Univerzita Karlova v Praze

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Autoreferát disertační práce

The effects of deep brain stimulation of the subthalamic nucleus on emotional and motivational processing in Parkinson's disease patients

Vliv hluboké mozkové stimulace subthalamického jádra na emoční a motivační procesy u pacientů s Parkinsonovou nemocí

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Summary:

The mechanisms of weight gain or behavioral and affective changes known to occur in patients with Parkinson's disease (PD) treated with deep brain stimulation of the subthalamic nucleus (STN DBS) are incompletely understood. We hypothesize that some of these non-motor side-effects may be related to changes in motivational processing due to STN DBS. Motivational processing to appetitive and aversive stimuli can be assessed using subjective evaluation of emotional relevance (i.e. incentive salience attribution) or affective modulation of the auditory blink reflex (ABR). The latter provides an objective measure of changes in emotional reactivity: ABRs are physiologically potentiated by unpleasant and inhibited by pleasant stimuli, reflecting activation of the aversive and appetitive motivational systems.

Our aim was to assess the effects of STN DBS on motivational processing of pictures from 4 categories, two representing primary rewards, erotica and food, one aversive fearful and one neutral, using the subjective evaluation of motivational relevance (Study 1.) and the modulation of the ABR reactivity (Study 2.) in off-medicated PD patients with DBS switched ON and OFF. The results were compared with those obtained in healthy controls using the same paradigms.

Study 1. Twenty PD patients in bilateral STN DBS switched ON and OFF conditions and 18 matched controls rated total 84 selected pictures (21 from each category) according to emotional valence (unpleasantness / pleasantness) and arousal on two independent visual scales ranging from 1 to 9. The mean postoperative weight gain in PD group was 8.1±8kg. In STN DBS ON condition the PD patients attributed lower valence scores to the aversive pictures (i.e. pictures were rated as more aversive) compared to OFF condition and when compared to controls. The difference between OFF condition and controls was less pronounced. Furthermore, postoperative weight gain correlated with arousal ratings from the food pictures in STN DBS ON condition.

Study 2. The ABR elicited during the viewing of 30% out of the 84 selected pictures (i.e. 7 from each category) was recorded together with the subjective ratings of affective valence and arousal in 11 off-medicated PD patients with the STN DBS switched ON and OFF, and in 11 control subjects. The mean postoperative weight gain in PD group was 5.6±7kg. Aversive stimuli caused a larger increase in the ABR in patients in ON condition than in controls. The ABR to erotic stimuli was larger in patients in ON condition compared to OFF condition and controls. No detectable between-group differences in subjective ratings were found. In addition, the ABR magnitude to food pictures in ON condition showed a significant negative correlation with weight gain following STN DBS.

Both subjective and objective measures of STN DBS effects on motivational processing indicated that STN DBS may increase activation of the aversive motivational system. They also suggest that the postoperative weight gain may be related to changes in the processing of food cues due to STN DBS. In addition, STN DBS may disturb engagement of the appetitive motivational system by erotic cues, which is not reflected in subjective ratings.

Souhrn:

Mechanismus nárůstu hmotnosti nebo afektivních a behaviorálních změn, které se vyskytují u pacientů s Parkinsonovou nemocí (PN) léčených hlubokou mozkovou stimulací subthalamického jádra (DBS STN) je nejasný. Domnívali jsme se, že některé tyto nonmotorické vedlejší účinky mohou být způsobené ovlivněním motivačních procesů. Motivační procesy vyvolané příjemnými a nepříjemnými podněty mohou být subjektivně hodnoceny pomocí přisouzení motivační důležitosti podnětům nebo pomocí afektivní modulace úlekové reakce. Ta poskytuje objektivní míru změn v emoční reaktivitě: úleková reakce je fyziologicky zesílena nepříjemnými a oslabena příjemnými podněty, tyto změny odráží aktivaci averzivního a apetitivního motivačního systému.

Cílem naší práce bylo hodnocení vlivu DBS STN na motivační procesy vyvolané obrázky ze 4 různých kategorií: dvě zobrazující primární odměny erotiku a jídlo, averzivní podněty (hrozby a oběti) a neutrální pomocí subjektivních přisouzení motivační důležitosti prezentovaným podnětům (Studie 1.) a pomocí modulace akustického blink reflexu (ABR) (Studie 2.) u pacientů s PN po celonočním vysazení dopaminergní medikace ve stavu s se zapnutou (DBS ON) a vypnutou (DBS OFF) stimulací. Výsledky byly porovnány s výsledky získanými u kontrol.

Studie 1. 20 pacientů s PN a 18 vázaných kontrol hodnotilo u celkem 84 obrázků (21 z každé kategorie) ve stavu DBS ON a DBS OFF emoční valenci (příjemnost/nepříjemnost) a arousal na dvou nezávislých vizuálních škálách v rozmezí od 1 do 9. Průměrný pooperační nárůst hmotnosti byl u pacientů 8±8 kg. V ON stavu pacienti přisoudili averzivním obrázkům nižší skóre valence (obrázky byly hodnoceny jako více averzivní) než v OFF stavu i než kontroly. Rozdíl mezi OFF stavem a kontrolami byl méně vyjádřen. Pooperační nárůst hmotnosti koreloval s hodnocením arousalu obrázků jídla v ON stavu.

Studie 2. ABR vyvolaný během prohlížení u 30% obrázků z celkem 84 obrázků (t.j. u 7 z každé kategorie) byl zaznamenán spolu s hodnoceními emoční valence a arousalu u 11 pacientů ve stavu DBS ON a DBS OFF a u 11 kontrol. Průměrný pooperační nárůst hmotnosti pacientů byl 5.6± 7kg. Averzivní podněty vyvolaly větší ABR u pacientů u ON stavu než u kontrol. V ON stavu byly ABR vyvolané během prohlížení erotických obrázků větší než v OFF stavu a než u kontrol. Nebyly zaznamenány žádné změny v subjektivních hodnoceních valence a arousalu. Velikost ABR při prohlížení obrázků jídla v ON stavu významně negativně korelovala s pooperačním váhovým příbytkem po zavedení DBS STN.

Výsledky subjektivních i objektivních hodnocení vlivu DBS STN na motivační procesy poukazují na možné zvýšení averzivní aktivace vlivem DBS. Dále tyto výsledky svědčí pro možnou souvislost pooperačního nárůstu hmotnosti se změnami v procesování podnětů spojených s jídlem (se zvýšenou motivací k jídlu) vlivem DBS STN. Zdá se také, že DBS STN může vést k poruše aktivace apetitivního motivačního systému erotickými podněty, která se nemusí odrazit v subjektivních hodnoceních.

I. INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder characterized by slowness of voluntary movement and resting tremor, rigidity or postural instability.(Halliday *et al.*, 2011)

The hallmark of PD is the response of motor symptoms to dopaminergic drugs with levodopa being still the most effective treatment available. Most patients however will notice a gradual increase in symptoms over time despite treatment. As the disease progresses the dose increase is required and patients on long-term levodopa therapy develop fluctuations in motor symptom control throughout the day in response to medication. Other motor complications following long-term levodopa treatment are involuntary choreiform or dystonic movements called dyskinesias. In advanced stages, dyskinesias can be troublesome and treatment may be difficult.(Voon *et al.*, 2009)

In advanced stages of severe levodopa-responsive forms of PD bilateral high-frequency deep brain stimulation stimulation (DBS) of the subthalamic nucleus (STN) can reduce motor disability and levodopa-related complication.For chronic stimulation a permanent lead is sterotacticaly implanted subcutaneously into the target area within the brain and connected to a fully implanted neurostimulation device. The stimulator settings can be adjusted telemetrically (Volkmann, 2007). Despite the remarkable therapeutic efficacy, the mechanisms of DBS effects are still not completely understood. (Johnson *et al.*, 2008) Beside the motor symptoms improvement, STN DBS treated patients can develop several neuropsychiatric side complications. The most common psychiatric symptoms following STN stimulation surgery are apathy, changes in emotional reactivity, depression, and hypomania. (Voon *et al.*, 2006) In addition, despite motor improvement and improvements of activities of daily living and quality of life, the social adjustment does not improve affecting the patient`s relations with themselves and their social interactions. (Schupbach *et al.*, 2006, Volkmann *et al.*, 2009) Weight gain has been also reported as common non-motor side effect of STN DBS. (Aziz *et al.*, 2008, Montaurier *et al.*, 2007) In our retrospective survey on weight changes in 23 PD patients treated with DBS STN there was a mean increase 9.4 kg (from 1 to 25 kg) during 1 to 45 months after DBS, weight gain was found in all patients comparing to pre-DBS period.(Novakova *et al.*, 2007) Suggested explanations of body weight gain after DBS STN include a reduction of energy output related to elimination of dyskinesias, improved alimentation or direct influence on function of lateral hypothalamus by DBS STN.(Rieu *et al.*, 2011)

Evidence on processing of non-motor information within STN from studies on effects of STN lesions and high frequency DBS in research animals and STN DBS treated PD patients and

he scrutiny of anatomic connectivity of the STN suggest an interesting position at the nexus of motor, associative, and limbic pathways with potentially integrative function of this nucleus. Anatomical data confirming that STN is part of the limbic loop involving the prefrontal cortex, the nucleus accumbens, and the ventral pallidum suggest that STN should be involved in the processing of motivational information. The role of STN in emotional and motivational processing was demonstrated in neurophysiological studies in monkeys and in PD patients.(Brucke *et al.*, 2007, Darbaky *et al.*, 2005, Kuhn *et al.*, 2005) The motivation for food 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. (Baunez *et al.*, 2007, Rouaud *et al.*) The changes in motivation of STN DBS treated PD patients however have been studied mainly with regard to apathy(Thobois *et al.*) and motor learning(Sauleau *et al.*, 2009) so far. The effects of STN DBS on emotional processing have been studied mostly in terms of emotion recognition. There are several studies reporting that STN DBS induced impaired facial expression recognition selective for negative emotions (Drapier *et al.*, 2008, Dujardin *et al.*, 2004, Schroeder *et al.*, 2004) and reduced differentiation and self-reported intensity of negative feelings induced by film excerpts.(Vicente *et al.*, 2009) One study with on-off study design using mood-induction procedure demonstrated that STN DBS may enhance emotional processing. (Schneider *et al.*, 2003)

In general, the precise mechanisms of the non-motor complications still remain unclear. The STN DBS effects might not necessarily be direct effects, as there are changes in medication after surgery. Other factors that may play a role include preoperative vulnerability, surgical effects, underlying PD-related factors, and psychosocial effects.(Voon *et al.*, 2009)

According to the theoretical model of emotion, emotions are products of Darwinian evolution. Expressed emotions developed from primitive actions that facilitated the survival of species and individuals. In man, the evolved emotions are best characterized as motivationally tuned states of readiness. They are constituted by a patterned collection of chemical and neural responses that the brain produces when it detects the presence of an emotionally competent stimulus (an object or a situation actually perceived or recalled from memory). These responses alter the state of the internal milieu, the state of viscera and the musculoskeletal system and lead a body now prepared into carrying out varied actions or complex behaviors. The physiologic changes that occur during an emotion are mapped in the appropriate body-sensing regions of the brain. The mental events that are associated with this neural mapping of the body state are the essence of what we call feelings. Feelings are the mental representation of the physiologic changes that occur during an emotion. They provide the organism with a

mental alert for the significance of the stimulus that caused the emotion and for the thoughts consequent to responding emotionally. The processing of the stimulus may be conscious or non-conscious, but in either case the responses are produced automatically(Damasio, 2004). Motivation for action is one of the key aspects of emotions. When motivation is aroused, action does or does not ensue, depending on emotion control or regulation, on the availability of resources and a meaningful action repertoire, on the acceptability of the available actions, and on the importance of the emotional event or its effects.(Fridja, 2004) Adaptive behaviors require a combination of stimulus appraisal, associative learning, and the ability to develop appropriate action plans and inhibit inappropriate choices on the basis of earlier experience. Reward is a central component for driving incentive-based learning, appropriate responses to stimuli, and the development of goal directed behaviors.(Haber and Knutson, 2010)

It has been also proposed, that the evolutionary foundation of emotion has a simpler, two-factor motivational organization. That is, emotion is considered here to be fundamentally organized around two motivational systems, one appetitive and one defensive. These systems are implemented by neural circuits in the brain, presumably with common outputs to structures mediating the somatic and autonomic physiological systems involved in attention and action. (Bradley *et al.*, 2001) Each of the two motivational systems can vary in terms of activation or arousal. That is, the motivational system determines the general behavioral strategy, defense or appetitive acquisition. The specific somatic and autonomic patterns of affective responding are tactical and adaptive, in that they are formed by the behavioral context.

The multivariate studies demonstrated that the principal variance in emotional meaning is accounted for by two predominant factors, affective valence (ranging from attraction and pleasure to aversion and displeasure) and arousal (from calm to aroused). In the current view, these factors are seen as reflecting motivational activation.(Bradley *et al.*, 2001)

In the laboratory emotional functioning can be assessed by presenting the individual with a standardized or personally tailored emotion-eliciting stimulus and assessing the processes that are included in the emotional processing.

Visually presented emotional material such emotionally evocative pictures have been perhaps most frequently used for emotion elicitation. The International Affective Picture System (IAPS) is a frequently used, large set of standardized emotionally evocative color photographs, which has been proven to activate either appetitive or aversive motivational functions.(Lang and Bradley, 2008) At conscious level, these activations can be expressed in subjective ratings along the dimension of emotional valence and emotional arousal or

intensity as personal relevance appraisal (incentive salience attribution).(Bradley *et al.*, 2001, Phan *et al.*, 2004)

Emotional response can be quantified in terms of changes in emotional expressive behavior and peripheral physiology.(Sequeira *et al.*, 2009). The startle reflex is a defensive reflex that is elicited in mammals by an abrupt sensory event. It consists in a chained series of rapid flexor movements that cascade throughout the body. 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(Vrana *et al.*, 1988). The startle reflex has been used to indicate which of the separable motivational systems, the appetitive or the defensive, is engaged (Bradley *et al.*, 2001).The startle modulation by food cues can be used to examine reactivity to food cues(Drobes *et al.*, 2001) and food craving(Hawk *et al.*, 2004), which is known to be relevant risk factor for weight gain.

II. **Hypothesis**

1. We hypothesized that STN DBS might alter the emotional and motivational processing of primary rewards and aversive stimuli in PD patients and that some of the non-motor side-effect in STN DBS treated PD patients such as emotional and behavioral disturbances and/or weight gain known to occur may be related to these motivational changes.
2. We hypothesized that the human STN is involved in motivational processing of primary rewards and aversive stimuli.

III. Aim of the study

In order to examine changes in activation of the appetitive motivational system we focused on the possible STN DBS-related effects on processing of pictures containing food or erotic material as they represent the two primary rewards and high sensitivity to rewards was found to be related to eating behaviors that contribute to excess body weight.(Davis *et al.*, 2007) Similarly, changes in activation of the aversive motivational system were analyzed from the perspective of two categories of aversive fearful stimuli – pictures of threats of aggression and pictures of victims of destructive or injurious actions.

1. The aim of the first study was to examine effects of the STN DBS on incentive salience attribution (i.e. attribution of motivational relevance) to rewarding and aversive stimuli. We compared ratings of pictures representing primary rewards and

aversive stimuli in a group of PD patients with DBS switched ON and OFF and in healthy controls.

2. The aim of the second study was the objective assessment of behavior such as startle reflex modulation by emotional stimuli which can provide useful information about underlying emotional processes in ways that are relatively free of demand characteristics and reporting biases. We compared the effects of STN DBS on modulation of the acoustic blink reflex (ABR) reactivity to pictures presenting rewarding and aversive stimuli in PD patients with DBS switched ON and OFF. The results were compared with those obtained in healthy controls using the same paradigm.

IV. STN DBS EFFECTS ON INCENTIVE SALIENCE ATTRIBUTION TO REWARDING AND AVERSIVE STIMULI (STUDY 1.)

4.1. Materials and methods

Twenty PD patients (mean age(SD), 58.3(6)) treated with bilateral STN DBS for motor fluctuations and/or dyskinesias and 18 matched controls (mean age(SD), 56.1(7)), all males were included in the study. Patients and controls were screened for their cognitive status and depression. Body weight in the PD group as measured within the last week before surgery was recorded from the documentation and again it was measured on the day of the study.

We selected a total of 84 pictures from the IAPS. 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. Three different picture orders were created with maximally two pictures from the same category presented in sequence. 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 two hours in order to reduce some of the longer-lasting effects of stimulation. Patients were pseudorandomly tested in two conditions DBS ON and DBS OFF using different picture order for each condition. The testing was performed one hour after the stimulators were switched OFF or ON. Healthy controls were tested once, using proportionally the same sets of picture order.

Each picture was presented on the touch sensitive screen for a period of 6s. Subjects were required to rate each picture separately along the dimension of emotional valence and arousal by touching the appropriate symbol on two independent visual scales that were presented on the screen after the picture offset. 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.

4.2. Analysis

For data analysis, non-parametric tests were applied, the Kruskal-Wallis test was used to analyze differences in valence and arousal between conditions and groups of subjects. The Mann-Whitney U test (to compare groups of subjects) and Wilcoxon signed-rank test (to compare DBS OFF and ON conditions) were used for post hoc analysis. Parameters with normal distribution were analyzed by Pearson correlation and partial correlation analysis. Bonferroni correction of multiple comparisons was used whenever appropriate.

4.3. Results

Affective ratings

i) Between groups and condition comparison:

The valence comparison for each of the four categories of the IAPS pictures revealed that only aversive pictures yielded significant differences among DBS conditions and/or groups of subjects (χ^2=7.4, P<0.05 corrected). No differences in valence ratings were found for the other picture categories (Figure 1). Post-hoc analyses disclosed that in the DBS ON condition, patients rated the valence of aversive pictures significantly lower compared to the DBS OFF condition (Z=2.7, P<0.01) and compared to the control group (Z=2.5, P<0.01). 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<0.05).

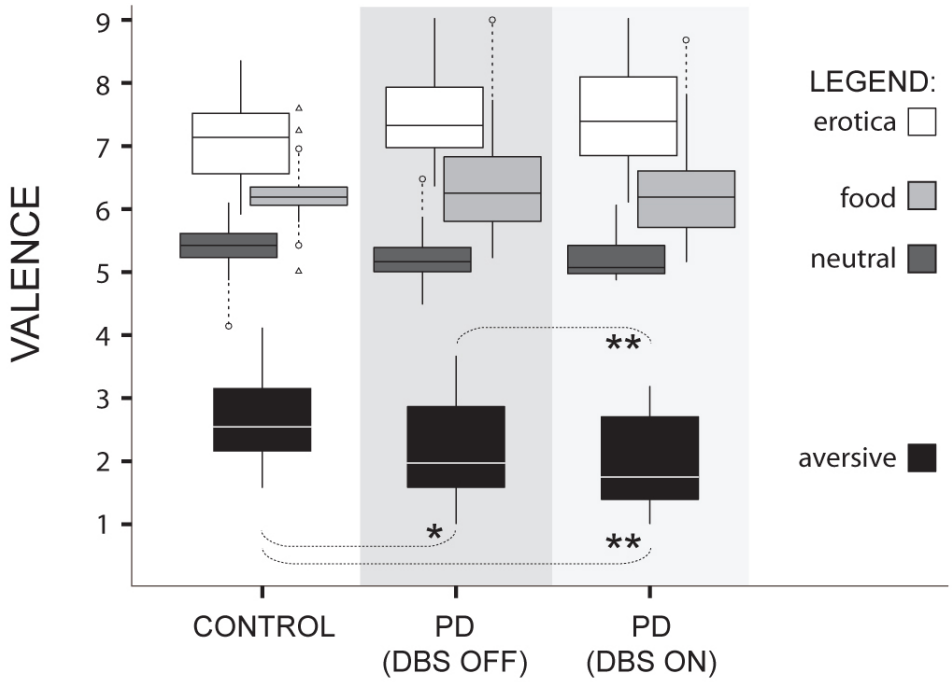

*Figure 1.Valence of selected pictures from four different categories (erotic, food, neutral, aversive content) as rated by controls (N=18) and PD patients (N=20) in conditions with the STN DBS switched OFF and ON. The only difference between conditions/groups of subjects was found for valence of pictures with the aversive content (*P<0.05, **P<0.01).*

Between the two sub-categories of aversive pictures, the pictures of victims elicited stronger effects in the post-hoc tests (conditions: Z=2.4, P<0.05; groups: Z=2.5, P<0.01) than the pictures of threats (conditions: n.s.; groups: Z=2.2, P<0.05) (Figure 2).

*Figure 2. Valence of two sub-categories of the pictures with aversive content as rated by controls (N=18) and PD patients (N=20) in conditions with the STN DBS switched OFF and ON. The victim pictures elicited more significant differences in valence between conditions/groups than the threat pictures (*P<0.05, **P<0.01)*

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<0.01). No other differences in arousal were detected by post hoc tests. There were 12 patients tested in OFF condition first (i.e. with STN DBS washout for 3 hours before testing in OFF condition) and 8 patients tested in ON condition first (STN DBS washout for 1 hour before testing in OFF condition). Within group post-hoc analyses demonstrated a significant effect of the order, as the changes in valence (Z=2.9, P<0.01) and arousal (Z=2.2, P<0.05) of aversive pictures were significant only for group of patients tested first in the OFF condition (N=12).

ii) Between picture category comparison:

Pictures of victims always had the highest mean arousal scores (P<0.0001 corrected) and showed a higher difference of valence scores from the valence of neutral pictures (p<0.0001 corrected) than those in the other categories (erotica, threat).

iii) Body weight change and affective ratings:

The mean body weight of patients increased postoperatively to 91.5±11 kg from preoperative weight of 83.4±14 kg (Z=3.6, P<0.001).

The weight change correlated positively with arousal ratings of food pictures in the DBS ON condition (r=0.69, P<0.01 corrected).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<0.05 corrected) (Figure 3.). In addition, the effect of order was analyzed post hoc and the partial correlation was found significant (r=0.61, P<0.05) only in the group of patient tested in the DBS OFF condition first (N=12).

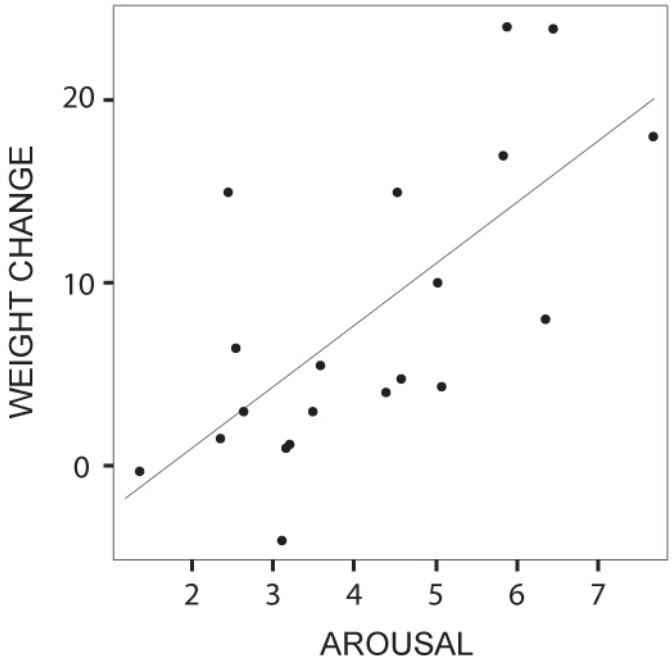

Figure 3. Correlation between the arousal of the food pictures rated by PD patients (N=20) with the STN DBS switched ON and the body weight change (kg) before/after STN DBS implantation.

4.4. Discussion

Our findings support the hypothesis that STN DBS influences the incentive salience attribution (i.e. 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 to OFF condition and to the controls. The change in valence ratings of aversive pictures due to STN DBS was demonstrated only for pictures of

victims and not threats. Findings from several fMRI studies implicated the existence of distinct neural substrates of disgust-relevant categories such as contamination and mutilation.(Wright *et al.*, 2004) Therefore one possible explanation could be a selective effect of DBS on structures involved in processing this content category. Nevertheless, other imaging and neurophysiological studies indicated the existence of a common subcortical network involved in the incentive salience attribution processing involving the mesolimbic dopamine system (Berridge, 2007, Phan *et al.*, 2004) and suggested the influence of arousal level on affective and motivational physiological responses.(Miller *et al.*, 2009) 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. This is in line with the finding that the mesolimbic dopamine system responds to both rewarding and aversive stimuli that are of high intensity.(Faure *et al.*, 2008, Horvitz, 2000)

The difference between valence and arousal ratings of aversive pictures in 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 one hour is insufficiently short compared to 3 hours 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.

For the appetitive stimuli the evidence of STN DBS influence on incentive salience attribution is rather indirect. While we could not find any conscious change in subjective ratings of appetitive stimuli due to the STN DBS, partial correlation analysis showed that patients with 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 due to STN DBS. This is in line with evidence from animal studies that STN DBS and STN lesions increased motivation for food.(Baunez *et al.*, 2002, Rouaud *et al.*) 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.(Vitek, 2008) In animals, STN DBS has been found to increase

activity of the dopamine system (Shon *et al.*, 2010) 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) and ventral pallidum(Parent and Hazrati, 1995) or by activating directly the mesolimbic dopaminergic projections from VTA to nucleus accumbens that are running within the adjacent medial forebrain bundle. (Vitek, 2008)

V. THE EFFECTS OF STN DBS ON MODULATION OF THE ACOUSTIC STARTLE RESPONSE BY REWARDING AND AVERSIVE STIMULI (STUDY II.)

5.1. Materials and Methods

Eleven PD patients (mean age (SD), 56.3(5)) treated with bilateral STN DBS for motor fluctuations and/or dyskinesias and 11 matched controls (mean age(SD), 54.4(8)), all males were included in the study. Patients and controls were screened for cognitive status and depression. Body weight in the PD group as measured within the last week before surgery was recorded from the documentation and again it was measured on the day of the study.

We used selection of 84 pictures from the International Affective Picture System (IAPS) involving 4 different categories as described in study 1.(Lang and Bradley, 2008)

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 two hours in order to reduce some of the longer-lasting effects of stimulation. Patients were pseudorandomly tested in two conditions DBS ON and DBS OFF using different picture order for each condition. The testing was performed one hour after the stimulators were switched OFF or ON. Healthy controls were tested once, using proportionally the same sets of picture order.

The participants were seated 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. Each picture out of 84 was presented for a period of 6 seconds and consequently rated by the participant as described in study 1. 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 pseudo-randomly 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 white cross in the center, with the SAS presented at random intervals of 10-16 seconds, 12 of them prior to the

beginning of the affective task and 3 additional were interspersed between the pictures presentation. Picture presentation and rating, variable SAS delivery and acquisition of physiologic data were performed by custom software.

Electromyographic (EMG) activity was recorded using Medelec Synergy (Oxford Instruments, Surrey, UK).Large artifacts related to monopolar STN DBS were removed by subtracting artifact templates in the spectral domain (Figure 1.).

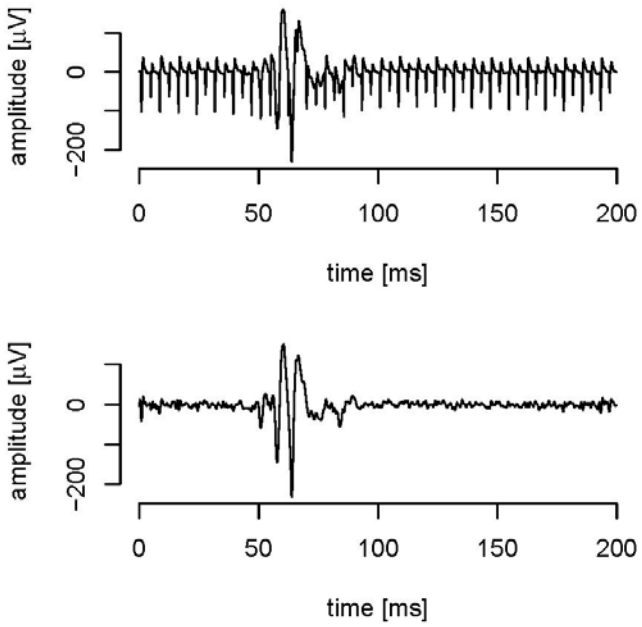

Figure 1. Recording of ABR from the orbicularis oculi muscle in DBS ON condition with an artifact related to monopolar STN DBS (top). The same recording after removal of the artifact by means of artifact template removal in spectral domain (bottom).

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 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. For further analyses, ABR magnitude from every trial was expressed in standardized t-scores to remove effects of inter-subject variability (Bradley *et al.*, 2001).

5.2. Analysis

For inter-group comparisons in which repeated measurements were available (PD patients versus controls; DBS ON versus 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. Parameters following normal distribution were subject to Pearson correlation and partial correlation analysis. The Bonferroni correction for multiple comparisons was used whenever appropriate.

5.3. Results

Affect modulated ABR magnitude

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) and than controls ($P<0.01$ corrected) (Figure 2). The increase in ABR magnitude in the DBS ON relative to the DBS OFF condition was observed in 10 out of 11 patients.

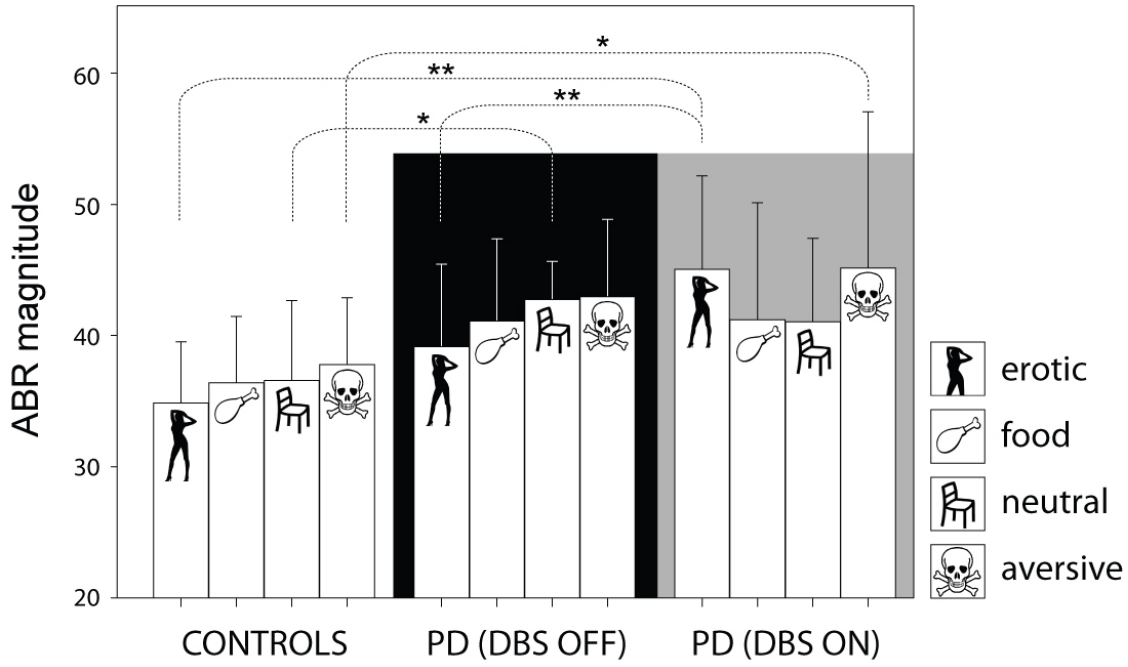

*Figure2. Magnitude of the ABR (in t-scores) presented during viewing of erotic, food, neutral, and aversive pictures from control subjects (N=11) and PD patients (N=11) in conditions with STN DBS OFF and ON. In the DBS ON condition, the physiological pattern of ABR modulation with inhibition to erotic pictures was lost and the ABR magnitude to erotic pictures were potentiated as if aversive. Corrected significance level *P<0.05, **P<0.01.*

Affective ratings

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

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)($P<0.05$).

Postoperative weight gain was negatively correlated with ABR magnitude to food pictures in the DBS ON condition ($r=-0.75$, 9 df,$P<0.01$). The correlation was significant even after suppressing the effect of the DBS OFF condition by partial correlation analysis ($r= -0.74$, 9 df, $P<0.01$) (see figure 3). Postoperative weight gain correlated positively with the intensity rating of food pictures ($r=0.70$, 9 df, $P<0.05$).

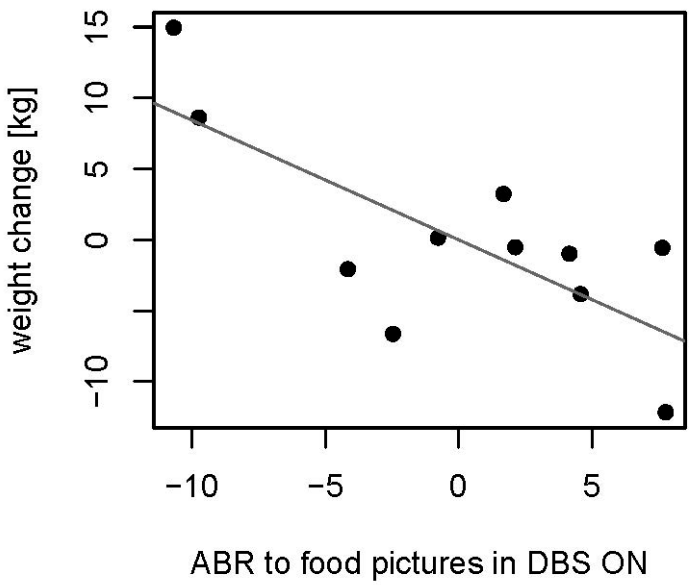

Figure 3. Partial correlation between ABR magnitude to pictures of food in Parkinson´s disease patients (N=11) with STN DBS ON, and body weight change after STN DBS implantation (kg), adjusted for ABR to pictures of food with STN DBS OFF.

5.4. Discussion

In the present study we observed changes in the affective modulation of the ABR due to STN DBS, which support our hypothesis that STN DBS modifies the emotional and motivational processing of primary reward cues and aversive stimuli. Due to succesfull removal of the

artifact related to monopolar DBS the patients were examined in their long-term therapeutic setting.

During viewing of affect-weighted pictures, ABRs are facilitated by aversive and inhibited by appetitive picture contents.(Vrana *et al.*, 1988) In our study the control subjects and PD patients in the OFF medication/OFF stimulation condition presented with the characteristic physiological pattern of modulation by aversive, appetitive and neutral stimuli, except in the DBS ON condition, in which the ABR was paradoxically potentiated by erotic stimuli. Similarly, ABR potentiation by pleasant pictures was reported in patients with severe depression(Allen *et al.*, 1999) and in patients with psychogenic movement disorder.(Seignourel *et al.*, 2007) The explanation for all these observations remains hypothetical, suggesting engagement of the aversive motivational system instead of the appetitive one. Furthermore, the ABR modulated by aversive stimuli was relatively larger in DBS ON than in controls, also suggesting an increased aversive engagement. Changes in motivational activation 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 our first study on 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. We suggest that abnormalities in brain structures, their functional connectivity or changes in emotion regulation processes could account for disordered reactivity of the ABR to pleasant or aversive pictures in various conditions.(Leppanen, 2006, Voon *et al.*, 2010) Interestingly enough, the extent of ABR inhibition by food pictures and their arousal ratings correlated with postoperative weight gain, suggesting increased appetitive motivational engagement by food cues in the DBS ON condition in patients with postoperative weight gain. This finding is consistent with increased motivation for food found in experimental animals after STN DBS (Rouaud *et al.*) and suggests that postoperative weight gain may be related to changes in the processing of food cues.

The affective modulation of ABR was caused by high frequency stimulation of the STN in PD patients who showed a normal pattern of startle reactivity when DBS was switched OFF. Recent studies on DBS mechanisms 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,(Vitek, 2008) which natural activity is replaced by a more regular, high

frequency activity that is time-locked to the stimulus.(Johnson *et al.*, 2008) These complex mechanisms may account for interference of STN DBS with the emotional and motivational processing 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(Parent and Hazrati, 1995) and the primary startle circuit, and are also known to mediate the affective modulation of the ABR.(Koch, 1999) It has been already demonstrated that STN DBS may modify activity of the amygdala during affective tasks in humans.(Le Jeune *et al.*, 2008)

Both appetitive and fearful motivation involve interaction between dopaminergic and different glutamatergic inputs (from the amygdala and the prefrontal cortex) that converge on nucleus accumbens in overlapping mesocorticolimbic circuits.(Humphries and Prescott, 2010) The STN DBS interactions with the ventral basal ganglia circuits including the non-physiological release of the mesolimbic dopamine (Shon *et al.*, 2010) may be therefore 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 pedunculopontine nucleus and the primary startle circuit as it was demonstrated for prepulse inhibition of the ABR.(Costa *et al.*, 2006)

VI. Conclusions

This is the first study on effects of the STN DBS on emotional and motivational processing of primary reward cues and aversive stimuli in PD patients.

We assume that our results support the hypothesis that STN DBS affects motivational processing in PD patients. Both the subjective and the objective measures suggest STN DBS increases activation of the aversive motivational system in a way that more emotional relevance is attributed to fearful aversive stimuli and the startle potentiation by aversive stimuli is increased. Additionally, STN DBS seems to disrupt physiological inhibition of ABR by appetitive (erotic) cues. These may be experienced as frustrative nonreward despite their positive subjective ratings. 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,(Schupbach *et al.*, 2006) mainly when they are in discrepancy with subjective evaluations. 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.

Additionally, both studies further support the second hypothesis that the human STN is involved in emotional and motivational processing of primary rewards and aversive stimuli, which may potentially influence food intake behavior and social interactions.

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Publications:

(Cumulative IF 13.8)

Original articles related to the Thesis:

1. **Serranova T**, Sieger T, Dusek P, Ruzicka F, Urgosik D, Ruzicka E, Valls-Sole J, Jech R. Subthalamic stimulation affects startle response modulation by reward cues in Parkinson's disease. Mov Disord. Under review.

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