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**

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

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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(***)

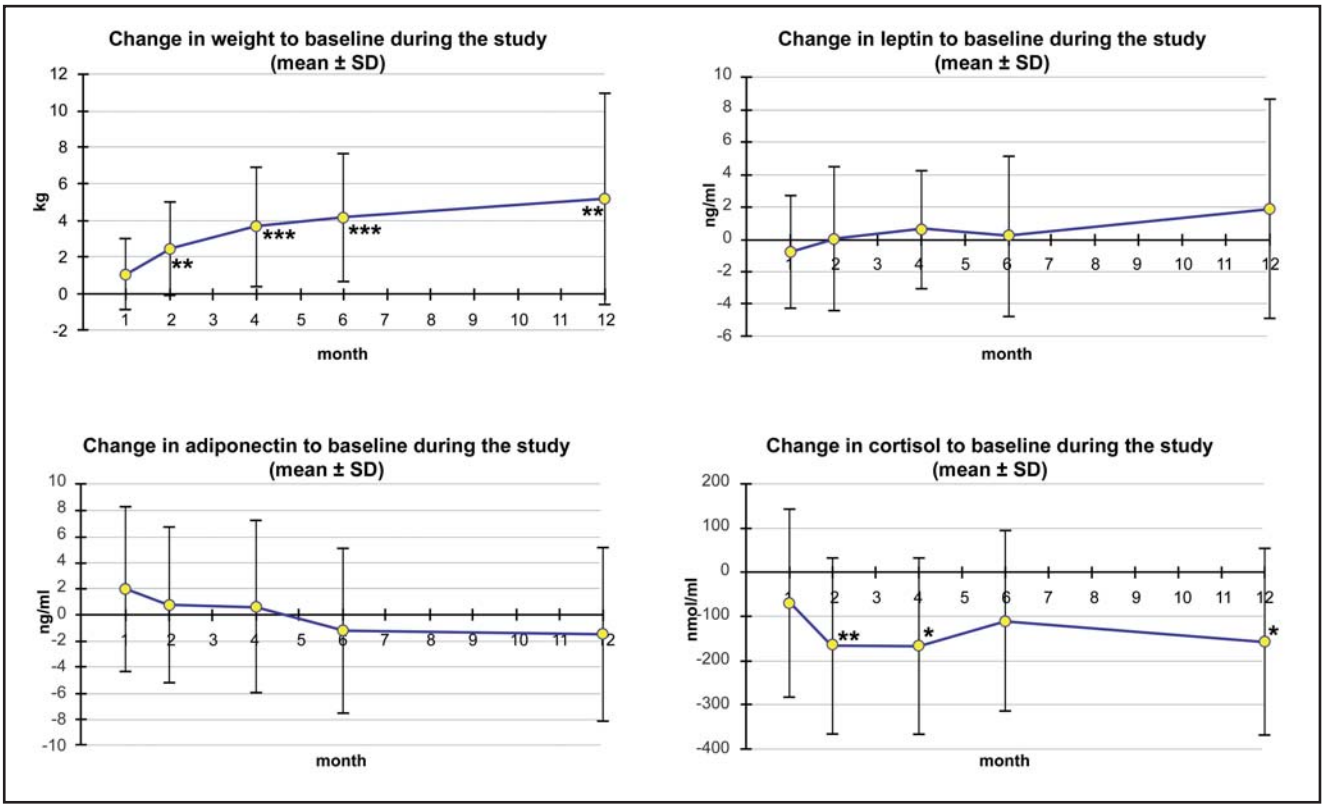

Fig. 1. Mean changes in weight, leptin, adiponectin, and cortisol during the study. X axis: individual measurements at 1, 2, 4, 6, and 12 months after surgery. Y axis: difference from baseline, measured parameter.

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.

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RESEARCH ARTICLE

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

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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.

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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.

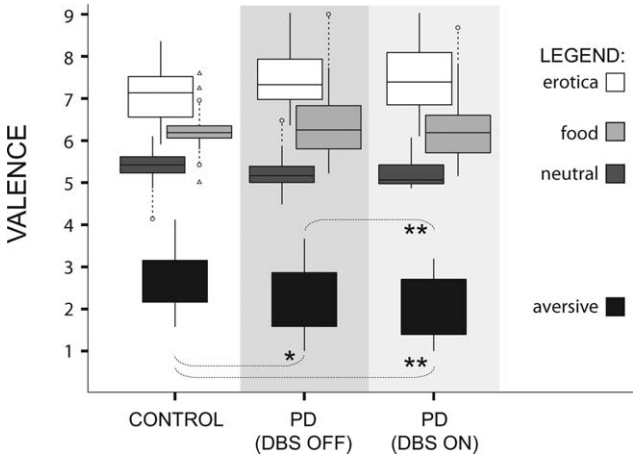

FIG. 1. Valence of selected IAPS pictures of 4 categories (erotic, food, neutral, aversive content) as rated by control subjects (n = 18) and PD patients (n = 20) in conditions with the STN DBS switched OFF and ON. The only difference between conditions/groups of subjects was found for the valence of 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

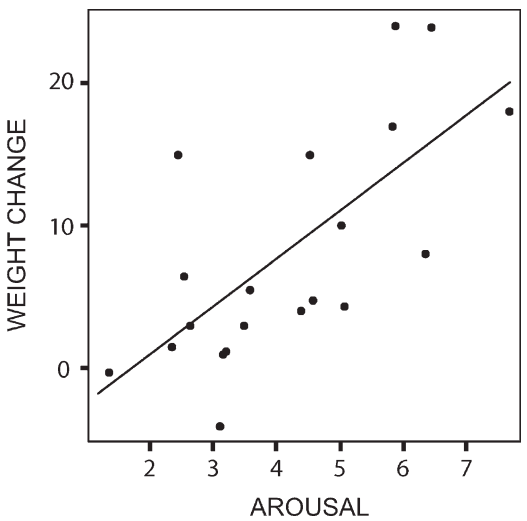

FIG. 3. Correlation between the arousal of the pictures with the food content rated by Parkinson's disease patients (n = 20) with the STN DBS switched ON and body weight change after STN DBS implantation (kg).

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).

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Letter to the Editor

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

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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.

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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.

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

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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.

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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.

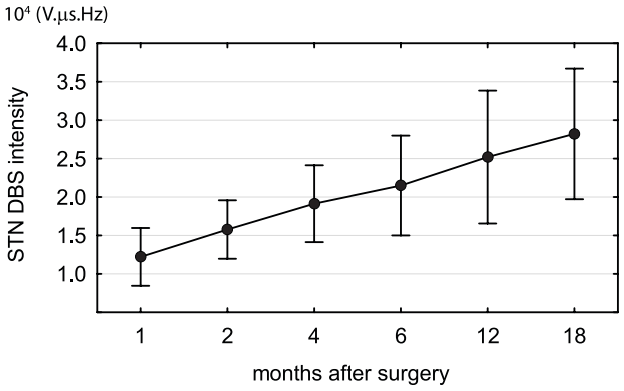

Figure 1. Mean stimulation intensity (±SD) of the STN-DBS at 1, 2, 4, 6, 12 and 18 months after implantation in 20 patients with Parkinson's disease. The stimulation intensity was calculated as the arithmetic product of the I-intensity, u-voltage, d-pulse duration and f-frequency from both hemispheres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

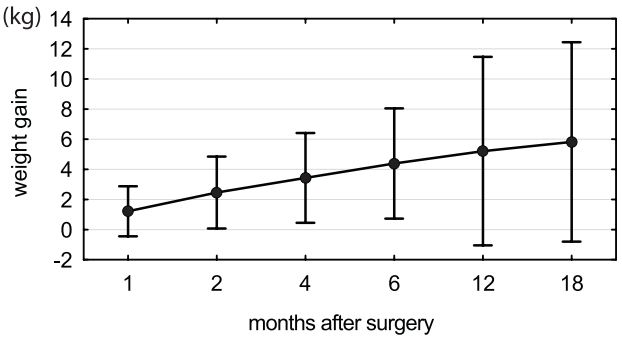

Figure 2. Mean changes in weight after implantation in 20 patients with Parkinson's disease. Body weight gradually increased during the study period. Weight gain represents the difference in weight (±SD) compared to the preoperative state.
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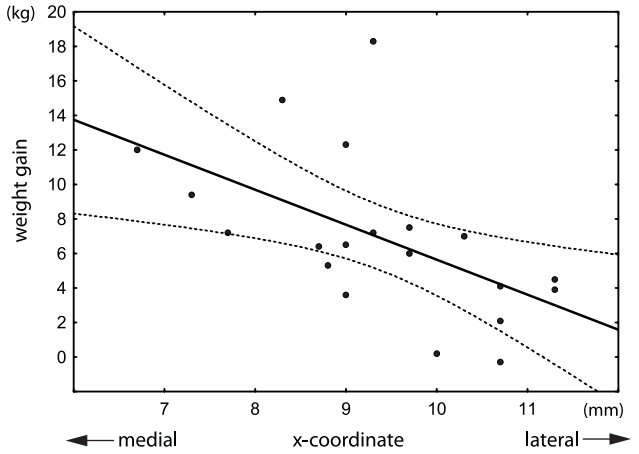

Figure 3. Weight gain in 20 patients with Parkinson's disease in relation to the mediolateral position of the active contact with bilateral STN-DBS (r = −0.55, p<0.01). Only one active contact (more medial contact from both hemispheres) was used in each patient. The x-coordinate represents the distance 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.
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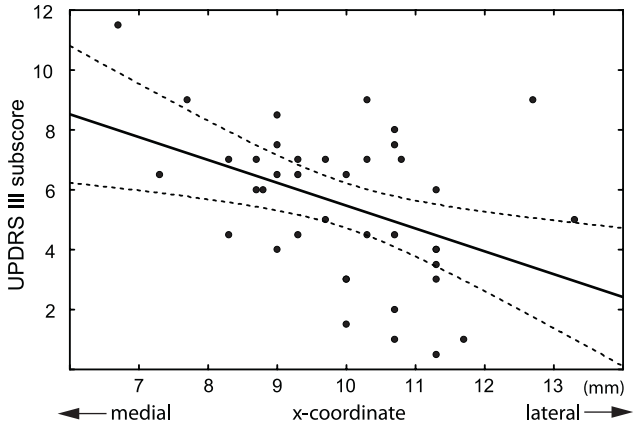

Figure 4. Hemi-body UPDRS-III subscores in the sON condition after overnight withdrawal of dopaminergic therapy in relation to the mediolateral position of the contralateral active contact. After initiation of STN-DBS, the hemi-body side with the lowest motor score (best motor condition) had the contralateral 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.
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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

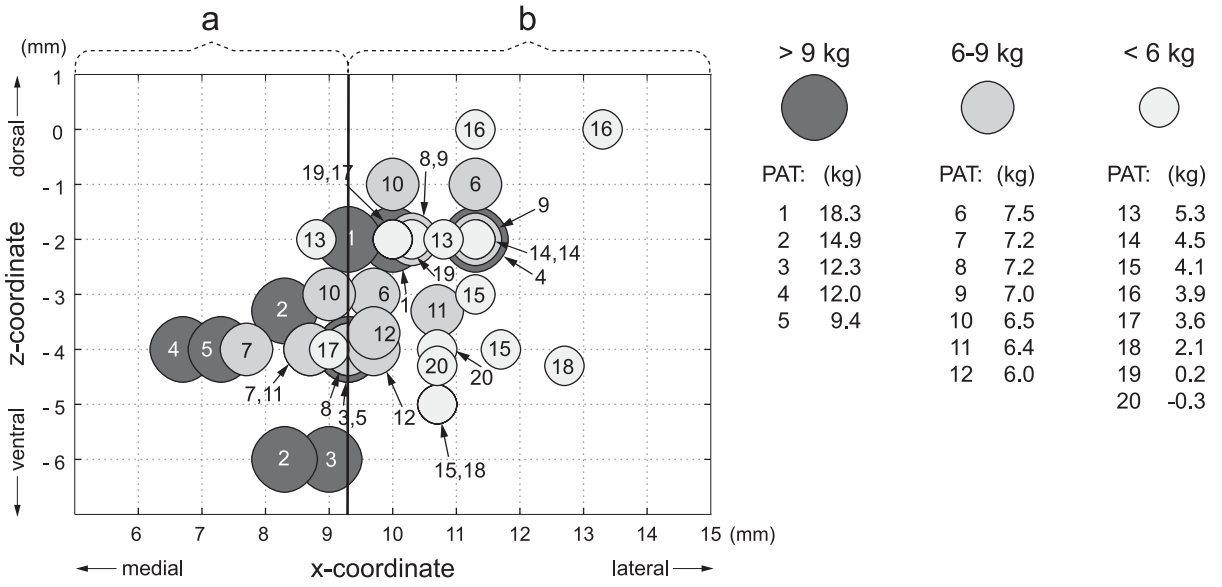

Figure 5. Bilateral STN-DBS active contact positions of 20 patients with Parkinson's disease plotted in the coronal plane with respect to weight gain. Patients (N = 11) with at least one active contact (a) placed within 9.3-mm of the wall of the third ventricle gained significantly more weight than patients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

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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.

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Original Articles

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

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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

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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.

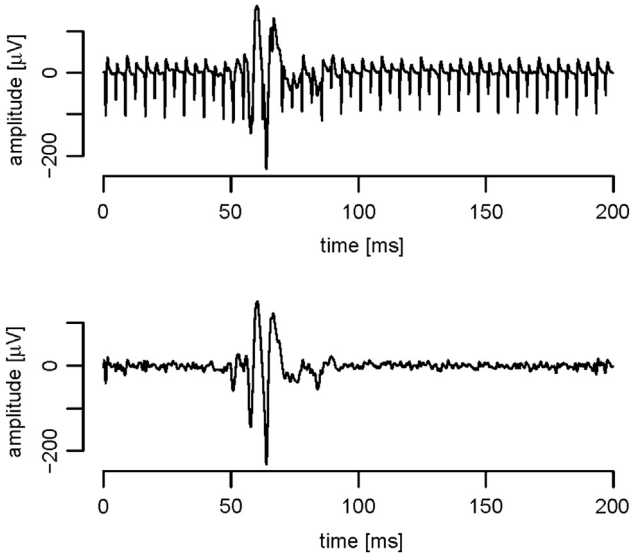

Figure 1. Recording of acoustic blink reflex from the orbicularis oculi muscle in DBS ON condition with an artifact related to monopolar deep brain stimulation of the subthalamic nucleus (top). The same recording after removal of the artifact by means of artifact template removal in spectral domain (bottom).

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

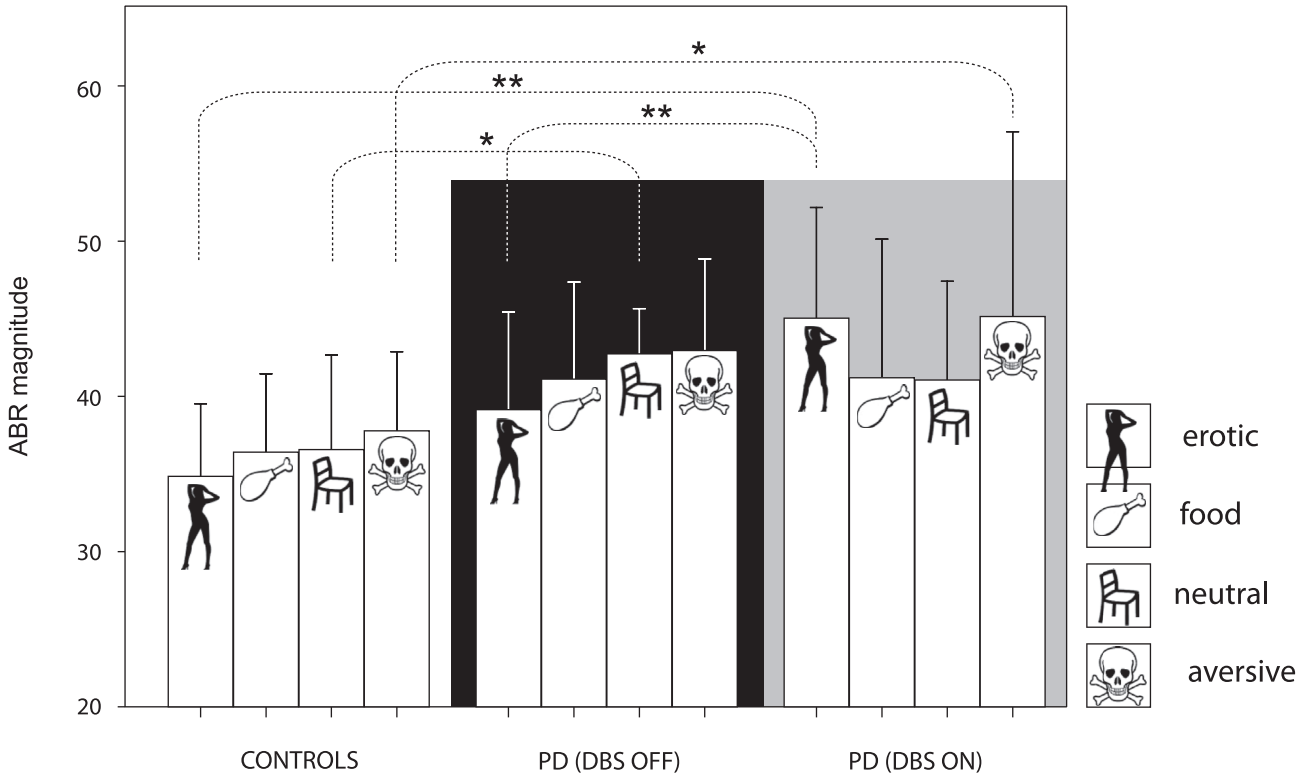

Figure 2. Magnitude of the blink reflex to an acoustic startle probe (in *t*-scores) presented during viewing of erotic, food, neutral, and aversive pictures from control subjects ($N = 11$) and Parkinson's disease patients ($N = 11$) in conditions with deep brain stimulation (DBS) of the subthalamic 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 $^{*}P < 0.05$, $^{**}P < 0.01$.

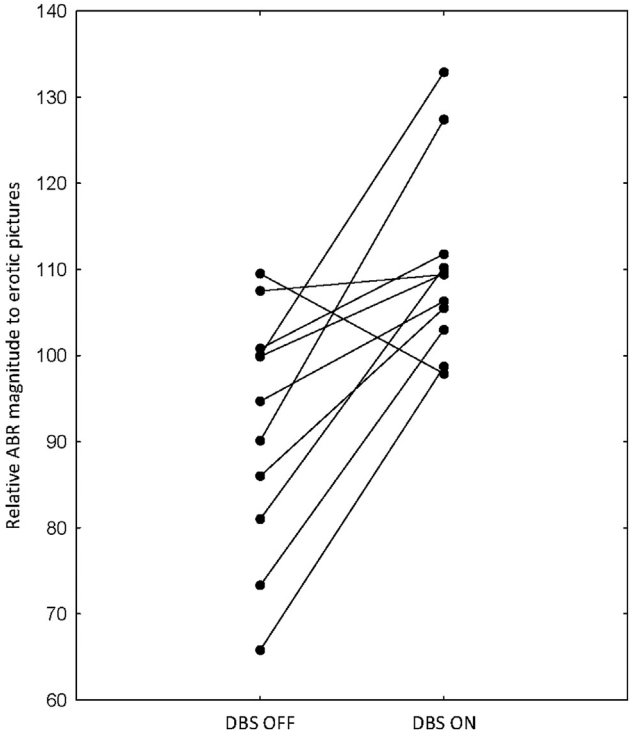

Figure 3. Relative magnitude of the acoustic blink reflex (ABR) in individual Parkinson's disease patients ($N = 11$) elicited during viewing of erotic pictures in subthalamic deep brain stimulation (STN DBS) OFF and ON conditions. In the STN DBS ON condition, there was an increase in ABR magnitude in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

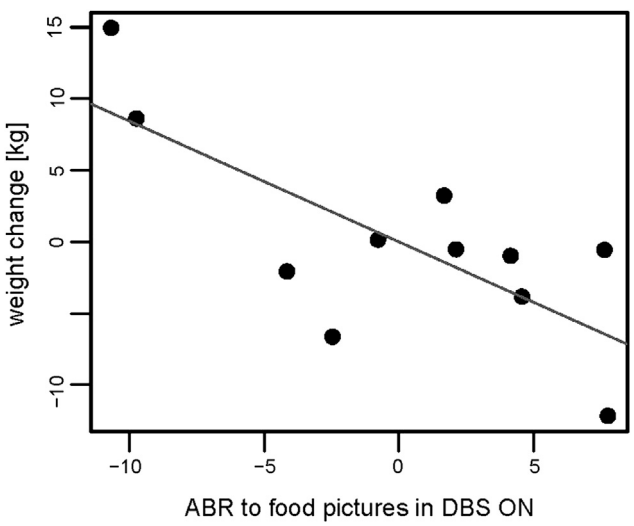

Figure 4. Partial correlation between acoustic blink reflex (ABR) magnitude to pictures of food in Parkinson's disease patients ($N = 11$) with deep brain stimulation of the subthalamic nucleus (STN DBS) ON, and body weight change after STN DBS implantation (kg), adjusted for ABR to pictures of food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

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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.

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

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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

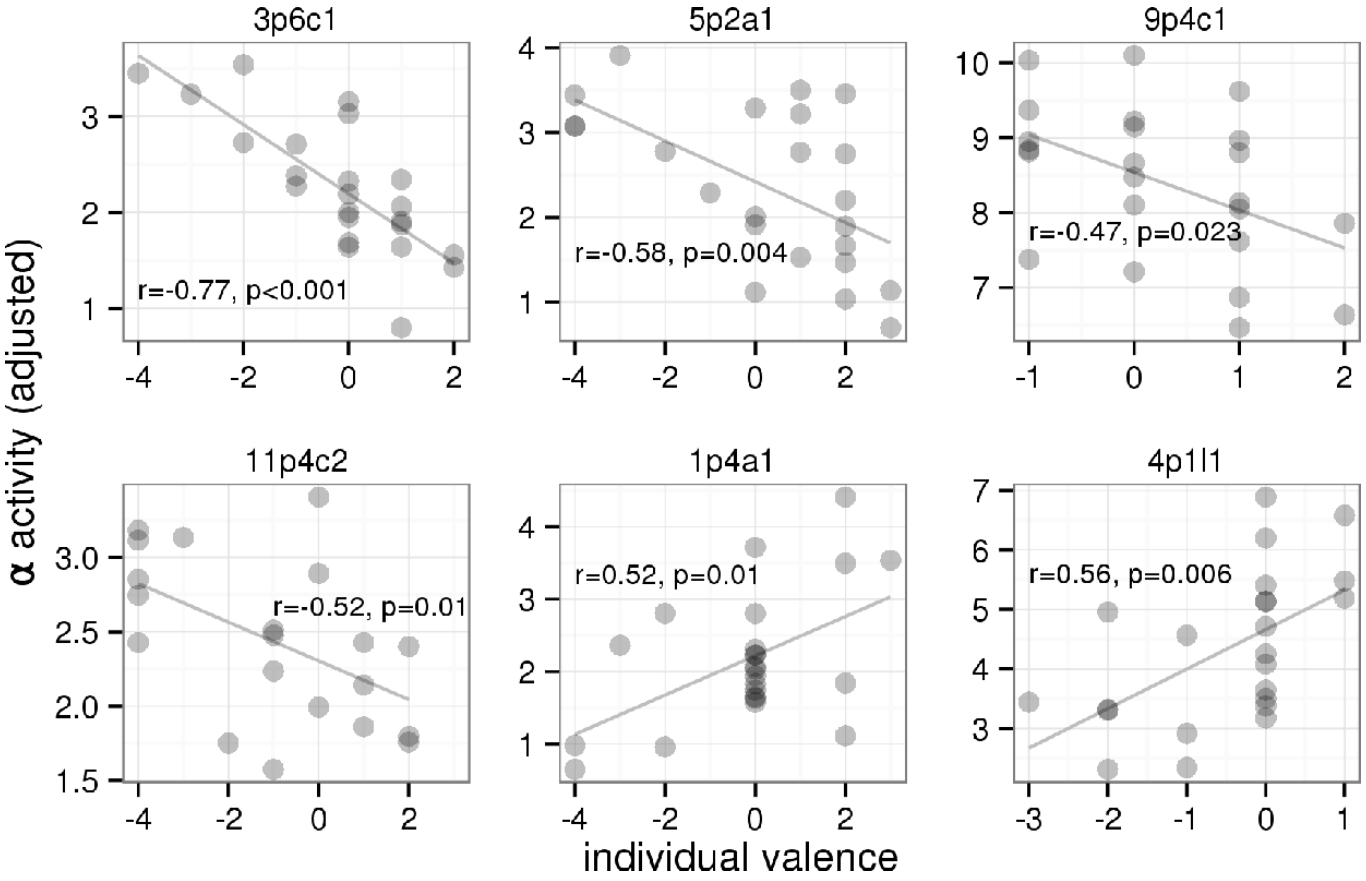

Fig. 1. The dependency of the single-neuron alpha band activity during picture presentation (PIC epochs in 500-2000 ms interval) on the individual valence ratings of the presented pictures in 6 neurons of the subthalamic nucleus in patients with Parkinson´s disease, for which the relationship was significant. 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

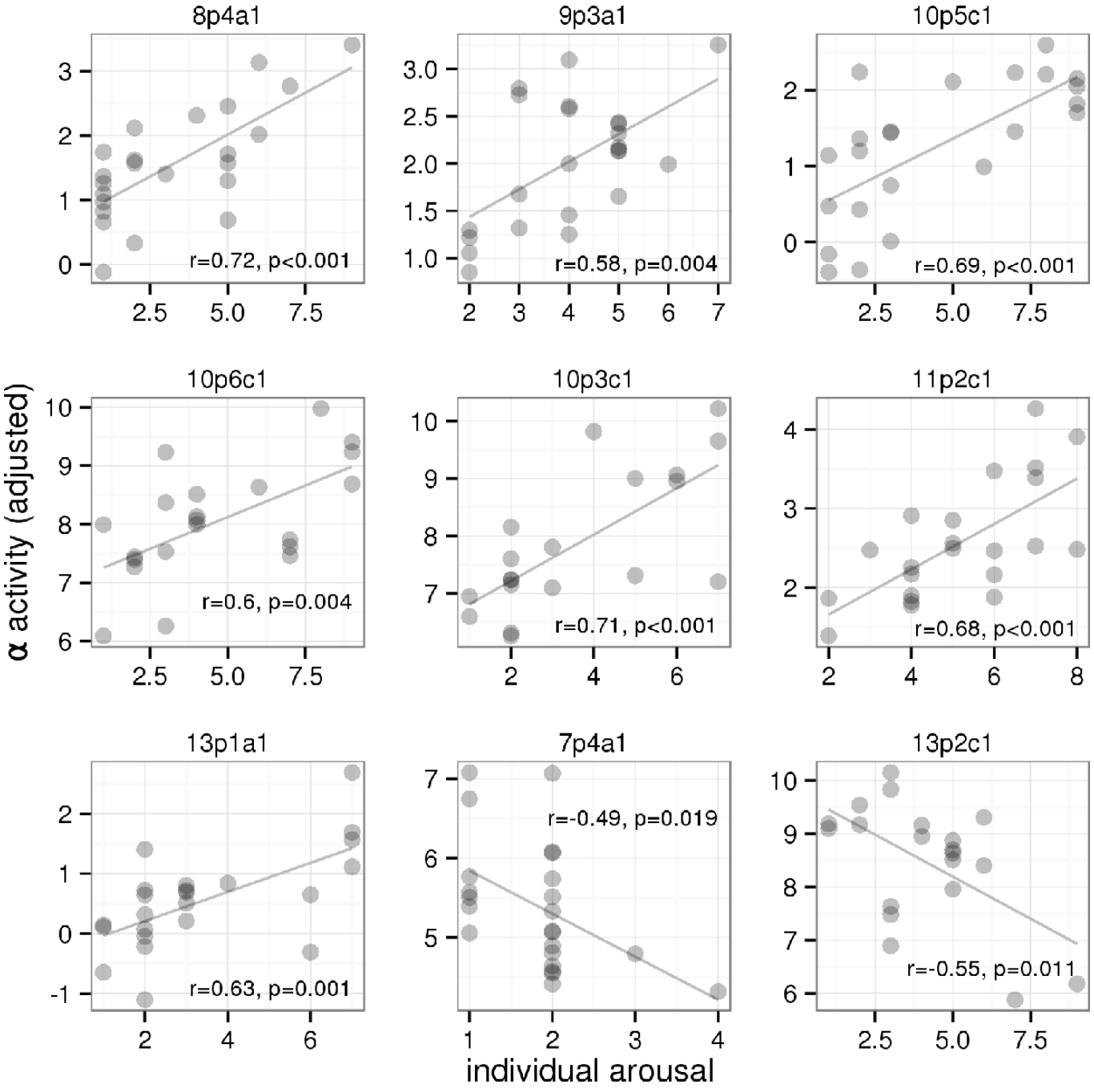

Fig. 2. The dependency of the single-neuron alpha band activity during picture presentation (PIC epochs in 500-2000 ms interval) on the individual arousal ratings of the presented pictures in 9 neurons of the subthalamic nucleus in patients with Parkinson´s disease, for which the dependency was significant. 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,

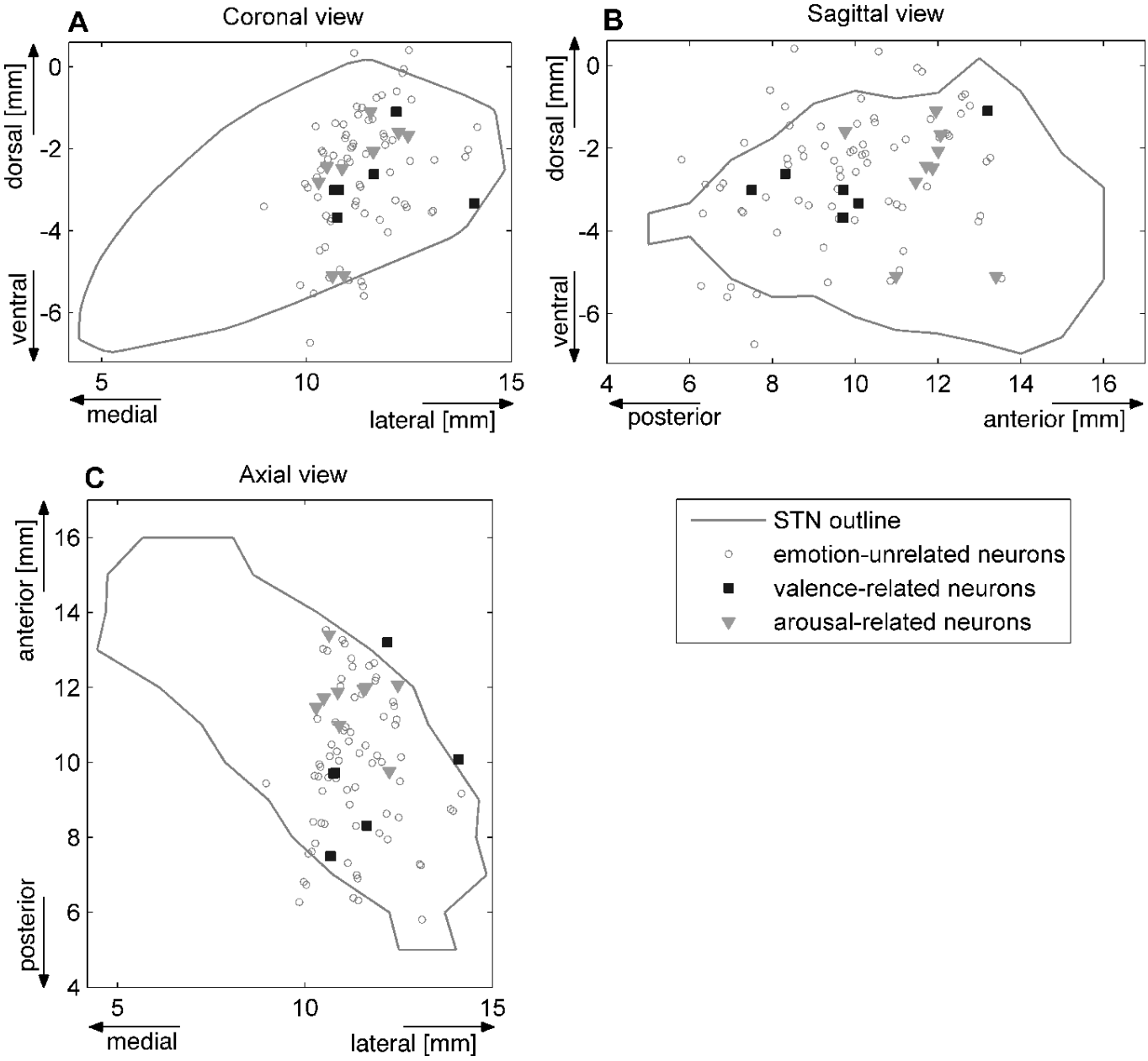

Fig. 3. Locations of STN neurons related to emotional content of the presented pictures in coronal (A), sagittal (B), and axial (C) view. The valence-related neurons were located more posteriorly compared to the arousal-related neurons.

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.

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