture was presented on the screen for a period of 6 seconds. Subjects were required to rate each picture separately along the dimension of emotional valence and arousal by touching the appropriate symbol on 2 independent visual scales that were presented on the screen after the picture offset. The scales were designed according to the original IAPS scales.[27] Valence was rated on a 1–9 scale, with 9 being the most pleasant, and arousal on a 1–9 scale, with 9 being the most arousing. Before testing, patients were instructed how to rate valence and arousal of each picture according to the IAPS manual. Then they were shown 8 representative pictures for training purposes.

Data Analysis

For statistical analysis SPSS 14.0.1 software (Chicago, IL) was used. As several parameters did not follow the normal distribution, nonparametric tests were applied. For each category of pictures, the Kruskal–Wallis test was used to analyze differences in valence and arousal between conditions and groups of subjects. The significant results were then analyzed post hoc by the Mann–Whitney *U* test (to compare groups of subjects) and the Wilcoxon signed-rank test (to compare DBS OFF and ON conditions). Parameters with normal distribution were analyzed by Pearson correlation and partial correlation analysis. Bonferroni correction of multiple comparisons was used whenever appropriate.

[#]The numbers of IAPS pictures were as follows: erotic pictures—4002, 4275, 4320, 4232, 4694, 4180, 4250, 4150, 4240, 4255, 4670, 4235, 4310, 4225, 4311, 4220, 4006, 4659, 4141, 4001, 4142; food pictures—sweet foods, 7200, 7220, 7283, 7286, 7320, 7330, 7340, 7402, 7487; salty foods, 7230, 7289, 7291, 7350, 7352, 7460, 7475, 7480, 7481, 7482, 7488; wines picture, 7280; neutral pictures—7235, 7175, 7185, 7110, 7491, 7179, 7035, 7705, 5510, 7059, 7041, 7010, 7090, 7950, 7080, 7000, 7187, 7006, 7050, 7020, 7004; aversive pictures—threats, 1050, 1120, 1300, 3500, 3530, 6230, 6260, 6350, 6510, 6550; victims, 3000, 3010, 3060, 3069, 3071, 3080, 3120, 3130, 3170, 3266; threat/victim picture, 9410.

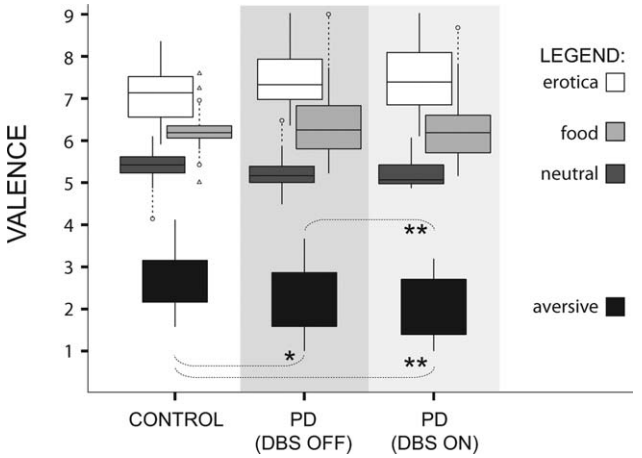

FIG. 1. Valence of selected IAPS pictures of 4 categories (erotic, food, neutral, aversive content) as rated by control subjects (n = 18) and PD patients (n = 20) in conditions with the STN DBS switched OFF and ON. The only difference between conditions/groups of subjects was found for the valence of pictures with aversive content (significance level of post hoc tests: $^{*}P < .05$, $^{**}P < .01$). The box plot represents the median (horizontal line), interquartile range (length of box plot), values within 1.5 interquartile range of the upper/lower quartile (whiskers), outliers—within 1.5 and 3.0 interquartile range (○), extreme values—>3.0 interquartile range (Δ); significance level of post hoc tests ($^{*}P < .05$, $^{**}P < .01$).

Results

Clinical Observations

The UPDRS III score decreased from 40.4 ± 11 in the DBS OFF condition to 17.5 ± 6 in the DBS ON condition ($Z = 3.9$, $P < .0001$).

Affective Ratings

Between-Groups and Condition Comparison

The valence comparison for each of the 4 categories of the IAPS pictures revealed that only aversive pictures yielded significant differences among DBS conditions and/or groups of subjects ($\chi^2 = 7.4$, $P < .05$ corrected). No differences in valence ratings were found for the other picture categories (Fig. 1). Post hoc analyses disclosed that in the DBS ON condition, patients rated the valence of aversive pictures significantly lower compared with the DBS OFF condition ($Z = 2.7$, $P < .01$) and compared with the control group ($Z = 2.5$, $P < .01$). The difference in valence of aversive pictures between patients in the DBS OFF and control subjects was less pronounced but still significant ($Z = 2.0$, $P < .05$). Of the 2 subcategories of aversive pictures, the pictures of victims elicited stronger effects in the post hoc tests (conditions: $Z = 2.4$, $P < .05$; groups: $Z = 2.5$, P

FIG. 2. Valence of 2 subcategories of the IAPS pictures with aversive content as rated by control subjects (n = 18) and PD patients (n = 20) in conditions with the STN DBS switched OFF and ON. The pictures showing victims elicited more significant differences in valence between conditions/groups than the pictures of threats (significance level of post hoc tests: $^{*}P < .05$, $^{**}P < .01$).

$< .01$) than did the pictures of threats (conditions: n.s.; groups: $Z = 2.2$, $P < .05$); see Figure 2.

Similar to the effects on valence, the only significant effect on arousal was found for pictures with aversive content ($\chi^2 = 7.8$, $P < .05$ corrected). The arousal elicited by aversive pictures was rated significantly higher by patients with the DBS switched ON than by control subjects ($Z = 2.7$, $P < .01$). No other differences in arousal were detected by post hoc tests.

To test a confounding effect of therapy, all patients on antidepressants (n = 5) were excluded and all analyses recalculated, achieving similar results. Therefore, the original group of patients (n = 20) did not have to be restricted.

Within-group post hoc analyses demonstrated a significant effect of the order, as the changes in valence ($Z = 2.9$, $P < .01$) and arousal ($Z = 2.2$, $P < .05$) of aversive pictures were significant only for group of patients tested first in the OFF condition (n = 12).

Between Picture Category Comparison

Mean valence and arousal ratings of aversive and erotic pictures were compared for each picture category in both groups of subjects. Pictures of victims always had the highest mean arousal scores ($P < .0001$ corrected) and showed a higher difference of valence scores from the valence of neutral pictures ($P < .0001$ corrected) than those in the other categories (erotica, threat).

Body Weight Change and Affective Ratings

The mean body weight of patients increased postoperatively to 91.5 ± 11 kg from a preoperative weight of 83.4 ± 14 kg ($Z = 3.6$, $P < .001$).

The weight change correlated positively with arousal ratings of appetitive stimuli in the DBS ON condition (erotic: $r = 0.66$, $P < .01$ corrected; food: $r = 0.69$, $P < .01$ corrected, see Figure 3) and weakly in the DBS OFF condition (erotic: $r = 0.53$, $P < .05$ corrected; food: $r = 0.49$, n.s.). For the ratings of food pictures, this positive correlation in the DBS ON condition remained significant for the food pictures even after suppression of the effect of DBS OFF condition by partial correlation analysis ($r = 0.59$, $P < .05$ corrected). No other correlations were found. These correlations remained significant even after exclusion of patients in whom antidepressants (n = 3) or dopamine agonists (n = 2) might have influenced body weight changes (see Supplementary Material). In addition, the effect of order was analyzed post hoc, and the partial correlation was found to be significant ($r = 0.61$, $P < .05$) only in the group of patient tested in the DBS OFF condition first (n = 12).

Discussion

This is the first study demonstrating STN DBS effects on motivational salience attribution (assigning relevance to a stimulus representation) in PD patients. Our findings support the hypothesis that STN DBS influences the incentive salience attribution (ie, assigning relevance to a stimulus representation).

According to the valence ratings, aversive stimuli were rated as more unpleasant in the STN DBS ON condition than when compared with the OFF condition and with the controls. The change in valence ratings of aversive pictures because of STN DBS was demonstrated only for pictures of victims, not threats. Findings from several fMRI studies implicated the existence of distinct neural substrates of disgust-relevant categories such as contamination and mutilation.[36] Therefore, one possible explanation could be a selective effect of DBS on structures involved in processing

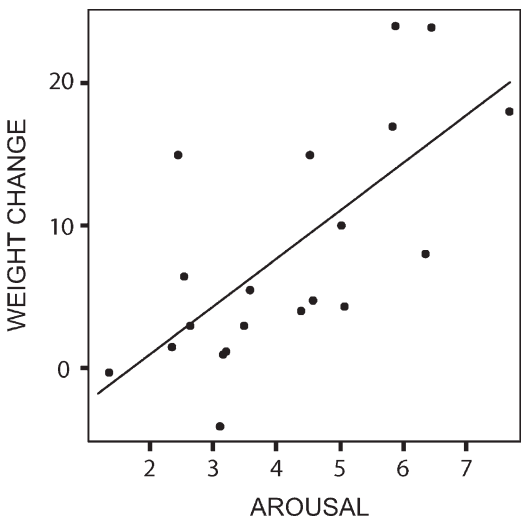

FIG. 3. Correlation between the arousal of the pictures with the food content rated by Parkinson's disease patients (n = 20) with the STN DBS switched ON and body weight change after STN DBS implantation (kg).

this content category. Nevertheless, other imaging and neurophysiological studies indicated the existence of a common subcortical network involved in the incentive salience attribution processing[29,37] and suggested the influence of arousal level on affective and motivational physiological responses.[38,39] In the present study the pictures of victims were stronger stimuli than pictures from the other content categories according to the valence and arousal ratings in all groups and conditions and may represent the most salient pictures that signal threat to one's own bodily integrity. This is in line with the finding that the mesolimbic dopamine system responds to both rewarding and aversive stimuli that are of high intensity.[14,15]

The difference between valence and arousal ratings of aversive pictures in the control group and PD patients was more pronounced in the DBS ON than in the DBS OFF condition. The separate analyses involving patients tested first in the OFF or the ON conditions nevertheless suggested that a DBS aftereffect contributed to our results. It seems that DBS switching-off for 1 hour is insufficiently short compared with a 3-hour interruption. According to our results, we assume that the STN DBS may drive the aversive motivational system in PD patients away from normal functioning and possibly interfere with social interactions. Moreover, the increased motivational relevance attribution to aversive pictures in the DBS OFF condition compared with controls could not be easily attributed to the neurodegenerative process itself or medication, as there is evidence for impaired incentive salience attribution by dopamine loss[40,41] or an inhibiting effect of antidepressants on aversive stimuli processing.[42,43]

For the appetitive stimuli, the evidence of STN DBS influence on incentive salience attribution is rather indirect. Although we could not find any conscious change in subjective ratings of appetitive stimuli because of the STN DBS, partial correlation analysis showed that patients with the higher postoperative weight increase rated food stimuli as more intense under STN DBS. Strictly speaking, a DBS-related increase by 1 point on the arousal scale of the food pictures was associated with an average postoperative body weight increase of 3.3 kg. We assume that this result is consistent with increased sensitivity to food reward cues because of STN DBS. This is in line with evidence from animal studies that STN DBS and STN lesions increased motivation for food but without eliciting binge eating.[21,44] Similarly in our patients, the increased weight gain did not appear related to binge eating. We suggest that such STN DBS–related sensitivity to food reward cues drives DBS-treated patients to higher food intake and subsequent weight gain.

We believe that our results support the hypothesis that STN DBS affects the incentive salience attribution in STN DBS–treated patients. It has been suggested that DBS activates axons surrounding the active contact of the implanted electrodes and increases output from the stimulated nucleus.[45–47] In animals, STN DBS has been found to increase the activity of the DA system.[48,49] STN DBS may therefore enhance the physiological function of the mesolimbic dopamine system, either by an increased output from the STN to its mesolimbic target structures such as the ventral tegmental area (VTA)[50,51] and ventral pallidum[50,52] or by directly activating the mesolimbic dopaminergic projections from the VTA to the nucleus accumbens that are running within the adjacent medial forebrain bundle.[45,53]

There are several limitations of our study. We are lacking data on food intake, hunger, or appetite and motivational salience attribution before surgery, and we can hardly exclude the effect of medication (antidepressants, dopamine agonists, levodopa decrease) on between-group comparisons and on the body weight of PD patients.[54–56]

Despite its drawbacks, the present study suggests that STN DBS activates the aversive motivational system in a way that more emotional relevance is attributed to fearful aversive stimuli. Our results further suggest that body weight gain in PD patients treated by STN DBS might be related to increased sensitivity to food reward cues, which may be of practical value for managing this side effect. In conclusion, this study further supports the role of the STN in emotional and motivational processing which may potentially influence food intake behavior and social interactions.

Supplementary Material

Additional Analyses

From correlation analysis, we excluded patients (n = 5) in whom weight changes were present after introduction of the antidepressants (ADs) or dopamine agonists (DAgs) before or after the surgery. This included remaining patients (n = 15) with a well-documented stable body weight after the preoperative introduction of ADs or DAgs and patients in whom this treatment was introduced shortly before testing and in whom no weight change has been detected since. The positive body weight change correlated positively with arousal ratings of appetitive stimuli in the DBS ON condition (erotic: $r = 0.70$, $P < .01$ corrected; food: $r = 0.77$, $P < .01$ corrected) and not in the DBS OFF condition (erotic: $r = 0.55$, n.s. corrected; food: $r = 0.57$, n.s.). This positive correlation between arousal and body weight change in the DBS ON condition remained significant for the food pictures even after suppression of the effect of the DBS OFF condition by partial correlation analysis ($r = 0.64$, $P < .05$ corrected).

There was no difference found either for valence or for arousal ratings from sweet and salty food pictures

in the between group (PD patients in OFF condition vs controls, patients in ON condition vs controls) and the between condition (DBS OFF vs ON condition) comparison. Postoperative body weight change correlated positively with arousal ratings of salty ($r = 0.70$, $P < .001$, uncorrected) and sweet ($r = 0.69$, $P < .002$ uncorrected) food pictures in the DBS ON condition. In the DBS OFF condition these correlation were weaker for both salty ($r = 0.46$, $P < .04$ uncorrected, n.s. corrected) and sweet ($r = 0.47$, $P < .04$ uncorrected, n.s. corrected) food pictures. The partial correlation analysis was also performed for salty food pictures ($r = 0.63$, $P < .004$ uncorrected) and for sweet food pictures ($r = 0.47$, $P < .04$ uncorrected).

Acknowledgments: We are grateful to Markéta Fialová for administrative support and to Martin Voleman for technical support.

References

1. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med. 2003;349:1925–1934.
2. Voon V, Kubu C, Krack P, Houeto JL, Tröster AI. Deep brain stimulation: neuropsychological and neuropsychiatric issues. Mov Disord. 2006;21(Suppl 14):S305–S327.
3. Temel Y, Blokland A, Steinbusch H, Visser-Vandewalle V. The functional role of the subthalamic nucleus in cognitive and limbic circuits. Prog Neurobiol. 2005;76:393–413.
4. Novakova L, Ruzicka E, Jech R, Serranova T, Dusek P, Urgosik D. Increase in body weight is a non-motor side effect of deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Neuro Endocrinol Lett. 2007;28:21–25.
5. McIntyre CC, Miocinovic S, Butson CR. Computational analysis of deep brain stimulation. Expert Rev Med Devices. 2007;4: 615–622.
6. Schneider F, Habel U, Volkmann J, et al. Deep brain stimulation of the subthalamic nucleus enhances emotional processing in Parkinson disease. Arch Gen Psychiatry. 2003;60:296–302.
7. Biseul I, Sauleau P, Haegelen C, et al. Fear recognition is impaired by subthalamic nucleus stimulation in Parkinson's disease. Neuropsychologia. 2005;43:1054–1059.
8. Drapier D, Péron J, Leray E, et al. Emotion recognition impairment and apathy after subthalamic nucleus stimulation in Parkinson's disease have separate neural substrates. Neuropsychologia. 2008;46:2796–2801.
9. Dujardin K, Blairy S, Defebvre L, et al. Subthalamic nucleus stimulation induces deficits in decoding emotional facial expressions in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2004;75: 202–208.
10. Schroeder U, Kuehler A, Hennenlotter A, et al. Facial expression recognition and subthalamic nucleus stimulation. J Neurol Neurosurg Psychiatry. 2004;75:648–650.
11. Vicente S, Biseul I, Péron J, et al. Subthalamic nucleus stimulation affects subjective emotional experience in Parkinson's disease patients. Neuropsychologia. 2009;47:1928–1937.
12. Adolphs R, Damasio H, Tranel D, Damasio A. Cortical systems for the recognition of emotion in facial expressions. J Neurosci. 1996;16:7678–7687.
13. Berridge K. The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology. 2007;191:391–431.
14. Horvitz JC. Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. Neuroscience. 2000;96: 651–656.
15. Faure A, Reynolds SM, Richard JM, Berridge KC. Mesolimbic dopamine in desire and dread: enabling motivation to be generated by localized glutamate disruptions in nucleus accumbens. J Neurosci. 2008;28:7184–7192.
16. Berridge K. 'Liking' and 'wanting' food rewards: brain substrates and roles in eating disorders. Physiol Behav. 2009;97:537–550.
17. Davis C, Patte K, Levitan R, Reid C, Tweed S, Curtis C. From motivation to behaviour: a model of reward sensitivity, overeating, and food preferences in the risk profile for obesity. Appetite. 2007; 48:12–19.
18. Beaver JD, Lawrence AD, van Ditzhuijzen J, Davis MH, Woods A, Calder AJ. Individual differences in reward drive predict neural responses to images of food. J Neurosci. 2006;26:160–166.
19. Lardeux S, Pernaud R, Paleressompoulle D, Baunez C. Beyond the reward pathway: coding reward magnitude and error in the rat subthalamic nucleus. J Neurophysiol. 2009;102:2526–2537.
20. Baunez C, Christakou A, Chudasama Y, Forni C, Robbins TW. Bilateral high-frequency stimulation of the subthalamic nucleus on attentional performance: transient deleterious effects and enhanced motivation in both intact and parkinsonian rats. Eur J Neurosci. 2007;25:1187–1194.
21. Rouaud T, Lardeux S, Panayotis N, Paleressompoulle D, Cador M, Baunez C. Reducing the desire for cocaine with subthalamic nucleus deep brain stimulation. Proc Natl Acad Sci U S A. 2010; 107:1196–1200.
22. Baunez C, Dias C, Cador M, Amalric M. The subthalamic nucleus exerts opposite control on cocaine and 'natural' rewards. Nat Neurosci. 2005;8:484–489.
23. Baunez C, Amalric M, Robbins TW. Enhanced food-related motivation after bilateral lesions of the subthalamic nucleus. J Neurosci. 2002;22:562–568.
24. Uslaner J, Dell'Orco J, Pevzner A, Robinson T. The influence of subthalamic nucleus lesions on sign-tracking to stimuli paired with food and drug rewards: facilitation of incentive salience attribution? Neuropsychopharmacology. 2008;33:2352–2361.
25. Darbaky Y, Baunez C, Arecchi P, Legallet E, Apicella P. Reward-related neuronal activity in the subthalamic nucleus of the monkey. Neuroreport. 2005;16:1241–1244.
26. Brucke C, Kupsch A, Schneider GH, et al. The subthalamic region is activated during valence-related emotional processing in patients with Parkinson's disease. Eur J Neurosci. 2007;26:767–774.
27. Lang PJ, Bradley MM, Cuthbert, BN. International affective picture system (IAPS): Affective ratings of pictures and instruction manual. In: Technical Report A-8. Gainesville, FL: University of Florida; 2008.
28. Bradley MM, Codispoti M, Cuthbert BN, Lang PJ. Emotion and motivation I: defensive and appetitive reactions in picture processing. Emotion. 2001;1:276–298.
29. Phan KL, Taylor SF, Welsh RC, Ho SH, Britton JC, Liberzon I. Neural correlates of individual ratings of emotional salience: a trial-related fMRI study. Neuroimage. 2004;21:768–780.
30. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry. 1992;55:181–184.
31. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–198.
32. Beck A, Steer R, Brown G. The Beck Depression Inventory–II. San Antonio, TX: Psychological Corporation; 1996.
33. Kleiner-Fisman G, Herzog J, Fisman D, et al. Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. Mov Disord. 2006;21(Suppl 14):S290–S304.
34. Christenson GA, Faber RJ, de Zwaan M, et al. Compulsive buying: descriptive characteristics and psychiatric comorbidity. J Clin Psychiatry. 1994;55:5–11.
35. Voon V, Fernagut PO, Wickens J, et al. Chronic dopaminergic stimulation in Parkinson's disease: from dyskinesias to impulse control disorders. Lancet Neurol. 2009;8:1140–1149.
36. Wright P, He G, Shapira NA, Goodman WK, Liu Y. Disgust and the insula: fMRI responses to pictures of mutilation and contamination. Neuroreport. 2004;15:2347–2351.
37. Liberzon I, Phan KL, Decker LR, Taylor SF. Extended amygdala and emotional salience: a PET activation study of positive and negative affect. Neuropsychopharmacology. 2003;28:726–733.
38. Bernat E, Patrick CJ, Benning SD, Tellegen A. Effects of picture content and intensity on affective physiological response. Psychophysiology. 2006;43:93–103.

39. Miller KM, Okun MS, Marsiske M, Fennell EB, Bowers D. Startle reflex hyporeactivity in Parkinson's disease: an emotion-specific or arousal-modulated deficit? Neuropsychologia. 2009;47:1917–1927.
40. Chinaglia G, Alvarez FJ, Probst A, Palacios JM. Mesostriatal and mesolimbic dopamine uptake binding sites are reduced in Parkinson's disease and progressive supranuclear palsy: a quantitative autoradiographic study using [3H]mazindol. Neuroscience. 1992;49:317–327.
41. Horvitz JC. Dopamine gating of glutamatergic sensorimotor and incentive motivational input signals to the striatum. Behav Brain Res. 2002;137:65–74.
42. McCabe C, Mishor Z, Cowen PJ, Harmer CJ. Diminished neural processing of aversive and rewarding stimuli during selective serotonin reuptake inhibitor treatment. Biol Psychiatry. 2009;67:439–445.
43. Rawlings NB, Norbury R, Cowen PJ, Harmer CJ. A single dose of mirtazapine modulates neural responses to emotional faces in healthy people. Psychopharmacology (Berl). 2010;212:625–634.
44. Baunez C, Amalric M, Robbins T. Enhanced food-related motivation after bilateral lesions of the subthalamic nucleus. J Neurosci. 2002;22:562–568.
45. Vitek JL. Deep brain stimulation: how does it work? Cleve Clin J Med. 2008;75(Suppl 2):S59–S65.
46. Johnson MD, Miocinovic S, McIntyre CC, Vitek J. Mechanisms and targets of deep brain stimulation in movement disorders. Neurotherapeutics. 2008;5:294–308.
47. Jech R, Urgosik D, Tintera J, et al. Functional magnetic resonance imaging during deep brain stimulation: a pilot study in four patients with Parkinson's disease. Mov Disord. 2001;16: 1126–1132.
48. Shon YM, Lee KH, Goerss SJ, et al. High frequency stimulation of the subthalamic nucleus evokes striatal dopamine release in a large animal model of human DBS neurosurgery. Neurosci Lett. 2010; 475:136–140.
49. Lee KH, Blaha CD, Harris BT, et al. Dopamine efflux in the rat striatum evoked by electrical stimulation of the subthalamic nucleus: potential mechanism of action in Parkinson's disease. Eur J Neurosci. 2006;23:1005–1014.
50. Parent A, Hazrati LN. Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Res Brain Res Rev. 1995;20:128–154.
51. Groenewegen HJ, Berendse HW. Connections of the subthalamic nucleus with ventral striatopallidal parts of the basal ganglia in the rat. J Comp Neurol. 1990;294:607–622.
52. Smith KS, Tindell AJ, Aldridge JW, Berridge KC. Ventral pallidum roles in reward and motivation. Behav Brain Res. 2009;196:155–167.
53. Wise RA. Forebrain substrates of reward and motivation. J Comp Neurol. 2005;493:115–121.
54. Aronne LJ, Segal KR. Weight gain in the treatment of mood disorders. J Clin Psychiatry. 2003;64(Suppl 8):22–29.
55. Kumru H, Santamaria J, Valldeoriola F, Marti MJ, Tolosa E. Increase in body weight after pramipexole treatment in Parkinson's disease. Mov Disord. 2006;21:1972–1974.
56. Palhagen S, Lorefalt B, Carlsson M, et al. Does L-dopa treatment contribute to reduction in body weight in elderly patients with Parkinson's disease? Acta Neurol Scand. 2005;111:12–20.

Letter to the Editor

Stereotactic and Functional Neurosurgery

Received: April 27, 2012
Accepted: July 5, 2012
Published online: October 17, 2012

Stereotact Funct Neurosurg 2012;90:410–411
DOI: 10.1159/000341707

Decrease in Blood Cortisol Corresponds to Weight Gain following Deep Brain Stimulation of the Subthalamic Nucleus in Parkinson's Disease

Evžen Růžička[a], *Lucie Nováková*[a], *Robert Jech*[a], *Dušan Urgošík*[a, c], *Filip Růžička*[a], *Martin Haluzík*[b],

[a]Department of Neurology and Centre of Clinical Neuroscience and [b]Department of Internal Medicine, Charles University in Prague, First Faculty of Medicine and General University Hospital in Prague, and [c]Department of Stereotactic and Radiation Neurosurgery, Na Homolce Hospital, Prague, Czech Republic

It has repeatedly been shown that patients with Parkinson's disease (PD) gain body weight under treatment with deep brain stimulation of the subthalamic nucleus (STN DBS) [1–3]. However, the mechanisms underlying this weight gain (WG) remain unclear. We, therefore, read with great interest the recently published article 'The role of ghrelin, neuropeptide Y and leptin peptides in weight gain after deep brain stimulation for Parkinson's disease' by Markaki et al. [4]. The authors performed body composition measurements and blood sampling before, and 3 and 6 months after STN DBS in 23 PD patients, looking for relations between WG and changes in blood levels of the metabolic hormones ghrelin, neuropeptide Y (NPY) and leptin. A significant WG (3.09 ± 5 kg, mean ± SD, p = 0.007) was observed 3 months after surgery, with no further increase at 6 months. Also the circulating levels of NPY increased significantly (p = 0.05) at 3 months, while the increase of ghrelin was significant only at 6 months (p = 0.001). WG was associated with changes of ghrelin and leptin levels at 3 and 6 months. The authors concluded that STN DBS may temporarily dysregulate the hypothalamic secretion of NPY and ghrelin, whereas the WG may be related to an increased production of ghrelin and leptin.

These observations bear remarkable similarities to our earlier study, in which we assessed anthropometric and hormonal profiles in 27 PD patients on the day of surgery and at 2, 4, 6 and 12 months on STN DBS [5]. Our patients' weight continuously increased throughout the study, with the mean body weight change with regard to baseline being +4.16 ± 3.5 kg ($p < 0.001$) at 6 months and +5.18 ± 5.8 kg ($p < 0.001$) at 12 months. Furthermore, in both studies, leptin and ghrelin levels correlated with body WG, corresponding to the known roles of the adipocyte-derived leptin and the orexigenic hormone ghrelin.

Curiously enough, Markaki et al. [4] do not pay much attention to their own finding of markedly decreased cortisol levels following STN DBS. Nevertheless, this result is in surprisingly precise agreement with our observation, probably shedding more light on the mechanisms of WG in PD following STN DBS (table 1). At 3 months after STN DBS, Markaki et al. [4] noticed a significant decrease in blood cortisol (–23.8%, p = 0.027). In our study, cortisol levels decreased at 2 months, (–23.9%, $p < 0.002$), still remaining significantly reduced compared to baseline at 12 months after DBS implantation (–22.9%, p = 0.008) [5]. These results seem to indicate the involvement of hypothalamic-pituitary-adrenal axis in the mechanisms of WG after STN DBS. It can be hypothesized that STN DBS acts on adjacent nerve fibers and structures including hypothalamic nuclei, where it suppresses secretion of corticotropin-releasing factor with a subsequent decrease in the production of cortisol. Since the level of corticotropin-releasing factor is low, its catabolic effect is mitigated; therefore, the homeostatic balance shifts towards predominance in

Table 1. Blood cortisol at different time points and its percent decrease versus baseline

		Baseline	1 month	2 months	3 months	4 months	6 months	12 months
Markaki et al. [4]	Cortisol, μg/dl	17.99	NA	NA	13.71	NA	15.81	NA
	Change to baseline, %		NA	NA	**–23.8**	NA	–12.1	NA
Novakova et al. [5]	Cortisol, nmol/l	688.96	618.78	524.26	NA	521.96	579.74	531.3
	Change to baseline, %		–10.2	**–23.9**	NA	**–24.2**	–15.9	**–22.9**

Bold print indicates significant changes. Conversion factor between conventional units (μg/dl) and SI units (nmol/l) for cortisol = 27.59 (source: http://www.globalrph.com/conv_si.htm). NA = Data not available.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1011–6125/12/0906–0410$38.00/0

Accessible online at:
www.karger.com/sfn

Prof. Evžen Růžička, MD, DSc
Department of Neurology, 1st Faculty of Medicine and General University Hospital
Katerinska 30
CZ–128 21 Prague (Czech Republic)
Tel. +420 224 965 550, E-Mail eruzi@lf1.cuni.cz

anabolic reactions. Interestingly, it has also been previously suggested that increased NPY levels are possibly related to diffusion of the electric current to the hypothalamus causing disruption of the melanocortin system, leading to WG [6].

Our hypothesis is indirectly supported by previous reports showing that cortisol levels were significantly higher in PD patients compared to healthy controls and that cortisol concentrations significantly decreased after levodopa intake, particularly in patients with a more advanced stage of PD [7, 8]. In fact, it has been demonstrated that PD patients lose weight throughout the progression of the disease [9]. The WG following STN DBS might thus mean a compensation of previous loss, rather than an excessive anabolic reaction. Accordingly, we suspect that the observation of a more sustained WG in our group may correspond to a lower initial body mass index than that reported by Markaki et al. (25.8 vs. 28.7), leading to a continued increase in weight in our patients, even if initial values were well above undernutrition in both groups [4, 5].

In conclusion, DBS in PD appears to act not only by exerting its motor effects through the stimulation of the STN, but also by influencing nonmotor functions, namely reversing catabolic processes and inducing WG, by diffusion of the electric current to the adjacent structures including hypothalamus and involving the hypothalamic-pituitary-adrenal axis.

Acknowledgment

Our studies have been supported by the Czech Science Foundation (GACR 309/09/1145), Czech Ministry of Education (VZ 0021620849), and Charles University in Prague (PRVOUK-P26/LF1/4).

References

1 Barichella M, Marczewska AM, Mariani C, Landi A, Vairo A, Pezzoli G: Body weight gain rate in patients with Parkinson's disease and deep brain stimulation. Mov Disord 2003;18:1337–1340.
2 Macia F, Perlemoine C, Coman I, Guehl D, Burbaud P, Cuny E, Gin H, Rigalleau V, Tison F: Parkinson's disease patients with bilateral subthalamic deep brain stimulation gain weight. Mov Disord 2004;19:206–212.
3 Novakova L, Ruzicka E, Jech R, Serranova T, Dusek P, Urgosik D: Increase in body weight is a non-motor side effect of deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Neuro Endocrinol Lett 2007;28:21–25.
4 Markaki E, Ellul J, Kefalopoulou Z, Trachani E, Theodoropoulou A, Kyriazopoulou V, Constantoyannis C: The role of ghrelin, neuropeptide Y and leptin peptides in weight gain after deep brain stimulation for Parkinson's disease. Stereotact Funct Neurosurg 2012;90:104–112.
5 Novakova L, Haluzik M, Jech R, Urgosik D, Ruzicka F, Ruzicka E: Hormonal regulators of food intake and weight gain in Parkinson's disease after subthalamic nucleus stimulation. Neuro Endocrinol Lett 2011;32:437–441.
6 Escamilla-Sevilla F, Pérez-Navarro MJ, Muñoz-Pasadas M, Sáez-Zea C, Jouma-Katati M, Piédrola-Maroto G, Ramírez-Navarro A, Mínguez-Castellanos A: Change of the melanocortin system caused by bilateral subthalamic nucleus stimulation in Parkinson's disease. Acta Neurol Scand 2011;124:275–281.
7 Charlett A, Dobbs RJ, Purkiss AG, Wright DJ, Peterson DW, Weller C, Dobbs SM: Cortisol is higher in parkinsonism and associated with gait deficit. Acta Neurol Scand 1998;97:77–85.
8 Müller T, Muhlack S: Acute levodopa intake and associated cortisol decrease in patients with Parkinson disease. Clin Neuropharmacol 2007;30:101–106.
9 Jaafar AF, Gray WK, Porter B, Turnbull EJ, Walker RW: A cross-sectional study of the nutritional status of community-dwelling people with idiopathic Parkinson's disease. BMC Neurol 2010;10:124.

OPEN ACCESS Freely available online

PLoS one

Weight Gain Is Associated with Medial Contact Site of Subthalamic Stimulation in Parkinson's Disease

Filip Růžička[1☯], Robert Jech[1*☯], Lucie Nováková[1], Dušan Urgošík[2], Josef Vymazal[3], Evžen Růžička[1]

1 Department of Neurology and Centre of Clinical Neuroscience, First Faculty of Medicine and General University Hospital, Charles University, Prague, Czech Republic, **2** Department of Stereotactic and Radiation Neurosurgery, Na Homolce Hospital, Prague, Czech Republic, **3** Department of Radiology, Na Homolce Hospital, Prague, Czech Republic

Abstract

The aim of our study was to assess changes in body-weight in relation to active electrode contact position in the subthalamic nucleus. Regular body weight measurements were done in 20 patients with advanced Parkinson's disease within a period of 18 months after implantation. T1-weighted (1.5T) magnetic resonance images were used to determine electrode position in the subthalamic nucleus and the Unified Parkinson's disease rating scale (UPDRS-III) was used for motor assessment. The distance of the contacts from the wall of the third ventricle in the mediolateral direction inversely correlated with weight gain ($r = -0.55$, $p < 0.01$) and with neurostimulation-related motor condition expressed as the contralateral hemi-body UPDRS-III ($r = -0.42$, $p < 0.01$). Patients with at least one contact within 9.3 mm of the wall experienced significantly greater weight gain (9.4±(SD)4.4 kg, N = 11) than those with both contacts located laterally (3.9±2.7 kg, N = 9) ($p < 0.001$). The position of the active contact is critical not only for motor outcome but is also associated with weight gain, suggesting a regional effect of subthalamic stimulation on adjacent structures involved in the central regulation of energy balance, food intake or reward.

Citation: Růžička F, Jech R, Nováková L, Urgošík D, Vymazal J, et al. (2012) Weight Gain Is Associated with Medial Contact Site of Subthalamic Stimulation in Parkinson's Disease. PLoS ONE 7(5): e38020. doi:10.1371/journal.pone.0038020

Editor: Kewei Chen, Banner Alzheimer's Institute, United States of America

Received October 18, 2011; **Accepted** May 2, 2012; **Published** May 30, 2012

Funding: This work was supported by the Czech Science Foundation: grant project 309/09/1145, Czech Ministry of Health: IGA NT12282-5/2011 and by the Czech Ministry of Education: research project MSM 0021620849 and PRVOUK-P26/LF1/4. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: R. Jech, D. Urgošík and Evžen Růžička received consulting fees from Medtronic Czechia. R. Jech received a travel grant from Medtronic Czechia to attend the XVIII World Congress of Parkinson's disease and Related Disorders in 2009. The authors declare no other potential conflicts of interest with respect to the authorship and/or publication of this article. This does not alter the authors' adherence to all the PLoS ONE policies on sharing data and materials.

* E-mail: jech@cesnet.cz

☯ These authors contributed equally to this work.

Introduction

Deep brain stimulation of the subthalamic nucleus (STN-DBS) is a remarkably effective method for treating motor manifestations of advanced Parkinson's disease (PD). In addition, a variety of non-motor effects related to STN-DBS have been described, including weight gain. Although the precise mechanism underlying changes in body weight has yet to be determined, several hypotheses have been advanced [1]. Some authors have suggested that weight gain may be related to changes in medication, especially to the reduction of dopaminergic drugs [2,3,4]. Others have emphasized that weight gain may be related to the normalization of energy expenditure due to decreased rigidity and the amelioration of dyskinesia [5,6]. Additionally, changes in weight could reflect the direct influence of STN-DBS on adjacent structures involved in the regulation of eating behavior or energy balance [3,5,7].

It has been proposed that DBS may cause the excitation of axons surrounding the electrode and increased output from stimulated nuclei [8,9]. The spread of current has been estimated to occupy approximately a 2–4 mm radius around the electrode contact [10,11,12]. Given structural and functional complexity of the subthalamic area, it is believed that the diffusion of stimulation current to its different parts plays a role in motor improvement as well as in the various side effects of DBS [10,11]. From this perspective, it is conceivable that the stimulating DBS electrode could influence body weight, especially if it was close to the structures involved in the regulation of energy expenditure, food intake or reward, such as the lateral hypothalamic area [13,14], medial forebrain bundle [15] or the limbic part of the STN [16,17,18]. Notably, all of these structures lie in the medial part of the subthalamic area [19,20]. On the other hand, in terms of motor improvement, subthalamic stimulation appears to be most effective in the dorsolateral border of the nucleus (sensorimotor part) [21,22,23]. Thus, the position of active contact relative to the intrinsic organization of the STN might differentially contribute to motor effects and weight changes.

Therefore, the aim of our study was to assess whether weight gain observed in PD patients treated by STN-DBS is dependent on the active electrode contact position in the STN, particularly with respect to mediolateral direction.

Methods

Patients and weight measurement

Regular body weight measurements were made on the day of surgery and one, two, four, six, twelve and eighteen months after electrode implantation in 20 patients with advanced PD (6 women, 14 men; mean age 56.6±(SD)5.8 years; disease duration 13.2±4.5

years). Demographic data of the patients that participated in the study are summarized in table 1. A maximum change in weight during the study period and weight change at the 18th month were considered in each patient. Weight changes were expressed in absolute values as well as in percentage of initial body weight. Eating related questionnaires were administered at each visit. Food intake, hunger, general appetite and preference for sweet food were rated by patients as (0) without any change, (−1) lower or (+1) higher than at the previous visit. 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.

Surgical procedure and stimulation settings

Bilateral DBS electrode implantation (model 3389, Medtronic, Minneapolis, MN, USA) was guided by MRI-based stereotaxy, microelectrode recordings and the test stimulation procedure as described elsewhere [24]. Within three days the electrodes were connected to a subcutaneously implanted pulse generator (Kinetra, Medtronic). Stimulation was initiated one month following implantation when each patient underwent standard screening of all electrode contacts in an off-medication state. Finally, one contact on each side and stimulation settings using a monopolar or bipolar (in one patient) setting were selected to obtain the best motor outcome. In the following month, the stimulation intensity was gradually increased (Figure 1) while dopaminergic medication was in most cases reduced to further optimize the motor outcome. For the purpose of our study, stimulation intensity was calculated as the mean of arithmetic products of all the parameters from both neurostimulators (I-intensity, u-voltage, d-pulse duration, f-frequency): $I = (u_L.d_L.f_L+u_R.d_R.f_R)/2$ [25]. At month 18, the stimulation parameters were 2.8±0.5 V, 60–120 μs and 130 Hz and the mean stimulation intensity was 2.8±0.8. 10^4 V μs Hz.

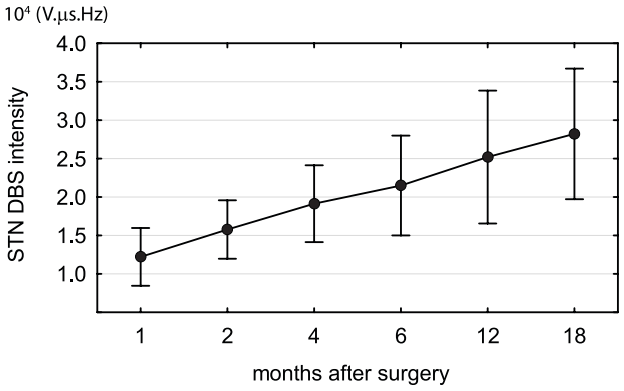

Figure 1. Mean stimulation intensity (±SD) of the STN-DBS at 1, 2, 4, 6, 12 and 18 months after implantation in 20 patients with Parkinson's disease. The stimulation intensity was calculated as the arithmetic product of the I-intensity, u-voltage, d-pulse duration and f-frequency from both hemispheres (uL.dL.fL+uR.dR.fR)/2. The stimulation intensity was gradually increasing during the study to optimize the motor outcome.
doi:10.1371/journal.pone.0038020.g001

Table 1. Clinical description of PD patients treated with subthalamic deep brain stimulation.

	gender	age at surgery (yrs)	PD duration before surg. (yrs)	UPDRSIII s-OFF	UPDRSIII s-ON	initial BMI (kg/m^2)	initial body weight (kg)	maximum weight gain (kg)
1	F	53	20	30	17	19,9	53,3	18,3
2	F	63	18	32	17	17,8	50,1	14,9
3	M	65	22	44	24	23,2	84,2	12,3
4	F	61	12	43	28	24,4	65,6	12
5	M	53	15	62	22	22	69,6	9,4
6	F	58	10	37	17	26,6	64,1	7,5
7	M	56	12	41	23	30,9	100	7,2
8	M	57	14	30	26	20,6	71,3	7,2
9	M	55	7	25	18	27,5	86	7
10	M	67	11	32	16	28,2	86,4	6,5
11	F	58	7	37	18	22,4	61,6	6,4
12	F	42	23	53	19	33,3	80	6
13	M	48	14	36	17	21,6	70	5,3
14	M	56	13	39	16	27,7	95,2	4,5
15	M	49	11	25	12	25,1	67,5	4,1
16	M	57	15	44	11	26,8	84,8	3,9
17	M	63	10	35	14	25,8	72,9	3,6
18	M	58	9	36	24	25	76,6	2,1
19	M	57	10	35	12	28,3	86,8	0,2
20	M	55	10	18	5	29,8	112,3	−0,3

F – female, M – male; PD – Parkinson's disease; UPDRS-III – motor subscore of the Unified Parkinson's Disease Rating Scale; sOFF – postoperative off-neurostimulation state; sON – postoperative on-neurostimulation state; BMI – body mass index; initial body weight – body weight assessed before implantation; maximum weight gain – maximum weight change over the whole study period.
doi:10.1371/journal.pone.0038020.t001

Motor outcome assessment of STN-DBS

Motor status was evaluated using the motor subscore of the Unified Parkinson's Disease Rating Scale (UPDRS-III). Each subject was examined postoperatively under two conditions at least 12 hours after discontinuing all antiparkinsonian drugs: (1) in the off-neurostimulation state (sOFF) and (2) in the on-neurostimulation state (sON). The change of motor status induced by stimulation was expressed as the percentage of UPDRS-III (100-100sON/sOFF). Additionally, hemi-body subscores derived from the UPDRS-III (items 20–26) were calculated as the sum of limb ratings of ridigity, akinesia and tremor, separately for the left and right extremities.

Assessment of active contact position

Magnetic resonance images were acquired at 1.5 T on a Siemens Avanto system (Siemens, Erlangen, Germany) in each patient approximately one year after DBS implantation. To obtain better image resolution, sagittal (0.9 mm isotropic) and axial ($1\times1\times1.6$ mm) T1-weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) images were automatically co-registered and averaged using SPM5 software (Wellcome Trust Centre for Neuroimaging, London, UK).

All four contacts (0,1,2,3) of the DBS electrode produced well-defined susceptibility artifacts on the T1-MPRAGE image in each patient [26]. While the coordinates of contacts 0 and 3 were established directly from the center of the distal and proximal artifacts using MRIcro 1.40 software (www.cabiatl.com/mricro), the coordinates of contacts 1 and 2 were calculated. The x-coordinate of each contact was measured from the wall of the third ventricle, whereas the y- and z-coordinates were measured from the midcommisural point. Two coordinate systems, native and normalized, were used in the study. During linear normalization, all dimensions were manually adjusted with respect to the standardized AC-PC length, to the distance of the midcommissural point from the lateral edge of the putamen, and to the distance of the optic tract from the dorsal edge of the putamen. Finally, the active contacts in both hemispheres were plotted on axial (xy), coronal (xz) and sagittal (yz) planes covering the whole subthalamic area.

Analysis

Statistical analysis was performed using SPSS 14.0.1 software (SPSS Inc, Chicago, IL, USA). For parameters with normal distribution, parametric tests (one sample t-test, paried t-test, Pearson correlation analysis) were used. The others were assessed with the non-parametric tests (Friedman test, Spearman rank correlation analysis).

Primary outcomes of the study were based on the maximum weight gain throughout the study and on the hemibody UPDRS-III in the sON state after initiation of neurostimulation. Their dependence on active contact position was analyzed for each x, y and z-axis separately by Pearson correlation analysis when considering the left and right hemispheres independently, as well as for all active contacts pooled bilaterally taking into account only one active contact (more medial or lateral contact from both hemispheres) in each patient.

In addition, we systematically sought a border dividing the subthalamic area into regions with higher and lower risk of weight gain. To do so, we compared weight gain relative to the active contact position in the subthalamic area divided into two regions of interest (ROI) by a movable yz-plane in the mediolateral direction (x-axis). The iterative general linear model (GLM) was used to compare weight gain in patients with at least one contact within one ROI and patients with both contacts in the other ROI. The factor GENDER and covariates AGE and TIME of postoperative maximum weight gain were included to control for possible confounding effects. The division yz-plane was then successively moved along the x-axis by 0.5–1 mm steps to define a BORDER with lowest p-value. A similar approach was used to compare weight gain considering active contacts in two subthalamic ROIs separated by a movable xz-plane in the anteroposterior direction (y-axis) and by the xy-plane in the ventrodorsal direction (z-axis).

Relationships between body weight, motor performance, eating behavior and intensity of stimulation were assessed separately as secondary outcomes. As they were based on multiple comparisons, the Bonferroni correction was applied whenever appropriate.

Results

After initiation of STN DBS, the UPDRS-III score dropped on average from 36.7±(SD)9.6 (sOFF) to 17.8±5.5 (sON) ($T = 7.3$, $p<10^{-7}$) showing good efficacy of neurostimulation treatment. The maximum change in body weight in the eighteen-month period after implantation was on average +6.9 kg±4.5 kg (−0.3 to +18.3 kg) and was strongly significant ($T = 6.6$, $p<10^{-5}$). Despite gradually increasing weight during the entire study period (Figure 2), nine patients reached the maximum body weight within the first 6 months after surgery, five patients in months 6–12 and six patients in months 12–18 after surgery.

As the analyses of active contact coordinates derived from native and normalized approaches yielded similar results, only statistics based on coordinates in native space are reported. In individual patients, the maximum weight gain correlated inversely along the x-axis with the distance of the active contact from the wall of the third ventricle in the left hemisphere ($r = -0.48$, $p<0.05$), right hemisphere ($r = -0.50$, $p<0.05$), and in pooled data ($r = -0.55$, $p<0.01$) if only more medial active contact regardless to hemisphere was considered (Figure 3). Similar results were obtained for maximum weight gain expressed in percentage of initial body weight as well as when considering weight gain at the end of the 18th month. In addition, the hemi-body UPDRS-III subscores in sON condition inversely correlated with the distance of the contralateral active contact from the wall of the third ventricle in the mediolateral direction ($r = -0.42$, $p<0.01$) (Figure 4). However, none of these parameters showed any relation to the active contact position along the y-axis or z-axis.

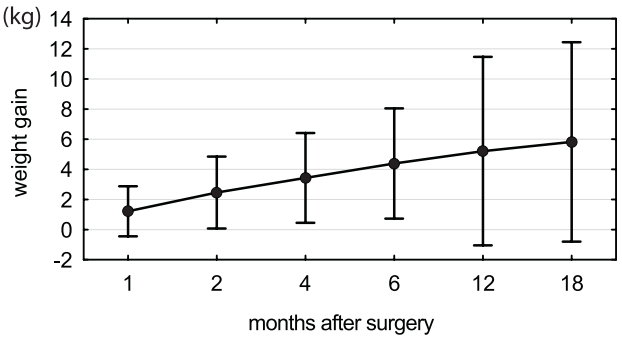

Figure 2. Mean changes in weight after implantation in 20 patients with Parkinson's disease. Body weight gradually increased during the study period. Weight gain represents the difference in weight (±SD) compared to the preoperative state.
doi:10.1371/journal.pone.0038020.g002

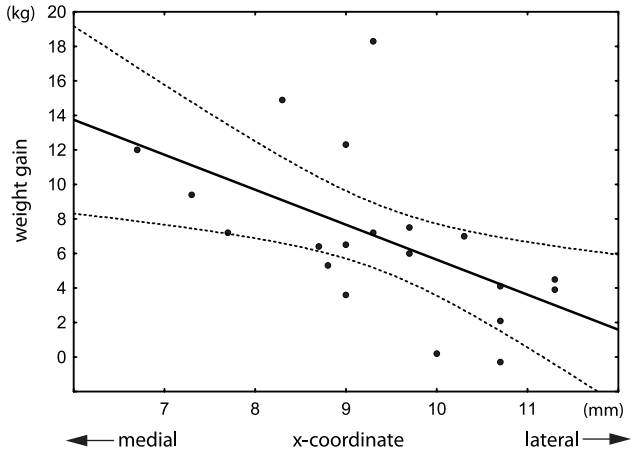

Figure 3. Weight gain in 20 patients with Parkinson's disease in relation to the mediolateral position of the active contact with bilateral STN-DBS (r = −0.55, p<0.01). Only one active contact (more medial contact from both hemispheres) was used in each patient. The x-coordinate represents the distance of the active contact from the wall of the third ventricle. Each millimeter in the medial direction was associated on average with a 1.6-kg increase in body weight. Dotted lines denote the 95% confidence interval of the regression line.
doi:10.1371/journal.pone.0038020.g003

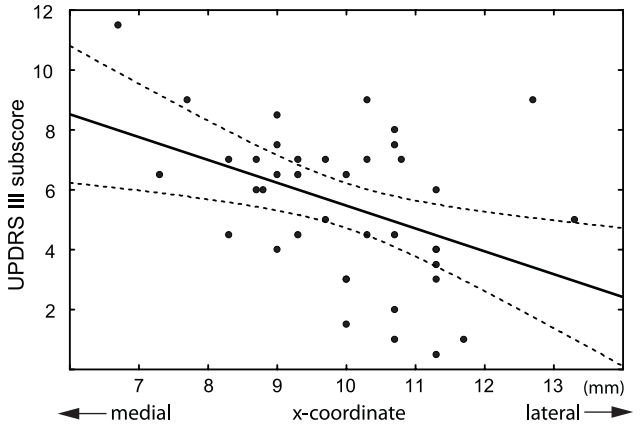

Figure 4. Hemi-body UPDRS-III subscores in the sON condition after overnight withdrawal of dopaminergic therapy in relation to the mediolateral position of the contralateral active contact. After initiation of STN-DBS, the hemi-body side with the lowest motor score (best motor condition) had the contralateral contacts located more laterally from the wall of the third ventricle (r = −0.42, p<0.01). Dotted lines denote the 95% confidence interval of the regression line.
doi:10.1371/journal.pone.0038020.g004

With the iterative moving plane approach, we found a border orthogonal to the x-axis dividing the subthalamic area into two ROIs that differed in postoperative weight gain. Patients with at least one active contact within 9.3 mm of the wall of the third ventricle demonstrated significantly greater weight gain (9.4±4.4 kg, N = 11) than those patients with both contacts located more laterally from the wall (3.9±2.7 kg, N = 9) (GLM, factor BORDER: F = 16.1, p<0.001)(Figure 5). The postoperative maximum weight gain significantly differed between genders, with a greater increase in women (N = 6, 10.9±(SD)4.8 kg) than in men (N = 14, 5.2±3.4 kg) (GLM, factor: GENDER, F = 10.7, p<0.01). However, no other covariates (factor AGE: F = 0.001, p = 0.99; factor TIME: F = 0.002, p = 0.96) nor interactions between BORDER, GENDER, AGE and TIME were significant.

In addition, the postoperative maximum weight gain in all patients inversely correlated with preoperative body weight (r = −0.62, p<0.05 corrected). Maximum weight gain did not significantly depend on UPDRS-III improvement after switching the stimulation on (r = −38, p = 0.1), and no correlation between weight gain at the 18th month and stimulation intensity was found. Analysis of eating behavior failed to demonstrate any change in hunger, appetite, preference for sweet food or food intake in our patients. However, there was a positive correlation between food intake and body-weight gain at the 18th month (rho = 0.66, P<0.05 corrected).

Discussion

We observed weight gain inversely related to the distance of the contacts from the wall of the third ventricle (Figure 3), and patients with at least one contact located medially in the STN experienced significantly greater weight gain than those with both active contacts located laterally (Figure 5). Thus, our results are consistent with the hypothesis that STN-DBS exerts a regional effect on adjacent structures involved in energy balance. In addition, our findings are also in agreement with reports of weight gain observed after unilateral STN-DBS [27,28]. As the position of each implanted electrode was verified by intraoperative microrecording and DBS caused clear motor improvement, we believe that our observations are not affected by electrode misplacement outside the STN. However, no correlation between stimulation intensity (Figure 1) and weight gain (Figure 2) was found in our study. This may be partly explained by low variability of stimulation parameters between patients or limited size of the patient group.

The maximum weight gain in our study was significantly larger in women than in men. Although women may be more susceptible to weight gain [29], previous studies have proven no significant sex-related differences in weight gain after unilateral or bilateral STN-DBS [2,4,5,7,27,28]. These findings are in agreement with our observation that weight gain in all six women of our study was associated with the medial contact site and that no interaction between active contact position and gender was found.

Similar to other studies [21,22,23], we found an inverse correlation between unilateral motor outcome (measured for rigidity, akinesia and tremor using hemi-body UPDRS-III subscore) and contralateral position of the active contact (Figure 4). Thus, patients with the lowest motor score (best motor condition) had contacts located more laterally from the wall of the third ventricle. Such results most likely reflect the internal organization of the STN with the sensorimotor part located dorsolaterally in the nucleus [20].

However, we did not observe any significant correlation between weight gain and change in UPDRS-III score. This finding is consistent with those published previously [2,4,30] and may indicate that the connection between changes in weight and motor outcomes is not as straightforward as has been proposed [31]. Unrelated weight gain to motor outcome was also shown in another study in which weight gain was more pronounced in patients with subthalamic stimulation than in patients with pallidal stimulation, despite similar motor improvement in both groups [30]. Thus, additional factors likely contribute to greater weight gain in subthalamic stimulation.

The central mechanism by which STN-DBS might cause weight gain remains unclear. It could be hypothesized that the spread of stimulation current beyond the borders of the STN may influence the hypothalamic regulation of energy metabolism or the

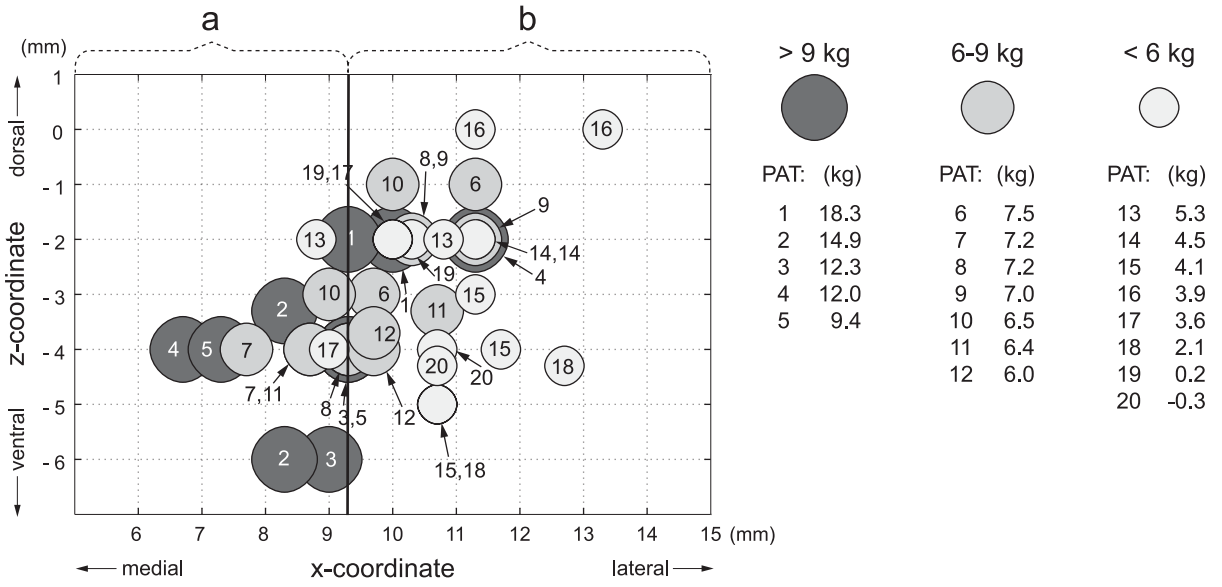

Figure 5. Bilateral STN-DBS active contact positions of 20 patients with Parkinson's disease plotted in the coronal plane with respect to weight gain. Patients (N = 11) with at least one active contact (a) placed within 9.3-mm of the wall of the third ventricle gained significantly more weight than patients (N = 9) with both contacts (b) located more laterally ($p<0.001$).
doi:10.1371/journal.pone.0038020.g005

homeostatic pathway of food intake. However, there are so far only a few studies on the effects of long-term STN-DBS on autonomic [32,33,34] or hormonal systems [35], and they have provided no clear explanation for weight gain.

Conversely, increased food intake by non-homeostatic or reward mechanisms may also provide a compelling hypothesis. The medial tip of the STN is involved in basal ganglia limbic and motivational functions [16,17,18,36]. It is connected to key structures of the reward system such as the ventral pallidum and the ventral tegmental area [37,38,39]. It has been shown that STN-DBS can affect the neural activity of these structures, as well as increase dopaminergic transmission in the striatum [40,41,42]. Moreover, the medial part of the STN is adjacent to the medial forebrain bundle which contains essential projections underlying reward functions [15]. Extensive research has demonstrated a close relationship between the mesolimbic system, medial forebrain bundle and ventral pallidum in motivational desire for food rewards, increase in food intake and obesity [43,44,45,46]. Therefore, it seems plausible that an active electrode in the proximity of the medial STN could be ideally positioned to stimulate the reward system, thereby contributing to changes in motivational behaviors related to food intake and weight gain. Our previous study supports this hypothesis, as it revealed that postoperative weight gain correlated with arousal ratings from food pictures in the STN-DBS ON condition, suggesting an altered attribution of incentive salience (i.e., emotional relevance) to rewarding stimuli [47].

Although most of the subjects did not report any changes in food intake, hunger or appetite in our study, the inaccuracy of self-reported intake [48,49,50] should prompt caution in the interpretation of these results. Food intake depends largely on reward or homeostatic systems and is only partly under cognitive control [45,51,52]. We can hypothesize that slight individual changes in motivational behavior and reward system induced by DBS of subcortical structures need not be reflected in subjective feelings such as hunger or appetite [47,53]. Further prospective studies taking into account changes in sensitivity to reward [45] and actual food intake would be necessary to clarify this question.

In agreement with another study [7], we found a significant inverse correlation between preoperative body weight and post-operative weight gain. Since weight has been reported to decrease with PD progression [54], it has been suggested that patients treated with DBS normalize their weight compared to their premorbid status because of motor improvement [4,5]. However, this hypothesis cannot fully account for the fact that although most patients indicated for DBS are normal weight or overweight, the majority of them experience continuous weight gain after surgery [2,7]. Yet it seems that changes in motor manifestations and energy expenditure can only partly explain both the weight loss in PD and weight gain after initiation of DBS [30,54,55]. It has been shown that overweight and obese individuals have higher sensitivity to reward which predicts the tendency for overeating and strengthens preferences for sweet and fatty foods [45]. We speculate that if STN-DBS increases sensitivity to reward in relation to the medial contact site in the subthalamic area, thereby modulating eating behavior, this effect would be more pronounced especially in patients with preoperatively lower body weight, lower sensitivity to reward and without previous, excessive caloric intake.

Some limitations have to be taken into account when interpreting our results. Since body weight may be reflected in local white matter changes [29] and the size and position of the STN varies [56,57] to some extent relative to the midcommisural point, the influence of anatomic variability cannot be excluded from our measurements. However, we compensated for the variable width of the third ventricle, which significantly affects the mediolateral position of the STN [57,58], by measuring the x-coordinate from the wall of the third ventricle.

In conclusion, our findings support the hypothesis that weight gain in PD patients treated by STN-DBS may, at least in part, result from the regional effect of stimulation on adjacent structures involved in the central regulation of energy balance or reward.

Acknowledgments

The authors are grateful to Dr. Aaron Rulseh for language revision, to Markéta Fialová and Anna Rezková for administrative assistance and to Martin Voleman for technical support.

Author Contributions

Conceived and designed the experiments: FR RJ ER. Performed the experiments: FR RJ DU LN. Analyzed the data: FR RJ. Contributed reagents/materials/analysis tools: RJ ER JV. Wrote the paper: FR RJ. Review and critique: RJ ER LN DU JV.

References

1. Rieu I, Derost P, Ulla M, Marques A, Debilly B, et al. (2011) Body weight gain and deep brain stimulation. J Neurol Sci 310: 267–270.
2. Barichella M, Marczewska AM, Mariani C, Landi A, Vairo A, et al. (2003) Body weight gain rate in patients with Parkinson's disease and deep brain stimulation. Mov Disord 18: 1337–1340.
3. Nováková L, Růžička E, Jech R, Serranová T, Dušek P, et al. (2007) Increase in body weight is a non-motor side effect of deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Neuro Endocrinol Lett 28: 21–25.
4. Macia F, Perlemoine C, Coman I, Guehl D, Burbaud P, et al. (2004) Parkinson's disease patients with bilateral subthalamic deep brain stimulation gain weight. Mov Disord 19: 206–212.
5. Montaurier C, Morio B, Bannier S, Derost P, Arnaud P, et al. (2007) Mechanisms of body weight gain in patients with Parkinson's disease after subthalamic stimulation. Brain 130: 1808–1818.
6. Perlemoine C, Macia F, Tison F, Coman I, Guehl D, et al. (2005) Effects of subthalamic nucleus deep brain stimulation and levodopa on energy production rate and substrate oxidation in Parkinson's disease. Br J Nutr 93: 191–198.
7. Bannier S, Montaurier C, Derost PP, Ulla M, Lemaire JJ, et al. (2009) Overweight after deep brain stimulation of the subthalamic nucleus in Parkinson disease: long term follow-up. J Neurol Neurosurg Psychiatry 80: 484–488.
8. Johnson MD, Miocinovic S, McIntyre CC, Vitek JL (2008) Mechanisms and targets of deep brain stimulation in movement disorders. Neurotherapeutics 5: 294–308.
9. Jech R, Urgošík D, Tintěra J, Nebuželský A, Krásenský J, et al. (2001) Functional magnetic resonance imaging during deep brain stimulation: a pilot study in four patients with Parkinson's disease. Mov Disord 16: 1126–1132.
10. McIntyre CC, Mori S, Sherman DL, Thakor NV, Vitek JL (2004) Electric field and stimulating influence generated by deep brain stimulation of the subthalamic nucleus. Clin Neurophysiol 115: 589–595.
11. Maks CB, Butson CR, Walter BL, Vitek JL, McIntyre CC (2009) Deep brain stimulation activation volumes and their association with neurophysiological mapping and therapeutic outcomes. J Neurol Neurosurg Psychiatry 80: 659–666.
12. Saint-Cyr JA, Hoque T, Pereira LC, Dostrovsky JO, Hutchison WD, et al. (2002) Localization of clinically effective stimulating electrodes in the human subthalamic nucleus on magnetic resonance imaging. J Neurosurg 97: 1152–1166.
13. Berthoud HR (2002) Multiple neural systems controlling food intake and body weight. Neurosci Biobehav Rev 26: 393–428.
14. Berthoud HR, Morrison C (2008) The brain, appetite, and obesity. Annu Rev Psychol 59: 55–92.
15. Wise RA (2005) Forebrain substrates of reward and motivation. J Comp Neurol 493: 115–121.
16. Haegelen C, Rouaud T, Darnault P, Morandi X (2009) The subthalamic nucleus is a key-structure of limbic basal ganglia functions. Med Hypotheses 72: 421–426.
17. Rouaud T, Lardeux S, Panayotis N, Paleressompoulle D, Cador M, et al. (2010) Reducing the desire for cocaine with subthalamic nucleus deep brain stimulation. Proc Natl Acad Sci U S A 107: 1196–1200.
18. Lardeux S, Pernaud R, Paleressompoulle D, Baunez C (2009) Beyond the reward pathway: coding reward magnitude and error in the rat subthalamic nucleus. J Neurophysiol 102: 2526–2537.
19. Morel A (2007) Atlas of the Human Thalamus and Basal Ganglia. New York: Informa Helthcare. 160 p.
20. Hamani C, Saint-Cyr JA, Fraser J, Kaplitt M, Lozano AM (2004) The subthalamic nucleus in the context of movement disorders. Brain 127: 4–20.
21. Hamel W, Fietzek U, Morsnowski A, Schrader B, Herzog J, et al. (2003) Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: evaluation of active electrode contacts. J Neurol Neurosurg Psychiatry 74: 1036–1046.
22. Herzog J, Fietzek U, Hamel W, Morsnowski A, Steigerwald F, et al. (2004) Most effective stimulation site in subthalamic deep brain stimulation for Parkinson's disease. Mov Disord 19: 1050–1054.
23. Godinho F, Thobois S, Magnin M, Guenot M, Polo G, et al. (2006) Subthalamic nucleus stimulation in Parkinson's disease: anatomical and electrophysiological localization of active contacts. J Neurol 253: 1347–1355.
24. Machado A, Rezai AR, Kopell BH, Gross RE, Sharan AD, et al. (2006) Deep brain stimulation for Parkinson's disease: surgical technique and perioperative management. Mov Disord 21 Suppl 14: S247–258.
25. Jech R, Růžička E, Urgošík D, Serranová T, Volfová M, et al. (2006) Deep brain stimulation of the subthalamic nucleus affects resting EEG and visual evoked potentials in Parkinson's disease. Clin Neurophysiol 117: 1017–1028.
26. Yelnik J, Damier P, Demeret S, Gervais D, Bardinet E, et al. (2003) Localization of stimulating electrodes in patients with Parkinson disease by using a three-dimensional atlas-magnetic resonance imaging coregistration method. J Neurosurg 99: 89–99.
27. Walker HC, Lyerly M, Cutter G, Hagood J, Stover NP, et al. (2009) Weight changes associated with unilateral STN DBS and advanced PD. Parkinsonism Relat Disord 15: 709–711.
28. Lee EM, Kurundkar A, Cutter GR, Huang H, Guthrie BL, et al. (2011) Comparison of weight changes following unilateral and staged bilateral STN DBS for advanced PD. Brain Behav 1: 12–18.
29. Mueller K, Anwander A, Moller HE, Horstmann A, Lepsien J, et al. (2011) Sex-dependent influences of obesity on cerebral white matter investigated by diffusion-tensor imaging. PLoS One 6: e18544.
30. Sauleau P, Leray E, Rouaud T, Drapier S, Drapier D, et al. (2009) Comparison of weight gain and energy intake after subthalamic versus pallidal stimulation in Parkinson's disease. Mov Disord 24: 2149–2155.
31. Gironell A, Pascual-Sedano B, Otermin P, Kulisevsky J (2002) [Weight gain after functional surgery for Parkinsons disease]. Neurologia 17: 310–316.
32. Ludwig J, Remien P, Guballa C, Binder A, Binder S, et al. (2007) Effects of subthalamic nucleus stimulation and levodopa on the autonomic nervous system in Parkinson's disease. J Neurol Neurosurg Psychiatry 78: 742–745.
33. Priori A, Cinnante C, Genitrini S, Pesenti A, Tortora G, et al. (2001) Non-motor effects of deep brain stimulation of the subthalamic nucleus in Parkinson's disease: preliminary physiological results. Neurol Sci 22: 85–86.
34. Holmberg B, Corneliusson O, Elam M (2005) Bilateral stimulation of nucleus subthalamicus in advanced Parkinson's disease: no effects on, and of, autonomic dysfunction. Mov Disord 20: 976–981.
35. Nováková L, Haluzík M, Jech R, Urgošík D, Růžička F, et al. (2011) Hormonal regulators of food intake and weight gain in Parkinson's disease after subthalamic nucleus stimulation. Neuro Endocrinol Lett 32: 437–441.
36. Temel Y, Blokland A, Steinbusch HW, Visser-Vandewalle V (2005) The functional role of the subthalamic nucleus in cognitive and limbic circuits. Prog Neurobiol 76: 393–413.
37. Groenewegen HJ, Berendse HW (1990) Connections of the subthalamic nucleus with ventral striatopallidal parts of the basal ganglia in the rat. J Comp Neurol 294: 607–622.
38. Groenewegen HJ, Berendse HW, Haber SN (1993) Organization of the output of the ventral striatopallidal system in the rat: ventral pallidal efferents. Neuroscience 57: 113–142.
39. Parent A, Hazrati LN (1995) Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Res Brain Res Rev 20: 128–154.
40. Winter C, Lemke C, Sohr R, Meissner W, Harnack D, et al. (2008) High frequency stimulation of the subthalamic nucleus modulates neurotransmission in limbic brain regions of the rat. Exp Brain Res 185: 497–507.
41. Turner MS, Lavin A, Grace AA, Napier TC (2001) Regulation of limbic information outflow by the subthalamic nucleus: excitatory amino acid projections to the ventral pallidum. J Neurosci 21: 2820–2832.
42. Shon YM, Lee KH, Goerss SJ, Kim IY, Kimble C, et al. (2010) High frequency stimulation of the subthalamic nucleus evokes striatal dopamine release in a large animal model of human DBS neurosurgery. Neurosci Lett 475: 136–140.
43. Berridge KC (2009) 'Liking' and 'wanting' food rewards: brain substrates and roles in eating disorders. Physiol Behav 97: 537–550.
44. Smith KS, Tindell AJ, Aldridge JW, Berridge KC (2009) Ventral pallidum roles in reward and motivation. Behav Brain Res 196: 155–167.
45. Davis C, Patte K, Levitan R, Reid C, Tweed S, et al. (2007) From motivation to behaviour: a model of reward sensitivity, overeating, and food preferences in the risk profile for obesity. Appetite 48: 12–19.
46. Beaver JD, Lawrence AD, van Ditzhuijzen J, Davis MH, Woods A, et al. (2006) Individual differences in reward drive predict neural responses to images of food. J Neurosci 26: 5160–5166.
47. Serranová T, Jech R, Dušek P, Sieger T, Růžička F, et al. (2011) Subthalamic nucleus stimulation affects incentive salience attribution in Parkinson's disease. Mov Disord 26: 2260–2266.
48. Jakes RW, Day NE, Luben R, Welch A, Bingham S, et al. (2004) Adjusting for energy intake–what measure to use in nutritional epidemiological studies? Int J Epidemiol 33: 1382–1386.
49. Hill RJ, Davies PS (2001) The validity of self-reported energy intake as determined using the doubly labelled water technique. Br J Nutr 85: 415–430.
50. Schoeller DA (1990) How accurate is self-reported dietary energy intake? Nutr Rev 48: 373–379.
51. Berridge KC, Ho CY, Richard JM, DiFeliceantonio AG (2010) The tempted brain eats: pleasure and desire circuits in obesity and eating disorders. Brain Res 1350: 43–64.

52. Peters JC, Wyatt HR, Donahoo WT, Hill JO (2002) From instinct to intellect: the challenge of maintaining healthy weight in the modern world. Obes Rev 3: 69–74.
53. Winkielman P, Berridge KC, Wilbarger JL (2005) Unconscious affective reactions to masked happy versus angry faces influence consumption behavior and judgments of value. Pers Soc Psychol Bull 31: 121–135.
54. Bachmann CG, Trenkwalder C (2006) Body weight in patients with Parkinson's disease. Mov Disord 21: 1824–1830.
55. Delikanaki-Skaribas E, Trail M, Wong WW, Lai EC (2009) Daily energy expenditure, physical activity, and weight loss in Parkinson's disease patients. Mov Disord 24: 667–671.
56. Richter EO, Hoque T, Halliday W, Lozano AM, Saint-Cyr JA (2004) Determining the position and size of the subthalamic nucleus based on magnetic resonance imaging results in patients with advanced Parkinson disease. J Neurosurg 100: 541–546.
57. Daniluk S, K GD, Ellias SA, Novak P, Nazzaro JM (2010) Assessment of the variability in the anatomical position and size of the subthalamic nucleus among patients with advanced Parkinson's disease using magnetic resonance imaging. Acta Neurochir (Wien) 152: 201–210; discussion 210.
58. Zhu XL, Hamel W, Schrader B, Weinert D, Hedderich J, et al. (2002) Magnetic resonance imaging-based morphometry and landmark correlation of basal ganglia nuclei. Acta Neurochir (Wien) 144: 959–969; discussion 968-959.

Brain Stimulation 6 (2013) 740–745

Contents lists available at SciVerse ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Original Articles

Sex, Food and Threat: Startling Changes after Subthalamic Stimulation in Parkinson's Disease

Tereza Serranová [a,*], Tomáš Sieger [a,b], Petr Dušek [a], Filip Růžička [a], Dušan Urgošík [a,c], Evžen Růžička [a], Josep Valls-Solé [d], Robert Jech [a]

[a] Department of Neurology and Center of Clinical Neuroscience, Charles University in Prague, 1st Faculty of Medicine and General University Hospital, Prague, Czech Republic
[b] Department of Cybernetics, Faculty of Electrical Engineering, Czech Technical University, Prague, Czech Republic
[c] Department of Stereotactic and Radiation Neurosurgery, Na Homolce Hospital, Prague, Czech Republic
[d] Neurology Service, Hospital Clínic, Facultad de Medicina, Universitat de Barcelona, Spain

ARTICLE INFO

Article history:
Received 12 December 2012
Received in revised form
19 March 2013
Accepted 20 March 2013
Available online 17 April 2013

Keywords:
Motivation
Deep brain stimulation
Weight gain
Acoustic blink reflex

ABSTRACT

Background: Changes in motivational processing may play a role in weight gain and other non-motor side effects in Parkinson's disease (PD) patients treated with deep brain stimulation of the subthalamic nucleus.

Objective/hypothesis: We aimed to assess changes in aversive and appetitive motivational activation using modulation of the acoustic blink reflex (ABR) by rewarding and aversive stimuli.

Methods: ABR elicited during the viewing of erotic, food, aversive and neutral pictures was recorded in 11 off-medicated patients with the subthalamic stimulation switched ON and OFF, and in 11 control subjects.

Results: ABR to erotic stimuli was larger in patients in the ON compared to the OFF condition and controls ($P < 0.01$). Aversive stimuli caused a larger increase in the ABR in patients with the ON condition than in controls ($P < 0.05$). Additionally, we found a negative correlation of the ABR magnitude to food pictures in the ON condition with weight gain following subthalamic stimulation ($P < 0.01$, after adjustment to OFF condition).

Conclusions: Our results suggest that subthalamic stimulation affects motivational processing. Subthalamic stimulation may disturb appetitive engagement by erotic cues and increase aversive activation in PD patients. Additionally, postoperative weight gain may be related to changes in the processing of food cues due to subthalamic stimulation.

Introduction

Deep brain stimulation of the subthalamic nucleus (STN DBS) has become a standard and highly effective treatment in advanced Parkinson's disease (PD) [1]. Apart from improvements in motor function, activities of daily living and quality of life, patients treated by STN DBS can develop mood and behavioral changes [2] that may affect their intra- and inter-personal relationships and social life [3]. In addition, weight gain has also been reported as a common, non-motor side effect [4,5]. The mechanisms of these complications remain unclear, however changes in motivational and goal-directed behavior may be important contributing factors.

The role of the subthalamic nucleus (STN) in emotional and motivational processing has been demonstrated in neurophysiological studies in monkeys [6] as well as in PD patients [7]. In experimental animals, both subthalamotomy and STN DBS increased motivation for food [8,9]. Motivational changes in PD patients treated by STN DBS have been studied mainly in regard to apathy [10] and motor learning [11]. A recent study on incentive salience attribution found that STN DBS increased motivational relevance of aversive stimuli together with increased sensitivity to food reward cues in PD patients with postoperative weight gain [12]. However, there is evidence for dissociation between motivational and esthetic value of stimuli [13]. Unconscious basic and affective reactions can interact with incentive motivation to

Financial disclosure: This work was supported by the Czech Science Foundation (GACR 309/09/1145), by the Czech Ministry of Health: IGA MZ ČR NT12282-5/2011, IGA MZ ČR NT12288-5/2011, IGA MZ ČR NT 11331-6/2010, by the Czech Ministry of Education (VZ 0021620849), by Czech Technical University in Prague, grant SGS10/279/OHK3/3T/13 and by the Charles University in Prague (PRVOUK-P26/LF1/4). Robert Jech, Dušan Urgošík, and Evžen Růžička received consulting fees from Medtronic.

* Corresponding author. Department of Neurology, First Medical Faculty, Charles University in Prague, Kateřinská 30, 120 00, Praha 2, Czech Republic. Tel.: +420 224 965550; fax: +420 224 922678.
E-mail address: tereza.serranova@gmail.com (T. Serranová).

1935-861X/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.brs.2013.03.009

influence behavior [14]. The startle reflex has been used to indicate which of the separable motivational systems, the appetitive or the defensive, is engaged [15]. When startle probes are administered in the context of picture perception, blink responses are reliably potentiated when viewing unpleasant pictures, and inhibited when viewing pleasant pictures, compared to neutral picture processing [16]. The startle modulation can be used to examine reactivity to food cues [17] and food craving [18], which are known to be relevant risk factors for weight gain [19].

We hypothesized that some changes induced by STN DBS in processing of primary rewards and aversive stimuli may be revealed by an objective assessment of behavior. We expected to find larger facilitation of the startle response by aversive cues due to the STN DBS along with an increased inhibition of the startle response by food cues in patients with higher postoperative weight gain.

The aim of our study was to assess the effects of STN DBS on modulation of the acoustic blink reflex (ABR) reactivity to pictures presenting rewarding and aversive stimuli in PD patients (DBS ON, DBS OFF). The results were compared with those obtained in healthy controls using the same paradigm.

Materials and methods

Subjects

The study was approved by the local Ethics Committee and all participants provided informed consent prior to their inclusion. We recruited eleven male PD patients treated with bilateral STN DBS for motor fluctuations and/or dyskinesias. The position of the electrode in the STN was verified by MRI. All patients fulfilled the UK Brain Bank Criteria for the diagnosis of PD [20]. The control group was composed of 11 age-matched healthy subjects.

Before recruitment, all participants were screened for cognitive and mood status using the Mini Mental State Examination (MMSE) [21] and the Beck Depression Inventory (BDI) [22]. We used a modified version of the Minnesota Impulsive Disorders Interview to rule out impulse control disorders and repetitive behaviors in patients and controls at the time of the experiment [23]. Body weight in the PD group was measured within the last week before surgery and, again, on the day of the study.

Demographic and disease-related characteristics of patients and healthy subjects are summarized in Table 1.

Electrode and active electrode contact positions

The position of the electrode in the STN was verified by MRI one year after surgery. The positions of active electrode contacts were assessed on T1-weighted images using Leksell Surgiplan software following the previously published approach [24]. The *x* coordinate of each contact was measured manually in native space from the wall of the third ventricle, whereas the *y* and *z* coordinates were measured from the midcommisural point. Mean positions of contacts are shown in Table 2.

Table 1
Demographic and disease characteristics of Parkinson's disease patients and control group.

	PD patients	Controls
Age (years)	56.3 (5)	54.4 (8)
Education duration (years)	13.7 (2)	16.6 (2)
MMSE	28.8 (1)	29.2 (1)
BDI	10.0 (6)	9.1 (6)
PD duration (years)	14.4 (3)	
Time interval after surgery (years)	3.0 (2)	
Levodopa equivalent (mg)	643.8 (459.0)	
STN DBS parameters		
Frequency (Hz)	130 (10 patients)	
	145 (1 patient)	
Pulse width (μs)	60 ($N = 9$)	
	90 ($N = 8$)	
	120 ($N = 5$)	
Amplitude (V)	2.8 (2.3–3.5)	

Table 2
Position of the active electrode contact in the subthalamic region.

Right hemisphere (mm)	
x	9.5 (1.3)
y	−1.2 (2.3)
z	−4.4 (2.0)
Left hemisphere (mm)	
x	−9.6 (1.4)
y	−1.8 (2.0)
z	−3.6 (1.6)

The *x* coordinate of each active contact was measured from the wall of the third ventricle (+ toward right; − toward left), whereas the *y* coordinate (+ toward anterior; − toward posterior) and *z* coordinate (+ toward vertex; − toward brainstem) were measured from the mid-commissural point. Values are expressed as mean (SD).

Procedure

We selected a total of 84 pictures from the International Affective Picture System (IAPS) [25]. They were chosen from four categories (21 each): neutral, erotic, food and aversive (victims and threats). Erotic and aversive pictures were valence and arousal matched according to normative ratings [25]. Three different picture orders were created with maximally two pictures from the same category presented in sequence.[1]

Patients were tested after an overnight withdrawal from dopaminergic medication. On the day of testing, STN DBS was switched OFF at 8 a.m. for 2 h in order to reduce some of the longer-lasting effects of stimulation. Patients were pseudorandomly tested in two conditions, STN DBS ON and STN DBS OFF using a different picture order for each condition. The testing was performed 1 h after the stimulators were switched OFF or ON. In each condition, the motor subscore of the Unified Parkinson's Disease Rating Scale (UPDRS-III) [26] was performed by a rater blinded to the DBS condition prior to testing. Healthy controls were tested once, using proportionally the same sets of picture order. Patients and controls were kept "normally satiated" during the examination; they were provided snacks and instructed to eat only lightly.

The participants were comfortably seated in a dark, quiet room in front of a touch sensitive screen. They wore headphones and 2 surface electrodes were positioned at each lower lid to record electromyographic (EMG) activity from the orbicularis oculi muscles. The participants were instructed to look at each picture during the period it was displayed, and to rate each picture along the dimensions of emotional valence and arousal by self-paced touching appropriate symbols on two independent visual scales presented on-screen after picture offset. The scales were designed

[1] Specific IAPS pictures selected: *Erotic pictures (females and couples)*: 4002*, 4275, 4320, 4232*, 4694, 4180, 4250, 4150, 4240, 4255, 4670*, 4235*, 4310*, 4225, 4311*, 4220, 4006, 4659, 4141, 4001, 4142*; *Food pictures (sweet and salty)*: 7402, 7481, 7230*, 7320, 7482*, 7200, 7350, 7330*, 7487, 7220, 7286*, 7488*, 7289*, 7291*, 7352, 7283, 7340, 7460, 7280, 7480, 7475; *Neutral pictures (household objects, buildings, plants)*: 7235, 7175*, 7185, 7110, 7491, 7179, 7035*, 7705, 5510, 7059, 7041, 7010*, 7090, 7950*, 7080, 7000, 7187*, 7006, 7050, 7020*, 7004*; *Aversive pictures*: *Threats (human/animal attacks, aimed guns)*: 1050, 1120, 1300, 3500, 3530, 6230*, 6260, 6350, 6510, 6550*, *Victims (mutilations)*: 3000*, 3010*, 3060*, 3069, 3071, 3080, 3120, 3130, 3170*, 3266, and *threat/victim picture*: 9410*. *Presented with startling acoustic stimulus.

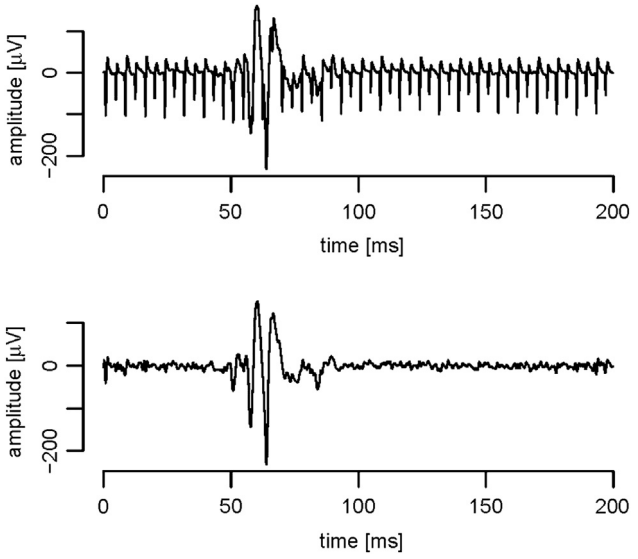

Figure 1. Recording of acoustic blink reflex from the orbicularis oculi muscle in DBS ON condition with an artifact related to monopolar deep brain stimulation of the subthalamic nucleus (top). The same recording after removal of the artifact by means of artifact template removal in spectral domain (bottom).

according to the original IAPS scales [25]. Valence was rated on scale of 1–9, with 9 being the most pleasant, and arousal on a scale of 1–9, with 9 being the most arousing. Prior to testing, patients were instructed how to perform the ratings according to the IAPS manual, and watched and rated 8 representative pictures with assistance in order to become familiar with the procedure.

Each picture out of 84 was presented for a period of 6 s and consequently rated by the participant. Seven pictures of each content category (i.e., 28 in total) were presented with a startling acoustic stimulus (SAS) (single 50 ms noise burst, 115 dB, <10 μs rise time). The SAS was delivered through headphones pseudorandomly across the different picture categories at one of three time intervals (4200, 5000, 5800 ms) following picture onset to avoid habituation. Sixteen unprimed ABRs were elicited while watching a dark screen with a white cross in the center, with the SAS presented at random intervals of 10–16 s, 12 of them prior to the beginning of the affective task and an additional 3 were interspersed between the picture presentation. The picture presentation and rating, variable SAS delivery and acquisition of physiologic data were performed by custom EVSENG software (J. Wackermann, T. Sieger, Prague, Czech Republic).

The electromyographic (EMG) activity was recorded using Medelec Synergy (Oxford Instruments, Surrey, UK). Frequencies <50 and >1000 Hz were filtered from the raw EMG signal. Large artifact related to the monopolar DBS was removed using the method of subtraction with artifact templates in the spectral domain (Fig. 1). See the Supplementary material for details. For off-line analysis of the waveforms, the EP analyzer 2.9 was used (A. Nebuželský & R. Jech, Prague, Czech Republic).

Each EMG activity recording related to one SAS delivery was referred to as a trial. Data from each subject were visually examined by a task-blinded examiner, only trials in which the ABR had a latency of 40–80 ms from the stimulus were included [27] and the ABR onset latency and duration were determined. The area under the curve (AUC) was calculated for each ABR as a measure of ABR magnitude. The average AUC from the right and left eye was calculated for each trial. When data from one side were invalid, only the valid data from the remaining side was used. As the first two unprimed ABR trials in many subjects had significantly larger magnitude, they were excluded from the analyses. Trials with clear artifacts or with a peak amplitude more than three standard deviations above or below the mean magnitude of each participant were also excluded. No more than one trial from each picture category, or two trials per subject, was discarded.

For further analyses, ABR magnitude from every trial was expressed in standardized *t*-scores to remove effects of inter-subject variability, *t*-score = 50 + (*z* score*10); *z* score = (AUC from given trial − mean AUC from unprimed startle responses)/ standard deviation of AUC from unprimed startle responses. This resulted in standardized scores with a mean of 50 and standard deviation of 10 [28].

Statistical analyses

Statistical analyses were performed in the R language and environment for statistical computing (R Development Core Team, 2011). For inter-group comparisons in which repeated measurements were available (PD patients vs. controls; DBS ON vs. DBS OFF), linear mixed-effects models were used. For the evaluation of ABR response, a fixed effect of the group and random effects of individual subjects and pictures were used. To assess the fixed effect of DBS condition in the ABR model, random effects of subjects, pictures, and their interactions were utilized respecting the paired nature of data. In models of picture ratings, the fixed effect of picture category and random effects of subjects and pictures were used. For the purpose of accuracy, the significance of fixed effects of interest was computed by a parametric bootstrap approach. The quality of each model was validated by visual inspection of the residuals in the model. UPDRS-III scores and weight changes were compared using *t*-tests, and the differences between the two groups in age, years of education, MMSE and BDI using the Wilcoxon exact test. Parameters following normal distribution were subject to Pearson correlation and partial correlation analysis. The Bonferroni correction for multiple comparisons was used whenever appropriate to maintain the 5% significance level.

Results

Clinical observations

No differences were found for age, MMSE, BDI or education level between the patient and control groups. The UPDRS-III score decreased from a mean of 43.7 (SD = 12.4) in the DBS OFF condition to 18.2 (SD = 7.3) in the DBS ON condition ($T = 8.56$, df = 10, $P < 0.001$).

Affect-modulated ABR magnitude

In comparison to controls, PD patients had larger ABR magnitude in both the DBS ON ($P < 0.01$ corrected) and OFF condition ($P < 0.05$ corrected). The inter-group (patients vs. controls) and condition (DBS ON/OFF) comparison for separate picture categories showed that PD patients had larger mean ABR to aversive pictures ($P < 0.05$ corrected) in the DBS ON condition than controls. They also showed larger mean ABR to neutral pictures ($P < 0.05$ corrected) in the DBS OFF condition than controls. In the DBS ON condition, they also had larger mean ABR magnitude to erotic pictures than in DBS OFF ($P < 0.01$ corrected) than controls ($P < 0.01$ corrected) (Figs. 2 and 3). Data on ABR magnitude in all groups and picture categories are shown in the Supplementary material.

In order to control for factors other than motivational ones that could contribute to ABR changes in different conditions (such as attention), we also compared the relative change in ABR magnitude

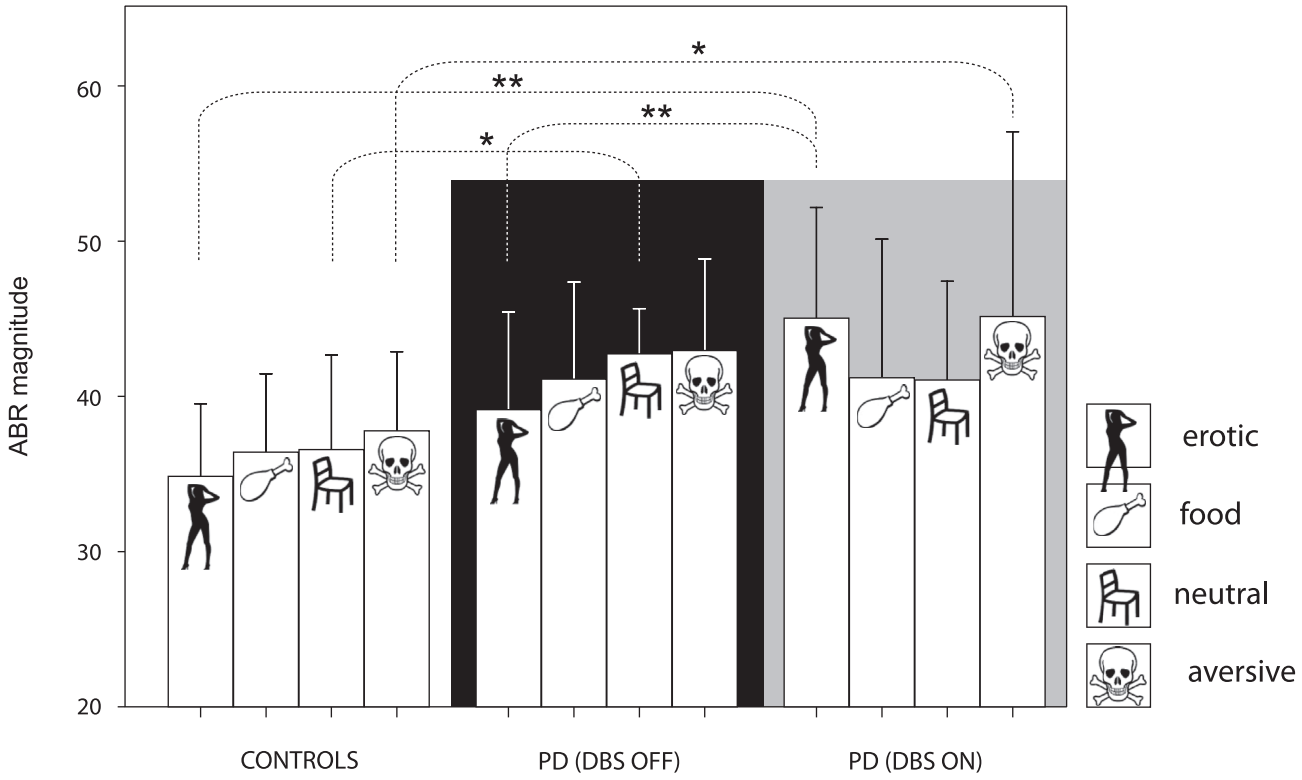

Figure 2. Magnitude of the blink reflex to an acoustic startle probe (in *t*-scores) presented during viewing of erotic, food, neutral, and aversive pictures from control subjects ($N = 11$) and Parkinson's disease patients ($N = 11$) in conditions with deep brain stimulation (DBS) of the subthalamic nucleus OFF and ON. In the DBS ON condition, the physiological pattern of acoustic blink reflex (ABR) modulation with pleasure inhibition to erotic pictures was lost and the ABR magnitude to erotic pictures was potentiated as if aversive. Corrected significance level $^{*}P < 0.05$, $^{**}P < 0.01$.

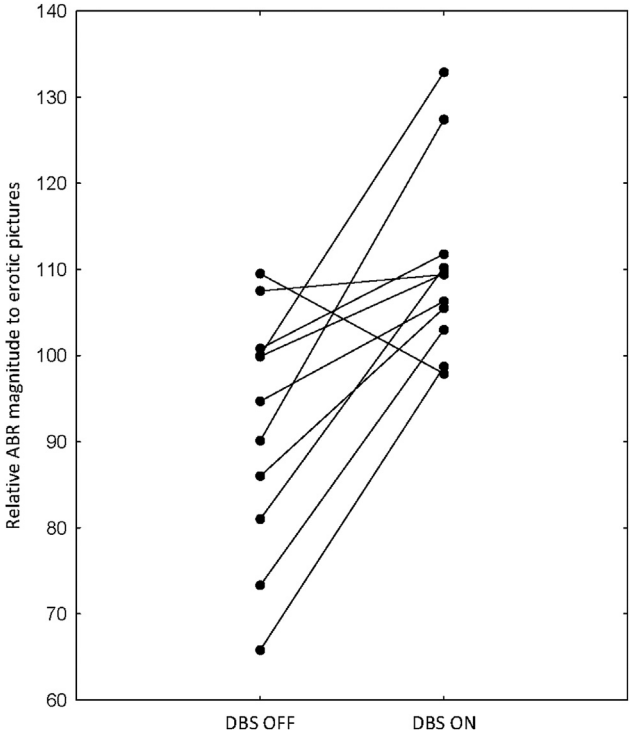

Figure 3. Relative magnitude of the acoustic blink reflex (ABR) in individual Parkinson's disease patients ($N = 11$) elicited during viewing of erotic pictures in subthalamic deep brain stimulation (STN DBS) OFF and ON conditions. In the STN DBS ON condition, there was an increase in ABR magnitude in 10 out of 11 patients. The relative ABR magnitude is expressed as percentage of the magnitude elicited during viewing neutral pictures in the given condition.

from different picture categories with respect to ABR magnitude to neutral pictures.

The relative change in ABR magnitude to erotic pictures with respect to neutral pictures was significant between DBS ON and controls ($P < 0.05$ corrected) and between DBS ON and DBS OFF ($P < 0.01$ corrected). No other relative changes in ABR magnitude to other picture categories or in other group-wise comparisons were significant.

The ABR magnitude differences between DBS ON and OFF condition were not related to the position of active electrode contact.

Affective ratings

No significant differences in affective valence and arousal ratings were found in group and DBS ON/OFF comparisons.

In all groups and conditions, the affective ratings of valence came in the same order: aversive pictures were rated the lowest, followed by neutral pictures, then food pictures, and finally erotic pictures (all pairwise comparisons of categories $P < 0.001$ corrected). Similarly, arousal ratings shared the same pattern in all groups and conditions, in which the neutral pictures were rated at the lowest arousal, followed by food pictures, then by erotic pictures, and finally with aversive pictures ($P < 0.001$ corrected). Data on valence and arousal ratings in all groups and picture categories are presented in the Supplementary material.

Body weight change

Compared to preoperative values, the mean body weight of patients increased postoperatively from 88.6 kg (SD = 15.2) to 94.2 kg (SD = 10.0). The difference value between means was 5.6 kg (95% CI: 0.3–10.9 kg; $T = -2.38$, df = 10, $P < 0.05$).

Furthermore, postoperative weight gain was negatively correlated with ABR magnitude to food pictures in the DBS ON condition ($r = -0.75$, df = 9, $P < 0.01$). The correlation was significant even after suppressing the effect of the DBS OFF condition by partial correlation analysis, i.e., after adjusting with respect to ABR to food pictures in the DBS OFF condition ($r = -0.74$, df = 9, $P < 0.01$) (Fig. 4).

Postoperative weight gain correlated positively with the arousal rating of food pictures in the DBS ON condition ($r = 0.70$, df = 9, $P < 0.05$). This correlation remained significant even after adjusting for arousal rating in the DBS OFF condition (partial correlation, $r = 0.67$, df = 9, $P < 0.05$).

Discussion

In the present study in PD patients treated by STN DBS, we observed changes in modulation of the ABR by primary rewarding and aversive cues, suggesting that STN DBS modifies motivational processing. In previous ABR studies carried out during STN DBS [29], artifacts were reduced by switching stimulation to bipolar mode, which could have caused a change in the efficacy of the stimulation. Instead, we were able to remove the artifact related to monopolar DBS and to study the patients in their long-term therapeutic setting.

We found larger ABRs in PD patients than in controls, regardless of DBS condition, larger mean ABR to aversive pictures in the DBS ON condition than controls, and larger ABR to neutral pictures in DBS OFF condition than in controls. The differences between the OFF condition and the controls could be explained by impaired attentional inhibition of the ABR in PD patients compared to normal subjects, as the ABR has been found to be attenuated by attentional processes during picture viewing [30]. The fact that larger ABR magnitudes were not reported in a previous study on affective modulation of the ABR in off-medicated PD patients [31] may be due to a substantially shorter disease duration than in our patients (mean 5.5 (SD = 4) vs. 14.4 (SD = 3) years). Indeed, attentional deficits have been documented in PD patients, and there is evidence for their progression with disease duration [32,33].

Affective modulation of the ABR becomes evident during viewing of affect-weighted pictures [30], with ABR facilitated by aversive and inhibited by appetitive picture contents reflecting the activation of the aversive and appetitive systems [16]. However, in our study the ABR to erotic stimuli was larger in DBS ON condition than in either the OFF condition or in the controls. In fact, ABRs appeared to be paradoxically potentiated by erotic pictures with respect to neutral pictures suggesting that STN DBS disturbs physiological engagement of the appetitive system (Fig. 2). Additionally, the ABR modulated by aversive stimuli was relatively larger in DBS ON than in controls, suggesting an increased activation of the aversive motivational system. The mechanisms of these effects might be very complex. Recent studies have suggested that while neuronal excitability near the DBS electrode is substantially inhibited, the axons surrounding the active contact of implanted electrodes are more likely excited. This leads to an increase in the output from the stimulated axons, whose natural activity is replaced by a more regular, high frequency activity that is time-locked to the stimulus [34]. Thus, the interference of STN DBS with the motivational processing could take place at the level of the STN or within the limbic and reward circuits that involve subcortical structures such as the amygdala and the ventral basal ganglia (the nucleus accumbens and the ventral pallidum) as well as the mesolimbic dopamine system. These structures have direct or indirect connections with both the STN [35–39] and the primary startle circuit, and are also known to mediate the affective modulation of the ABR [40,41]. It has already been demonstrated that STN DBS may modify activity of the amygdala during affective tasks in humans [42]. Indeed, changes in arousal and attention allocation to emotional stimuli may also play a role.

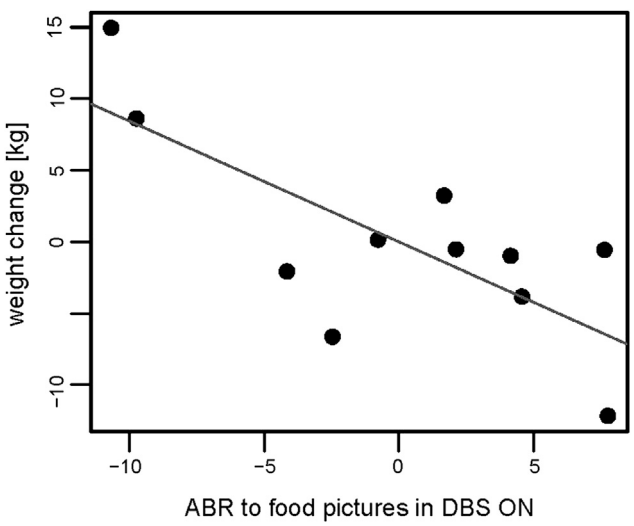

Figure 4. Partial correlation between acoustic blink reflex (ABR) magnitude to pictures of food in Parkinson's disease patients ($N = 11$) with deep brain stimulation of the subthalamic nucleus (STN DBS) ON, and body weight change after STN DBS implantation (kg), adjusted for ABR to pictures of food with STN DBS OFF.

Interestingly enough, the extent of ABR inhibition by food pictures and their arousal ratings correlated with postoperative weight gain in ON condition even after adjustment for the OFF condition, suggesting increased appetitive motivational engagement by food cues in the DBS ON condition. This finding is consistent with increased motivation for food found in experimental animals after STN DBS [8,9] and suggests that postoperative weight gain may be related to changes in the processing of food cues. Both fearful and appetitive motivation (including motivation for food) involve interaction between dopaminergic and different glutamatergic inputs (from the amygdala and the prefrontal cortex) that converge on nucleus accumbens in overlapping mesocorticolimbic circuits [43]. Neurochemical manipulations at different rostrocaudal points in medial shell of nucleus accumbens involving different sets of dopamine receptors generate many graded combinations of appetitive and/or defensive behaviors including mixed bouts of both positive eating behavior and negative fearful treading in experimental animals [44–46]. The STN DBS interactions with the ventral basal ganglia circuits including the non-physiological release of the mesolimbic dopamine [47] may therefore be one of the mechanisms contributing to both the increased aversive activation and the increased motivation for food. Another explanation for our findings could be a direct effect of electrical stimulation on the circuits linking the ventral basal ganglia with the pedunculo-pontine nucleus and the primary startle circuit as it was demonstrated for prepulse inhibition of the ABR [48].

Changes in motivational reactivity according to the ABR modulation were not reflected in subjective ratings of our patients. The lack of significant difference might be a consequence of a relatively low number of subjects in our study. However, in another study assessing changes in incentive salience attribution related to STN DBS in a larger group of PD patients, aversive pictures from the same sets were rated as more negative in the DBS ON than in the DBS OFF condition, thus also demonstrating increased aversive activation, but no change was detected for erotic or food picture ratings [12].

In conclusion, our results support the hypothesis that STN DBS affects motivational processing in PD patients. STN DBS appears to

disrupt physiological inhibition of ABR by appetitive (erotic) cues. These may be experienced as frustrative nonreward [49] despite their positive subjective ratings. In addition, the aversive motivational system was increasingly activated by aversive stimuli in PD patients compared to the control subjects. Further research is needed to determine whether changes in affective state and motivational processing can lead to difficulties in self-perception or account for problems in the social adjustment of patients treated by STN DBS [3]. Also, our results suggest that STN DBS may increase motivation for food cues, thereby contributing to postoperative weight gain, which may be of practical value for management of this side effect.

Acknowledgments

We are grateful to Markéta Fialová, Anna Rezková and Martin Voleman for administrative and technical support.

Supplementary material

Supplementary material related to this article can be found in the online version at http://dx.doi.org/10.1016/j.brs.2013.03.009.

References

[1] Volkmann J. Deep brain stimulation for Parkinson's disease. Parkinsonism Relat Disord 2007;13(Suppl. 3):S462–5.
[2] Temel Y, Kessels A, Tan S, Topdag A, Boon P, Visser-Vandewalle V. Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: a systematic review. Parkinsonism Relat Disord 2006;12(5):265–72.
[3] Schupbach M, Gargiulo M, Welter ML, Mallet L, Behar C, Houeto JL, et al. Neurosurgery in Parkinson disease: a distressed mind in a repaired body? Neurology 2006;66(12):1811–6.
[4] Walker HC, Lyerly M, Cutter G, Hagood J, Stover NP, Guthrie SL, et al. Weight changes associated with unilateral STN DBS and advanced PD. Parkinsonism Relat Disord 2009;15(9):709–11.
[5] Novakova L, Ruzicka E, Jech R, Serranova T, Dusek P, Urgosik D. Increase in body weight is a non-motor side effect of deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Neuro Endocrinol Lett 2007;28(1):21–5.
[6] Darbaky Y, Baunez C, Arecchi P, Legallet E, Apicella P. Reward-related neuronal activity in the subthalamic nucleus of the monkey. Neuroreport 2005;16(11): 1241–4.
[7] Brucke C, Kupsch A, Schneider GH, Hariz MI, Nuttin B, Kopp U, et al. The subthalamic region is activated during valence-related emotional processing in patients with Parkinson's disease. Eur J Neurosci 2007;26(3):767–74.
[8] Baunez C, Amalric M, Robbins T. Enhanced food-related motivation after bilateral lesions of the subthalamic nucleus. J Neurosci 2002;22(2):562–8.
[9] Rouaud T, Lardeux S, Panayotis N, Paleressompoulle D, Cador M, Baunez C. Reducing the desire for cocaine with subthalamic nucleus deep brain stimulation. Proc Natl Acad Sci U S A 2010;107(3):1196–200.
[10] Thobois S, Ardouin C, Lhommee E, Klinger H, Lagrange C, Xie J, et al. Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. Brain 2010;133(Pt 4):1111–27.
[11] Sauleau P, Eusebio A, Vandenberghe W, Nuttin B, Brown P. Deep brain stimulation modulates effects of motivation in Parkinson's disease. Neuroreport 2009;20(6):622–6.
[12] Serranova T, Jech R, Dusek P, Sieger T, Ruzicka F, Urgosik D, et al. Subthalamic nucleus stimulation affects incentive salience attribution in Parkinson's disease. Mov Disord 2011;26(12):2260–6.
[13] Aharon I, Etcoff N, Ariely D, Chabris CF, O'Connor E, Breiter HC. Beautiful faces have variable reward value: fMRI and behavioral evidence. Neuron 2001;32(3):537–51.
[14] Winkielman P, Berridge KC, Wilbarger JL. Unconscious affective reactions to masked happy versus angry faces influence consumption behavior and judgments of value. Pers Soc Psychol Bull 2005;31(1):121–35.
[15] Lang PJ, Bradley MM, Cuthbert BN. Emotion, attention, and the startle reflex. Psychol Rev 1990;97(3):377–95.
[16] Vrana SR, Spence EL, Lang PJ. The startle probe response: a new measure of emotion? J Abnorm Psychol 1988;97(4):487–91.
[17] Drobes DJ, Miller EJ, Hillman CH, Bradley MM, Cuthbert BN, Lang PJ. Food deprivation and emotional reactions to food cues: implications for eating disorders. Biol Psychol 2001;57(1–3):153–77.
[18] Hawk Jr LW, Baschnagel JS, Ashare RL, Epstein LH. Craving and startle modification during in vivo exposure to food cues. Appetite 2004;43(3):285–94.
[19] Davis C, Patte K, Levitan R, Reid C, Tweed S, Curtis C. From motivation to behaviour: a model of reward sensitivity, overeating, and food preferences in the risk profile for obesity. Appetite 2007;48(1):12–9.
[20] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55(3):181–4.
[21] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189–98.
[22] Beck A, Steer R, Brown G. The Beck depression inventory-II. San Antonio, TX: Psychological Corporation; 1996.
[23] Christenson GA, Faber RJ, de Zwaan M, Raymond NC, Specker SM, Ekern MD, et al. Compulsive buying: descriptive characteristics and psychiatric comorbidity. J Clin Psychiatry 1994;55(1):5–11.
[24] Ruzicka F, Jech R, Novakova L, Urgosik D, Vymazal J, Ruzicka E. Weight gain is associated with medial contact site of subthalamic stimulation in Parkinson's disease. PloS One 2012;7(5):e38020.
[25] Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS): affective ratings of pictures and instruction manual. Technical Report A-8. Gainesville, FL: University of Florida; 2008.
[26] Fahn S, Marsden C, Calne D, Goldstein M. Recent developments in Parkinson's disease. Florham Park NJ: Macmillan Health Care Information; 1987. p. 153–63, p. 293–304.
[27] Chokroverty S, Walczak T, Hening W. Human startle reflex: technique and criteria for abnormal response. Electroencephalogr Clin Neurophysiol 1992;85(4):236–42.
[28] Bradley MM, Codispoti M, Cuthbert BN, Lang PJ. Emotion and motivation I: defensive and appetitive reactions in picture processing. Emotion 2001;1(3):276–98.
[29] Potter M, Herzog J, Siebner HR, Kopper F, Steigerwald F, Deuschl G, et al. Subthalamic nucleus stimulation modulates audiospinal reactions in Parkinson disease. Neurology 2008;70(16 Pt 2):1445–51.
[30] Bradley MM, Codispoti M, Lang PJ. A multi-process account of startle modulation during affective perception. Psychophysiology 2006;43(5):486–97.
[31] Miller KM, Okun MS, Marsiske M, Fennell EB, Bowers D. Startle reflex hyporeactivity in Parkinson's disease: an emotion-specific or arousal-modulated deficit? Neuropsychologia 2009;47(8–9):1917–27.
[32] Maetzler W, Liepelt I, Berg D. Progression of Parkinson's disease in the clinical phase: potential markers. Lancet Neurol 2009;8(12):1158–71.
[33] Sampaio J, Bobrowicz-Campos E, Andre R, Almeida I, Faria P, Januario C, et al. Specific impairment of visual spatial covert attention mechanisms in Parkinson's disease. Neuropsychologia 2011;49(1):34–42.
[34] Johnson MD, Miocinovic S, McIntyre CC, Vitek JL. Mechanisms and targets of deep brain stimulation in movement disorders. Neurotherapeutics 2008;5(2):294–308.
[35] Parent A, Hazrati LN. Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Res Brain Res Rev 1995;20(1):128–54.
[36] Groenewegen HJ, Berendse HW. Connections of the subthalamic nucleus with ventral striatopallidal parts of the basal ganglia in the rat. J Comp Neurol 1990;294(4):607–22.
[37] Winter C, Lemke C, Sohr R, Meissner W, Harnack D, Juckel G, et al. High frequency stimulation of the subthalamic nucleus modulates neurotransmission in limbic brain regions of the rat. Exp Brain Res 2008;185(3):497–507.
[38] Turner MS, Lavin A, Grace AA, Napier TC. Regulation of limbic information outflow by the subthalamic nucleus: excitatory amino acid projections to the ventral pallidum. J Neurosci 2001;21(8):2820–32.
[39] Ghashghaei HT, Hilgetag CC, Barbas H. Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. NeuroImage 2007;34(3):905–23.
[40] Koch M. The neurobiology of startle. Prog Neurobiol 1999;59(2):107–28.
[41] Koch M, Schmid A, Schnitzler HU. Pleasure-attenuation of startle is disrupted by lesions of the nucleus accumbens. Neuroreport 1996;7(8):1442–6.
[42] Le Jeune F, Peron J, Biseul I, Fournier S, Sauleau P, Drapier S, et al. Subthalamic nucleus stimulation affects orbitofrontal cortex in facial emotion recognition: a PET study. Brain 2008;131(Pt 6):1599–608.
[43] Humphries MD, Prescott TJ. The ventral basal ganglia, a selection mechanism at the crossroads of space, strategy, and reward. Prog Neurobiol 2010;90(4):385–417.
[44] Reynolds SM, Berridge KC. Positive and negative motivation in nucleus accumbens shell: bivalent rostrocaudal gradients for GABA-elicited eating, taste "liking"/"disliking" reactions, place preference/avoidance, and fear. J Neurosci 2002;22(16):7308–20.
[45] Faure A, Reynolds SM, Richard JM, Berridge KC. Mesolimbic dopamine in desire and dread: enabling motivation to be generated by localized glutamate disruptions in nucleus accumbens. J Neurosci 2008;28(28):7184–92.
[46] Richard JM, Berridge KC. Metabotropic glutamate receptor blockade in nucleus accumbens shell shifts affective valence towards fear and disgust. Eur J Neurosci 2011;33(4):736–47.
[47] Shon YM, Lee KH, Goerss SJ, Kim IY, Kimble C, Van Gompel JJ, et al. High frequency stimulation of the subthalamic nucleus evokes striatal dopamine release in a large animal model of human DBS neurosurgery. Neurosci Lett 2010;475(3):136–40.
[48] Costa J, Valls-Sole J, Valldeoriola F, Pech C, Rumia J. Single subthalamic nucleus deep brain stimuli inhibit the blink reflex in Parkinson's disease patients. Brain 2006;129(Pt 7):1758–67.
[49] Amsel A. Frustrative nonreward in partial reinforcement and discrimination learning: some recent history and a theoretical extension. Psychol Rev 1962;69:306–28.

Distinct Populations of Neurons Respond to Emotional Valence and Arousal in the Human Subthalamic Nucleus

Tereza Serranová[1]*, Tomáš Sieger[1,2]*, Filip Růžička[1], Pavel Vostatek[2], Jiří Wild[2], Daniela Šťastná[3], Cecilia Bonnet[1], Daniel Novák[2], Evžen Růžička[1], Dušan Urgošík[3], Robert Jech[1‡]

[1] Dept. of Neurology and Center of Clinical Neuroscience, Charles University in Prague, 1st Faculty of Medicine and General University Hospital, Prague, Czech Republic [2] Dept. of Cybernetics, Faculty of Electrical Engineering, Czech Technical University, Prague, Czech Republic [3] Dept. of Stereotactic and Radiation Neurosurgery, Na Homolce Hospital, Prague, Czech Republic

Submitted to Proceedings of the National Academy of Sciences of the United States of America

Both animal studies and studies using deep brain stimulation in humans have demonstrated the involvement of the subthalamic nucleus in motivational and emotional processes. However, participation of this nucleus in processing human emotion has not been investigated directly at the single-neuron level. We analyzed the relationship between the neuronal firing from intraoperative microrecordings from the subthalamic nucleus during affective picture presentation in Parkinson's disease patients and the affective ratings of emotional valence and arousal performed subsequently. We observed response to visual stimuli in 19% of neurons. In addition, 15% of neurons responded to emotional valence and arousal of visual stimuli according to individual ratings. Activity of some neurons was related to emotional valence while different neurons responded to arousal. Our results suggest that there are neurons involved in processing or transmission of visual and emotional information in the human STN and provide evidence of separate processing of the affective dimensions of valence and arousal also at the level of single neurons.

Eye movements | basal ganglia | subthalamic nucleus | single neuron | emotion

Introduction

Once the subthalamic nucleus (STN) which is an important target for deep brain stimulation (DBS) in treatment of motor symptoms in Parkinson´s disease (PD) was considered as an important regulator of motor function (1, 2). However, the occurrence of postoperative neuropsychiatric complications has expanded interest in the non-motor function of the STN (3, 4). Animal and human studies have already demonstrated the additional functional role of the STN in emotional and motivational processes (5-12). In addition, recent fMRI studies found STN activation in response to emotional stimuli in healthy subjects (13, 14). Therefore we hypothesized that emotional activity related neurons should exist in the STN. However, participation of this nucleus in processing emotion has not been investigated directly at the single-cell level in humans before.

Single-neuron activity related to a priori emotional categories has already been detected in humans in a few brain regions such as in the hippocampus, amygdala and in the prefrontal and subcallosal cortex (15-19). It has been proposed that emotional behavior is organized along two psycho-physiological dimensions: emotional valence, varying from negative to positive, and arousal, varying from low to high (20). We used individual ratings of valence and arousal as a tool for detection of emotion-related neurons in our study as the individual assessment these dimensions is well correlated with somatic and autonomic measures of emotions and contrary to a priori categories they can better reflect emotional characteristics of the stimulus in an individual context (21, 22).

The aim of our study was to find firing pattern changes in STN neurons related to emotional content of visual stimuli. We recorded the STN single-neuron activity during a presentation of sets of emotionally charged (pleasant and unpleasant) and neutral pictures in PD patients undergoing DBS electrode implantation. Following previous studies using local field potential recordings that revealed emotion-related desynchronization of the STN in alpha band (7, 23) we focused on single-neuron activity in the alpha frequency band as well. We compared the individual firing of single-neurons with specific affective experience expressed in subjective ratings of the emotional valence and arousal of each presented picture and we mapped these neurons into the STN model (24).

Results

We acquired 97 MER signals recorded from 47 positions in the STN where 125 neurons were totally detected. The activity of 35 neurons was related to eye movements and were excluded from further analysis. The remaining 90 neurons (69 in the left hemisphere) were searched for visual and emotional characteristics. Individual and normative valence and arousal ratings for each picture category are presented in Table 2.

In 17 (19%) neurons, a significant difference in the alpha band activity between the PIC (0-500ms) and FIX epochs was found ($p<0.05$). The alpha band activity of 15 (17%) neurons during the PIC (500-2000 ms) epochs was related to the emotional content of the presented pictures expressed in individual valence or arousal ratings ($p<0.05$): the activity of 6 (7%) neurons correlated with the valence ratings (4 neurons negatively, 2 neurons positively – Figure 1); the activity of 9 (10%) neurons correlated with the arousal ratings (7 neurons positively, 2 neurons nega-

Significance

The involvement of the subthalamic nucleus (STN) in affective processing has been suggested with the appearance of neuropsychiatric side-effects of deep brain stimulation in Parkinson's disease (PD), but direct evidence was missing. In our study, single-neuron activity was recorded from the STN during affective picture presentation to PD patients intraoperatively. We discovered two spatially distinct populations of "affective" neurons responding to the emotional dimensions of the stimuli: the valence (pleasantness-unpleasantness), and arousal (intensity). As believed previously, neural circuits underlying these two affective dimensions are functionally segregated. Here we observed separated emotional processing even at the single neuron level. These results extend our knowledge on the emotional role of the STN and the neural basis of emotions.

Reserved for Publication Footnotes

Table 1. Descriptive data of patients with Parkinson's disease.

patient	Age [years]	DD [years]	Preoperative levodopa [mg]	UPDRS III	neurons	emotion-related neurons
1	64	14	1375	31	8	1
2	61	14	1200	37	5	0
3	46	15	1000	40	10	1
4	63	30	1250	50	2	1
5	53	12	700	37	7	1
6	69	9	750	47	2	0
7	49	12	1550	65	4	1
8	53	11	1663	45	5	1
9	64	17	1500	31	11	2
10	42	9	740	33	16	3
11	55	19	1980	35	8	2
12	60	14	1060	18	7	0
13	43	9	1100	34	5	2

Age – age on the day of surgery; DD – Parkinson´s disease duration; Preoperative levodopa – dose/day in mg including levodopa equivalent dosage of dopamine agonist; patient 4 was also treated with mianserin; patients 6, 7 with citalopram; UPDRS III – motor score of the Unified Parkinson´s Disease Rating Scale in OFF medication condition; neurons – number of subthalamic neurons unrelated to eye movements; emotion-related neurons – number of neurons responding to emotional stimuli.

Table 2. Patients' and normative ratings of emotional stimuli used. Patients' ratings represent subjective ratings assessed post-operatively. Normative ratings are those available from International Affective Picture System (IAPS) (Lang and Bradley, 2008).

	Patients' rating		Normative rating	
Category	Mean (SD) valence	Mean (SD) intensity	Mean (SD) valence	Mean (SD) intensity
Negative	3.1 (1.6)	5.1 (2.6)	3.4 (0.7)	5.2 (1.1)
Neutral	5.2 (1.0)	2.6 (1.7)	5.0 (0.2)	2.8 (0.3)
Positive	6.0 (1.3)	4.0 (2.1)	6.6 (0.8)	5.2 (1.1)

tively – Figure 2). In addition, 3 neurons demonstrated an alpha band activity change related both to visual stimulus up to 500 ms from its onset and simultaneously to its emotional content during the following period.

The locations of the neurons sensitive to emotional content are depicted in Figure 3. The valence-related neurons in the STN were located more posteriorly compared to the arousal-related neurons (permutation test, $p<0.05$). The antero-posterior difference in the mean position of the neuronal populations was 1.9 mm.

Discussion

Using perioperative microrecordings from the subthalamic nucleus of patients with Parkinson's disease, we analyzed changes in the firing pattern of single-neurons in relationship to visually presented emotional material and found a relatively large proportion of neurons with activity related to visual and emotional processing. In addition, we showed how easy it is to transform the single-neuron action potentials to continuous signal to perform spectral analysis typical for conventional electroencephalography. Using this approach we documented the impact of a visual emotional task on single-neuron activity in the alpha band similar to those previously shown with local field potentials (7, 23).

Visual neurons in the STN

Nineteen percent of the subthalamic neurons responded with a change in the alpha band firing activity during first 500 ms after the picture presentation onset suggesting their connection with visual circuitry. Neuronal short-latency activity changes related to visual processing have already been found in animal STN (25-27) and confirmed in humans by distortion of visual evoked potentials due to STN DBS (28). However, the difference in neural activity between fixation and picture viewing periods is not necessary the evidence of visual processing since it may also reflect an engagement of selective attention, a shift from gaze fixation to scanning eye movements or other cognitive processing intervening between vision and action – memory involvement, target selection, saccade choice or content valuation (29).

Affective neurons in the STN

Sixteen percent of the STN neurons whose activity in the alpha band was analyzed in our study responded to emotional stimuli. We found different neurons responding to changes in emotional valence or in arousal ratings. Additionally, these two populations were also separated spatially with the valence-related neurons located more posteriorly compared to the arousal-related neurons. Behavioral responses to emotional valence and arousal are assumed to be mediated by different brain circuits. As for the character of changes in neuronal activity, both the increase or decrease were observed in either population of neurons suggesting a further level of specialization within each emotional dimension. The independence of valence and arousal have already been demonstrated for a variety of physiological reactions, (22, 30, 31) or in affect-related cognitive processing (32). Functional imaging and animal studies have also showed their functional segregation as several brain regions have been associated with affective valence (the orbitofrontal cortex, the mesolimbic dopamine system) while the others with affective arousal (the amygdala, the mesencephalic reticular activating system)(33-37). In addition, the STN has known direct or indirect connections with these limbic and reward circuits (38-41) and that the STN DBS may modify activity of the amygdala during affective tasks

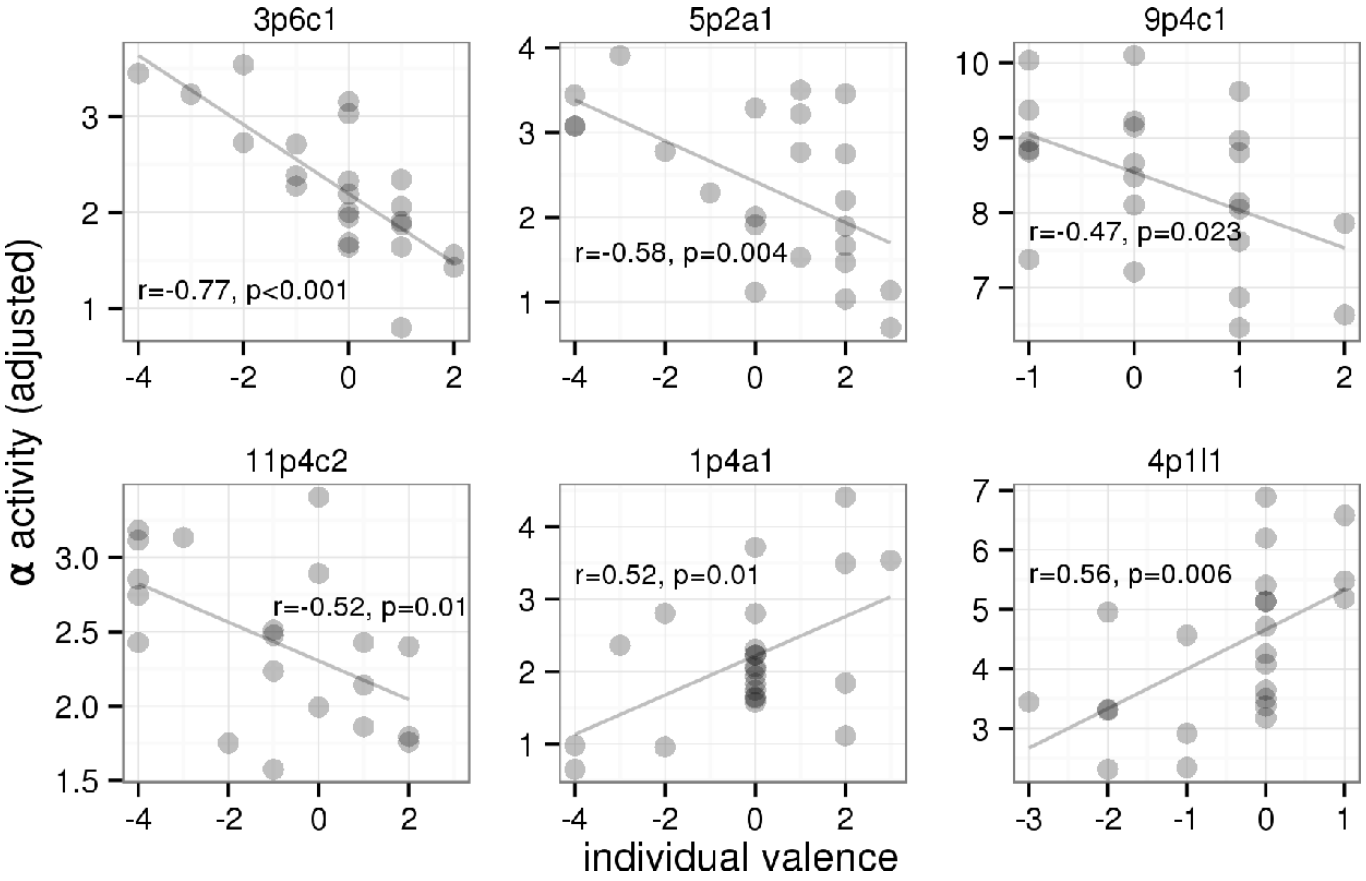

Fig. 1. The dependency of the single-neuron alpha band activity during picture presentation (PIC epochs in 500-2000 ms interval) on the individual valence ratings of the presented pictures in 6 neurons of the subthalamic nucleus in patients with Parkinson´s disease, for which the relationship was significant. The activity was adjusted for the past activity (two immediately preceding FIX and PIC epochs). For visualization purposes, correlation coefficients and their significances were included. Neuron identifications come in titles and consist of the patient number, the recording position, the abbreviation of the identification of the recording electrode, and the serial number of the neuron detected using the electrode (for example, the identification "3p6c1" refers to the first neuron detected using the central electrode in the sixth recording position in patient 3).

(42). Thus we confirm the importance of the STN as a hub within the limbic circuits involved in both emotional valence and arousal processing, surprisingly with both functional and spatial segregation of the two systems. These results paralleled with a limited number of neurons co-activated during both visual and emotional processing further corroborate the integrative role of the STN (7, 43).

Limitations

There are several factors that could affect our results and reduce the inferences that can be drawn with regards to physiology of emotional processing and the role of the STN in the limbic circuits. One limitation is that the study was conducted with PD patients, who are known to have a widespread central nervous system pathology (44) and experience problems in emotional processing (45). Therefore the number of neurons responding to emotional stimuli in the STN might be artificially reduced. Moreover, emotional pictures were selected according to normative ratings that were acquired in a healthy, younger population with a culturally different background. Finally, some our PD patients rated the stimuli less variable along the dimensions of emotional valence and arousal making the mathematical model less sensitive (21).

This is the first study demonstrating visual and emotion related single-neuron activity in the human STN which corroborates its participation in non-motor circuits. The STN has been associated with different components of emotional processing such as emotion recognition and subjective feelings (4, 43). Our results confirm the role of the STN in affective processing as documented at the single-neuron level and segregated between valence and arousal as two separate emotional dimensions. This together with finding of several neurons involved in both visual and emotional processing suggests a complex perhaps integrative role of the STN. Our results thus extend our knowledge on the STN role in limbic circuits and contribute to understanding of affective disturbances seen in Parkinson's disease patients treated with subthalamic stimulation.

Experimental procedures

Subjects

Thirteen PD patients (11 men, 2 women; mean (SD) age 55.5 (8.7), range 42-69 years; mean PD duration 14.2 (5.6), range 9-30; mean motor score of the Unified Parkinson's Disease Rating Scale (UPDRS-III) in off-medication condition was 38.7 (11.4) range 18-65) undergoing bilateral electrode implantation for the STN DBS due to motor fluctuations and/or disabling dyskinesias were enrolled. All patients met the UK Brain Bank Criteria for diagnosis of PD. Patients with dementia and/or depression had been excluded by routine psychiatric examination and neuropsychological testing (Mini-mental state examination, Mattis dementia rating scale, Beck depression inventory). Four days before surgery, dopamine agonists were substituted by equivalent doses of levodopa. Other anti-PD medication (amantadine, anticholinergics) was suspended earlier during preparation for the surgery. Levodopa was withdrawn at least 12 hours before the surgery. Five of the patients were on antidepressant therapy (1 on mianserin, 4 on citalopram) which had not been discontinued. The study was approved by the Ethics Committee of the General University Hospital in Prague, Czech Republic and all patients gave their written informed consent with participation in the study.

Affective task

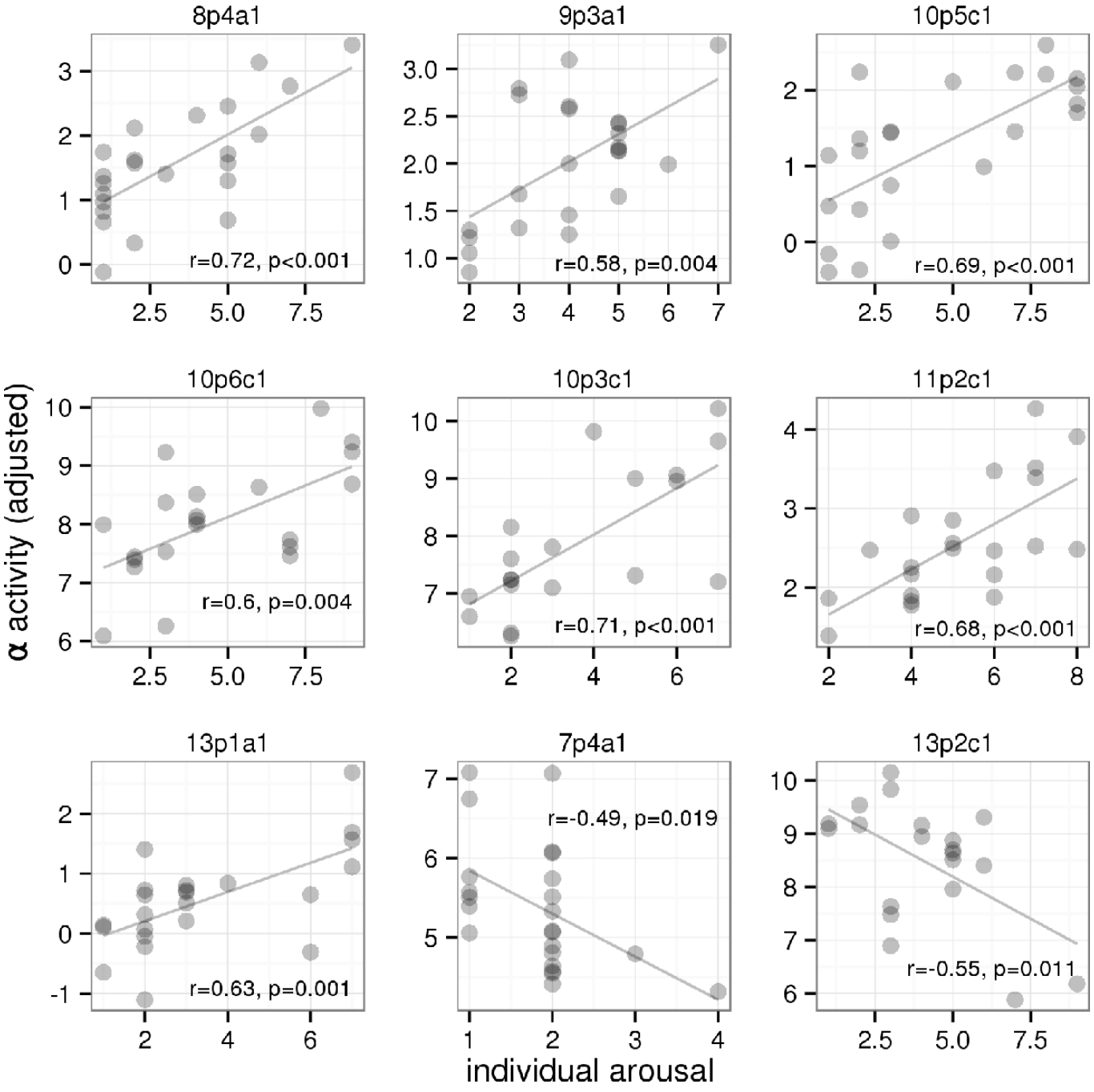

Fig. 2. The dependency of the single-neuron alpha band activity during picture presentation (PIC epochs in 500-2000 ms interval) on the individual arousal ratings of the presented pictures in 9 neurons of the subthalamic nucleus in patients with Parkinson´s disease, for which the dependency was significant. The activity was adjusted for the past activity (two immediately preceding FIX and PIC epochs) and picture categories. Neuron identification explanation is given in Figure 1.

Emotionally charged pictures of three categories were selected from the International Affective Picture System (IAPS) (21). The pleasant category involved pictures with erotic themes (people, romantic couples) and adventure (exotic landscapes, animals, sports), the unpleasant category involved pictures of victims (mutilations) and threats (human or animal attacks, aimed guns) and the neutral category comprised of pictures of household objects, buildings, and plants. Out of 144 unique pictures six different variants of the task containing 24 pictures were compiled involving 8 pictures from each category. Pleasant and unpleasant pictures were selected in a way so they represented emotional stimuli scaled from weak to strong according to normative emotional valence and arousal. Additionally, the pictures were pseudo-randomly organized so that no more than two pictures from one category followed. Each picture was presented for 2 s and preceded by a black screen with a white cross in the center for various durations (3500-5500 ms). Patients were instructed to fix their eyes on the cross on the black screen and then to simply watch the pictures presented and stay motionless until the end of the task.

Surgery and intraoperative microrecording

DBS electrodes (model 3389, Medtronic, Minneapolis, MN) were implanted bilaterally under local anesthesia, guided by stereotactic magnetic resonance, microelectrode recordings (MER) and macroelectrode intraoperative stimulation as described elsewhere (46, 47). Presurgical planning was done in SurgiPlan software system (Elekta, Stockholm, Sweden) and was based on co-registration of preoperative frameless 3.0 Tesla magnetic resonance imaging (MRI) using T1-weighted images (MP-RAGE sequence, 160 sagittal slices 1.0-mm thick with x-y resolution 1 x 1 mm, TR = 2300 ms, TE = 4.4ms, FA = 10 degrees) and T2-weighted images (28 axial slices and 21 coronal slices 2-mm thick with x-y resolution 0.9 x 0.9 mm, TR = 2430 ms,

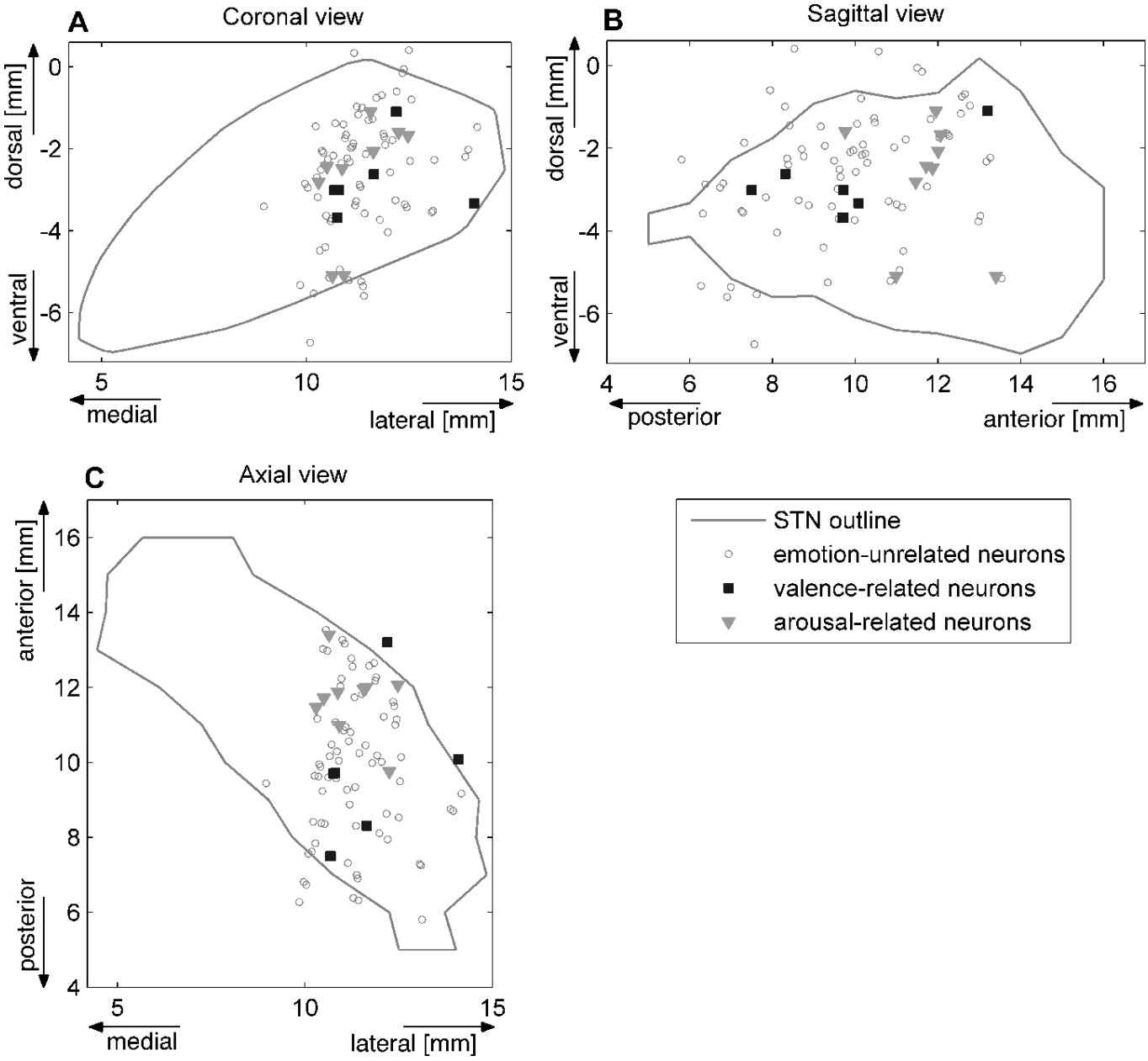

Fig. 3. Locations of STN neurons related to emotional content of the presented pictures in coronal (A), sagittal (B), and axial (C) view. The valence-related neurons were located more posteriorly compared to the arousal-related neurons.

TE = 80 ms) with preoperative frame-based 1.5 Tesla T1-weighted images (MP-RAGE sequence, 160 sagittal slices 1.25-mm thick with x-y resolution 1 x 1 mm, TR = 2500 ms, TE = 3.1 ms, FA = 45 degrees) obtained immediately before surgical procedure with the stereotactic Leksell frame attached.

The central trajectory of the exploratory microelectrode was aimed at the STN center near the anterior part of the red nucleus. The extracellular single-neuron activity was mapped by the MER using parallel insertion of five tungsten microelectrodes spaced 2-mm apart in a "Ben-gun" configuration to select sites for the macroelectrode intraoperative stimulation. The five parallel microelectrodes were advanced simultaneously with a motor microdrive in 0.5-mm steps, beginning 10 mm above the target. Depending on the length of STN positive signals, the MER were extended approximately 2–3 mm beyond the STN. Four out of five channels of the Leadpoint recording system (Medtronic, Mineapolis, MN) were used for the MER, filtered with 500 Hz high pass filter and 5 kHz low pass filter, sampled at 24kHz and stored for off-line processing. For analyses of eye movement-related neuronal activity a single-channel electrooculography was recorded (48). In up to six regions with easily classifiable neuronal pattern specific for STN, the neuronal activity was recorded during the affective task presentation with a unique variant of affective pictures in each position. The number of positions depended on the time course of the surgery and patient's decision, clinical condition and compliance. Patients were observed during the affective task and if there appeared to be any distracting discomfort or sleepiness during surgery the experimental part was shortened or not performed. The affective task was presented on a 17"-computer screen placed approximately 55 cm in front of patient's eyes who were lying motionless in the supine position, customary for this surgical procedure. The MER signals were acquired in 2 s epoch intervals recorded both during the picture presentation (PIC epoch) and the black screen (FIX epoch), producing a sequence of 48 MER epochs (FIX_1, PIC_1, ..., FIX_{24}, PIC_{24}) for a total duration of 96s.

Rating of emotional valence and arousal

A subjective rating of the emotional content of the pictures was not performed during the surgery to avoid possible contamination of neuronal activity by voluntary movements during the rating process. Emotional valence and arousal ratings of each picture in the employed task were assessed before initiation of the chronic DBS, 4-5 weeks after implantation, i.e. with sufficient delay from the surgery enabling cessation of transitory microlesion effect related to penetration of the DBS electrode (49). There were no changes in medication since the surgery in any of the patients. Patients were assessed under similar conditions like during surgery in the off stimulation and off medication state (after withdrawal of the dopaminergic treatment at least for 12 hours). Each picture was presented on a touch sensitive screen

for a 6 s period. The patients were instructed to look at each picture and to rate it along the dimensions of emotional valence and arousal by self-paced touching appropriate symbols on two independent visual scales presented on-screen after picture offset. The scales were designed according to the original IAPS scales. The valence was rated on a scale of 1-9, with 9 being the most pleasant stimulus, and the arousal on a scale of 1-9, with 9 being the most arousing stimulus.

Data analysis

WaveClus (50), an unsupervised spike detection and sorting tool, which performed reasonably well on the single-channel MER (51), was used to extract the series of action potentials of single-neurons from MER signals. Neurons related to eye movements were excluded from further analysis (48). For other neurons, the alpha band activity was computed as follows: the number of action potentials in 5 ms segments was calculated and concatenated to form a discrete signal, which was standardized to zero mean and the fast Fourier transform was carried out applying the Hann window of length 100 with 75% overlap. The mean power in the alpha band (8-12 Hz) was then extracted and subjected to the square root transform to stabilize variance.

To detect neurons sensitive to visual stimuli, differences in the alpha band activity between the FIX epoch and the following PIC epoch in the 0-500 ms interval were analyzed using the paired t-test. To detect neurons with emotion-related activity, a linear model of the alpha band activity obtained during PIC epochs in the 500-2000 ms interval after the picture onset was built. The PIC epoch onset was chosen according to previous studies with local field potentials as an emotion-related activity was detected only in the alpha band (8-12 Hz) 500 ms after the stimulus onset (7, 23). A strong serial correlation was observed in the alpha band (see supplementary material), each model also included two covariates representing the alpha band activity in the last FIX and PIC epoch preceding the analyzed PIC epoch.

To find valence-related neurons, the alpha band activity during PIC epochs was modeled in terms of the valence ratings. To find arousal-related neurons, the alpha band activity during PIC epochs was modeled in terms of the arousal ratings including additional covariates to adjust for each picture category (neutral, positive, negative). A neuron was considered to be related to valence (arousal), if the valence (arousal) covariate was significant.

Data processing and analyses were performed in MATLAB (R2007b, The MathWorks, Natick, MA) and "R" software (52).

Each neuron was finally mapped into reference STN space by assessing the position of the neuron within patient's STN, and aligning each STN with the model (24). To assess the position of a neuron within STN, preoperative STN-delineating frame-based MRI used for presurgical planning was co-registered with frameless postoperative MRI displaying the position of the permanent electrode being in a known position relatively to the microelectrode used for MER. To align each STN with the model, 12 points delineating anatomically the STN, and the anterior and posterior commissures were identified in both the model and the preoperative T2-weighted MRI, and fitted to each other by a linear transform (see supplementary material). A permutation test was used to assess the difference in the relative location of valence-related and arousal-related neurons.

Acknowledgments.

This work was supported by the Czech Science Foundation: grant project 309/09/1145, the Czech Ministry of Health: IGA MZ ČR NT12282-5/2011, the Czech Ministry of Education: grant LH13256 (VES13-KontaktII), research project MŠM 0021620849 and by the Charles University in Prague: research project PRVOUK-P26/LF1/4. We are grateful to Markéta Fialová, Anna Rezková and Martin Voleman for their administrative and technical support.

Authors roles Conception and design of experiments, results interpretation, writing manuscript: TSe, TSi, RJ Results interpretation, critical review of the manuscript: FR, CB, DN, ER, DŠ, DU MER data acquisition: RJ, FR, DU MER data processing and analyses: TSi, TSe, DN, JW, CB MRI data acquisition and processing: FR, DŠ, RJ, DU MRI data analyses: PV, DN, FR, TSi

1. Okun MS (2012) Deep-brain stimulation for Parkinson's disease. *N Engl J Med* 367(16):1529-1538.
2. Alexander GE, Crutcher MD, & DeLong MR (1990) Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Prog Brain Res* 85:119-146.
3. Voon V, Kubu C, Krack P, Houeto JL, & Troster AI (2006) Deep brain stimulation: neuropsychological and neuropsychiatric issues. *Mov Disord* 21 Suppl 14:S305-327.
4. Castrioto A, Lhommee E, Moro E, & Krack P (2014) Mood and behavioural effects of subthalamic stimulation in Parkinson's disease. *Lancet Neurol* 13(3):287-305.
5. Dujardin K, *et al.* (2004) Subthalamic nucleus stimulation induces deficits in decoding emotional facial expressions in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 75(2):202-208.
6. Schneider F, *et al.* (2003) Deep brain stimulation of the subthalamic nucleus enhances emotional processing in Parkinson disease. *Arch Gen Psychiatry* 60(3):296-302.
7. Kuhn AA, *et al.* (2005) Activation of the subthalamic region during emotional processing in Parkinson disease. *Neurology* 65(5):707-713.
8. Schroeder U, *et al.* (2004) Facial expression recognition and subthalamic nucleus stimulation. *J Neurol Neurosurg Psychiatry* 75(4):648-650.
9. Baunez C, Amalric M, & Robbins TW (2002) Enhanced food-related motivation after bilateral lesions of the subthalamic nucleus. *J Neurosci* 22(2):562-568.
10. Rouaud T, *et al.* (2010) Reducing the desire for cocaine with subthalamic nucleus deep brain stimulation. *Proc Natl Acad Sci U S A* 107(3):1196-1200.
11. Serranova T, *et al.* (2011) Subthalamic nucleus stimulation affects incentive salience attribution in Parkinson's disease. *Mov Disord* 26(12):2260-2266.
12. Serranova T, *et al.* (2013) Sex, Food and Threat: Startling Changes After Subthalamic Stimulation in Parkinson's Disease. *Brain stimul* 6(5):740-5
13. Karama S, Armony J, & Beauregard M (2011) Film excerpts shown to specifically elicit various affects lead to overlapping activation foci in a large set of symmetrical brain regions in males. *PLoS One* 6(7):e22343.
14. Fruhholz S & Grandjean D (2012) Towards a fronto-temporal neural network for the decoding of angry vocal expressions. *Neuroimage* 62(3):1658-1666.
15. Kawasaki H, *et al.* (2005) Analysis of single-unit responses to emotional scenes in human ventromedial prefrontal cortex. *J Cogn Neurosci* 17(10):1509-1518.
16. Kawasaki H, *et al.* (2001) Single-neuron responses to emotional visual stimuli recorded in human ventral prefrontal cortex. *Nat Neurosci* 4(1):15-16.
17. Rutishauser U, *et al.* (2011) Single-unit responses selective for whole faces in the human amygdala. *Curr Biol* 21(19):1654-1660.
18. Laxton AW, *et al.* (2013) Neuronal Coding of Implicit Emotion Categories in the Subcallosal Cortex in Patients with Depression. *Biol Psychiatry* 74(10):714-9.
19. Fried I, MacDonald KA, & Wilson CL (1997) Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron* 18(5):753-765.
20. Russell JA (2003) Core affect and the psychological construction of emotion. *Psychological rev* 110(1):145-172.
21. Lang PJ & Bradley MM, & Cuthbert, B.N. (2008) International affective picture system (IAPS): Affective ratings of pictures and instruction manual. in *Technical Report A-8* (University of Florida, Florida, Gainesville).
22. Lang PJ, Greenwald MK, Bradley MM, & Hamm AO (1993) Looking at pictures: affective, facial, visceral, and behavioral reactions. *Psychophysiology* 30(3):261-273.
23. Brucke C, *et al.* (2007) The subthalamic region is activated during valence-related emotional processing in patients with Parkinson's disease. *Eur J Neurosci* 26(3):767-774.
24. Morel A (2007) Atlas of the Human Thalamus and Basal Ganglia. (Informa Helthcare, New York), p 160.
25. Matsumura M, Kojima J, Gardiner TW, & Hikosaka O (1992) Visual and oculomotor functions of monkey subthalamic nucleus. *J Neurophysiol* 67(6):1615-1632.
26. Coizet V, *et al.* (2009) Short-latency visual input to the subthalamic nucleus is provided by the midbrain superior colliculus. *J Neurosci* 29(17):5701-5709.
27. Rolland M, Carcenac C, Overton PG, Savasta M, & Coizet V (2013) Enhanced visual responses in the superior colliculus and subthalamic nucleus in an animal model of Parkinson's disease. *Neuroscience* 252:277-88.
28. Jech R, *et al.* (2006) Deep brain stimulation of the subthalamic nucleus affects resting EEG and visual evoked potentials in Parkinson's disease. *Clin Neurophysiol* 117(5):1017-1028.
29. Shires J, Joshi S, & Basso MA (2010) Shedding new light on the role of the basal ganglia-superior colliculus pathway in eye movements. *Curr Opin Neurobiol* 20(6):717-725.
30. Cacioppo JT, Petty RE, Losch ME, & Kim HS (1986) Electromyographic activity over facial muscle regions can differentiate the valence and intensity of affective reactions. *Journal of personality and social psychology* 50(2):260-268.
31. Vrana SR, Spence EL, & Lang PJ (1988) The startle probe response: a new measure of emotion? J Pers Soc Psychol 97(4):487-491.
32. Kuhbandner C & Zehetleitner M (2011) Dissociable effects of valence and arousal in adaptive executive control. PLoS One 6(12):e29287.
33. Faure A, Reynolds SM, Richard JM, & Berridge KC (2008) Mesolimbic dopamine in desire and dread: enabling motivation to be generated by localized glutamate disruptions in nucleus accumbens. *J Neurosci* 28(28):7184-7192.
34. Anders S, Lotze M, Erb M, Grodd W, & Birbaumer N (2004) Brain activity underlying emotional valence and arousal: a response-related fMRI study. *Hum Brain Mapp* 23(4):200-209.
35. Colibazzi T, *et al.* (2010) Neural systems subserving valence and arousal during the experience of induced emotions. *Emotion* 10(3):377-389.
36. Small DM, *et al.* (2003) Dissociation of neural representation of intensity and affective valuation in human gustation. *Neuron* 39(4):701-711.
37. Anderson AK, *et al.* (2003) Dissociated neural representations of intensity and valence in human olfaction. *Nat Neurosci* 6(2):196-202.
38. Parent A & Hazrati LN (1995) Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. *Brain Res Brain Res Rev* 20(1):128-154.
39. Turner MS, Lavin A, Grace AA, & Napier TC (2001) Regulation of limbic information outflow by the subthalamic nucleus: excitatory amino acid projections to the ventral pallidum. *J Neurosci* 21(8):2820-2832.
40. Groenewegen HJ & Berendse HW (1990) Connections of the subthalamic nucleus with ventral striatopallidal parts of the basal ganglia in the rat. *J Comp Neurol* 294(4):607-622.
41. Lambert C, *et al.* (2012) Confirmation of functional zones within the human subthalamic nucleus: patterns of connectivity and sub-parcellation using diffusion weighted imaging. *Neuroimage* 60(1):83-94.
42. Ghashghaei HT, Hilgetag CC, & Barbas H (2007) Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. *Neuroimage* 34(3):905-923.
43. Peron J, Fruhholz S, Verin M, & Grandjean D (2013) Subthalamic nucleus: A key structure for emotional component synchronization in humans. *Neurosci Biobehav Rev* 37(3):358-373.
44. Braak H, *et al.* (2002) Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). *J Neurol* 249 Suppl 3:III/1-5.

45. Peron J, Dondaine T, Le Jeune F, Grandjean D, & Verin M (2012) Emotional processing in Parkinson's disease: a systematic review. *Mov Disord* 27(2):186-199.
46. Gross RE, Krack P, Rodriguez-Oroz MC, Rezai AR, & Benabid AL (2006) Electrophysiological mapping for the implantation of deep brain stimulators for Parkinson's disease and tremor. *Mov Disord* 21 Suppl 14:S259-283.
47. Pollak P, *et al.* (2002) Intraoperative micro- and macrostimulation of the subthalamic nucleus in Parkinson's disease. *Mov Disord* 17 Suppl 3:S155-161.
48. Sieger T, *et al.* (2013) Basal ganglia neuronal activity during scanning eye movements in Parkinson's disease. *PLoS One* 8(11):e78581.
49. Jech R, *et al.* (2012) The subthalamic microlesion story in Parkinson's disease: electrode insertion-related motor improvement with relative cortico-subcortical hypoactivation in fMRI. *PLoS One* 7(11):e49056.
50. Quiroga RQ, Nadasdy Z, & Ben-Shaul Y (2004) Unsupervised spike detection and sorting with wavelets and superparamagnetic clustering. *Neural Comput* 16(8):1661-1687.
51. Wild J, Prekopcsak Z, Sieger T, Novak D, & Jech R (2012) Performance comparison of extracellular spike sorting algorithms for single-channel recordings. *J Neurosci Methods* 203(2):369-376.
52. Team RC (2012) A language and environment for statistical computing. ed Computing RFfS.