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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

Disertační práce

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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 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 differences in subjective ratings were found. In addition, the ABR magnitude to food pictures in ON condition showed a significant negative correlation with postoperative weight gain.

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.

OBSAH

I. INTRODUCTION

1.1. Parkinson's disease

1.1.1. Parkinson's disease: motor and non-motor symptoms

Parkinson's disease is a neurodegenerative disorder that leads to very specific disturbance of movement, characterized by slowness of initiation of voluntary movement with a progressive reduction in speed and amplitude of sequential motor tasks.(Halliday *et al.*, 2011)

Other cardinal signs of PD related to motor dysfunction are resting tremor, rigidity and postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction. There is no diagnostic test for PD, and the diagnosis is made on clinical grounds. A set of well-validated criteria (the United Kingdom Parkinson's disease Society Brain Bank Clinical Criteria) exists to assist in the clinical diagnosis of PD and have a specificity of 98.1% and sensitivity of 90.4%.(Hughes *et al.*, 1992)

The pathological confirmation of PD consists in finding of severe selective loss of the dopaminergic neurons of the pars compacta of the substantia nigra with the presence of Lewy bodies composed of aggregates of a-synuclein and Lewy neuritis in specific regions of the nervous system.(Dickson *et al.*, 2009)

Damage to the substantia nigra is recognized as a hallmark of PD and is probably the major cause of motor symptoms. The motor symptoms do not develop until about 50–60% of the nigral neurons are lost and about 80–85% of the dopamine content of the striatum is depleted.(Marsden, 1996)

However, in the last 25 years it has been confirmed that pathological lesions are much more extensive and involve a number of ascending projection pathways in the brainstem and areas of the neocortex that may precede the damage to the substantia nigra and have been related to a variety of non-motor manifestations. (Braak *et al.*, 2002, Hawkes *et al.*, 2010, Jellinger, 2010) These include neuropsychiatric symptoms such anxiety, depression and apathy, and dysautonomic symptoms such as postural hypotension and constipation, sleep disturbances such as REM sleep behavior disorder and periodic limb movements of sleep, sensory symptoms such as paresthesias, cramps and other disorders such as

olfactory dysfunction, and seborrheic dermatitis. As the disease progresses, decreased cognitive ability may appear. (Chaudhuri and Schapira, 2009)

Numerous studies have revealed that patients with PD lose weight and have a lower body weight when compared to matched control populations which can be ascribed, primarily, to a loss of fat tissue.(Bachmann and Trenkwalder, 2006) A recent large-scale prospective study showed that weight loss in PD patients is a continuous, progressive process, which commences years before a formal diagnosis is made, and cannot be ascribed to a decreased energy intake.(Chen *et al.*, 2003) Treatment with levodopa also seems to affect the body weight. The 2-year prospective study conducted by Palhagen and colleges showed a modest body weight loss before patients begin L-dopa treatment (1.1 kg versus control) that becomes significant after 2 years of L-dopa therapy (5.6 kg versus control). The mechanisms involved remain unknown.(Palhagen *et al.*, 2005)

1.1.2. Emotional and motivational changes in PD

In addition to mood disturbances, changes in emotional processing such as blunted facial expressivity and mild deficits in appraising emotional prosody and facial expressions have also been described. (Blonder *et al.*, 1989, Borod *et al.*, 1990, Dujardin *et al.*, 2004, Jacobs *et al.*, 1995, Suzuki *et al.*, 2006) The precise mechanisms for these various emotional changes remain unknown, but they seem to be related to neurotransmitter-induced alterations in limbic (amygdala, ventral striatum, anterior cingulate), cortical, and subcortical regions that are integral parts of the fronto-striatal and mesolimbic circuitry.(Alexander *et al.*, 1986) Studies on affective modulation of the acoustic blink reflex showed blunted reactivity to aversive stimuli in PD patients on-medication. This impairment seemed to be selective for mutilation pictures relative to other types of aversive stimuli as suggested another study in off-medicated PD patients.(Bowers *et al.*, 2006, Miller *et al.*, 2009)

The abnormalities of motivational processes have been studies mainly in terms of apathy. It seems to be related to neuronal loss within the mesolimbic dopaminergic system and may preceed the development of the motor symptoms.(Chaudhuri *et al.*, 2011) PD patients have also an impaired in explicit and implicit reinforcement associated learning and in „sensitivity to reward“ flexibility in comparison to the controls.(Czernecki *et al.*, 2002)

The dopamine dysregulation syndrom (addiction to the dopaminergic medication) and the impulse control disorder (such as pathological gambling) are can occur in PD patients with dopaminergic treatment. The disruption of the dopaminergic mesolimbic and mesocortical circuits in PD patients, along with premorbid personality profile and the persistently elevated dopaminergic stimulation due to replacement therapy seem to be the factors that interplay in the etiopathogenesis of these conditions.(Dagher and Robbins, 2009)

1.1.3. Pharmacological treatment in PD

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. They experience an early return of symptoms before their next dose of medication is due, a delay in response to a dose of medication, a dose failure or a sudden disappearing of the effect of medication. Other motor complications following long-term levodopa treatment are involuntary choreiform or dystonic movements called dyskinesias. Dyskinesias are clearly related to the pulsatile nature of levodopa therapy. In the normal basal ganglia, there is constant low level activity at dopaminergic synapsis, with transient increases during particular tasks such as voluntary movements and learning. In advanced stages dyskinesias can be troublesome and treatment may be difficult.(Voon *et al.*, 2009)
For also non-motor symptoms are a common source of disability in PD and treatment can be difficult, management of PD should involve a multidisciplinary team that can respond quickly to the needs of a particular patient at a particular time.

1.1.4. Deep brain stimulation

Surgical treatment was described as early as 1940 and, until recently, had focused on ablative procedures of the thalamus and globus pallidus pars interna. They were rapidly replaced in the

late 1990s by chronic deep brain stimulation (DBS), mainly as a result of concerns for adverse effects resulting from bilateral lesions as well as the irreversible effects resulting from poorly placed lesions. DBS has become a standard surgical treatment for medication-refractory movement disorders. In advanced stages of severe levodopa-responsive forms of PD bilateral high-frequency stimulation of the STN can reduce motor disability and levodopa-related complication due to the levodopa dose reduction.

DBS is based on the observation that high-frequency electrical stimulation of specific brain targets can mimic the effect of a lesion. For chronic stimulation a permanent lead is stereotactically implanted subcutaneously into the target area within the brain and connected to a fully implanted neurostimulation device. The stimulator settings can be adjusted telemetrically with respect to electrode configuration, current amplitude, pulse width and pulse frequency. DBS has replaced ablative stereotactic surgery in movement disorders due to several advantages: DBS does not require making a destructive lesion in the brain; it can be performed bilaterally with relative safety in contrast to most lesioning procedures, stimulation parameters can be adjusted postoperatively to improve efficacy, to reduce adverse effects and to adapt DBS to the course of disease; and DBS is in principle reversible and, finally, does not preclude the use of possible future therapies in Parkinson's disease, which may require the integrity of the basal ganglia circuitry (Volkmann, 2007).

The STN and the globus pallidus internus were identified to be effective targets, with STN being the most common site for DBS electrode placement. Since its approval by the Food and Drug Administration for PD in 2002, more than 70 000 patients have undergone DBS surgery, according to Medtronic Inc. (Bronstein *et al.*, 2011). In Movement Disorders center of the Department of Neurology and Center of Clinical Neuroscience, Charles University in Prague 93 PD patients have undergone the DBS surgery for PD since 2001.

1.1.4.1. Mechanism of deep brain stimulation

Despite the remarkable therapeutic efficacy, the mechanisms of DBS effects are still not completely understood. Because DBS mimics the clinical effects of lesions it was thought it decreased the output from the stimulated structure and thus causing a physiologic ablation in the overactive structures, the STN and the globus pallidus internus, that have

become main targets for treatment of motor complications in advanced PD. (Benazzouz and Hallett, 2000, Dostrovsky *et al.*, 2000).

Recent studies have suggested that while somatic activity near the DBS electrode may exhibit substantial inhibition or complex modulation patterns, the output from the stimulated nucleus follows the DBS pulse train by direct axonal excitation. The intrinsic activity is thus replaced by high frequency activity that is time-locked to the stimulus with more regular pattern. These changes in firing pattern are thought to prevent transmission of pathologic bursting and oscillatory activity resulting in the reduction of disease symptoms through compensatory processing of sensorimotor information. A further understanding these processes on a physiological level will be needed if we are to reach the full potential of this powerful tool. (Johnson *et al.*, 2008)

The effects of STN DBS can reach far beyond the motor system, as suggested our study on changes of the EEG spectral power and changes of visual evoked potentials (VEP) induced by STN DBS in PD patients. Changes of the EEG spectral power and VEP indicated STN DBS could influence the basic mechanisms of rhythmic cortical oscillations.(Jech *et al.*, 2006)

1.1.4.2. Non-motor complications of the STN DBS

Beside the motor symptoms improvement, STN DBS treated patients can develop several neuropsychiatric side complications and also weight gain has been consistently reported. (Rieu *et al.*, 2011, Voon *et al.*, 2006, Witt *et al.*, 2008)

1.1.4.2.1. Cognitive complications

In the assessment of cognitive functions in STN DBS treated PD patients the most consistent and robust findings the decline in word fluency, although impairments in various other executive functions have been also reported.(Voon *et al.*, 2006)

1.1.4.2.2. Affective and behavioral complications in STN DBS

The most common psychiatric symptoms following STN stimulation surgery are apathy, changes in emotional reactivity, depression, and hypomania. Individual episodes of

postoperative depression have been reported in up to 25% of patients; postoperative hypomania has been documented in 4% to 15% of patients, usually occurring within the first 3 postoperative months.(Voon *et al.*, 2006) Changes in emotional reactivity, or excessive mood-congruent emotional responses to minor triggers, was identified in 75% of STN stimulation patients.(Houeto *et al.*, 2002) Suicide attempts and/or suicides have been reported in uncontrolled series ranging from 0.5% to 2.9%.(Voon *et al.*, 2006) Within the first 3 postoperative months, transient apathy occurs as part of the dopaminergic withdrawal syndrome. The incidence is not known, but according to a study on long-term outcome for apathy it increased from 8.7% at baseline to 24.6 % at the third postoperative year.(Funkiewiez *et al.*, 2004)

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. (Moro *et al.*, 2010, Schupbach *et al.*, 2006, Volkmann *et al.*, 2009) According to one study 25% of DBS STN treated patients had deterioration in marital relations following surgery.(Houeto *et al.*, 2002)

So far, little is known about the relationship between STN DBS and impulse control disorders and dopamine dysregulation syndrom. According to a review on the available studies, the STN DBS is associated with both favorable and negative outcome in terms of impulse control and related disorders. Preoperative disorders may resolve or improve after STN DBS (possibly due to reduction of the dopaminergic therapy), but these can also worsen or show no change at all. Moreover, STN DBS can also reveal or even induce new impulse control disorder.(Broen *et al.*, 2011)

1.1.4.2.3. Effects of STN DBS on emotional and motivational processing

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 (Biseul *et al.*, 2005, 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) With except of one study all these studies were based on preoperative versus postoperative performance comparison.(Schroeder *et al.*, 2004) One study with on-off

study design using mood-induction procedure demonstrated that STN DBS may enhance emotional processing. (Schneider *et al.*, 2003) Changes in brain activation during affective tasks have been also found in functional imaging studies.(Geday *et al.*, 2006, Le Jeune *et al.*, 2008) Changes in motivation of STN DBS treated PD patients however have been studied mainly with regard to apathy(Le Jeune *et al.*, 2009, Thobois *et al.*) and motor learning(Sauleau *et al.*, 2009) so far.

1.1.4.2.4. Weight gain after STN DBS: epidemiology and mechanisms

Weight gain has been also reported as common non-motor side effect of STN DBS. (Aziz *et al.*, 2008, Barichella *et al.*, 2003, Gironell *et al.*, 2002, Macia *et al.*, 2004, Montaurier *et al.*, 2007, Moro *et al.*, 1999, Novakova *et al.*, 2007, Perlemoine *et al.*, 2005, Tuite *et al.*, 2005) The body weight gain has been observed in up to 30% of patients after DBS-STN implantation, reaching close to 8% of pre-surgery body weight at 3 months post-surgery. Certain patients have presented a weight gain of up to 20 kg within the first 12 months post-surgery.(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. In the repeated survey one year later, in 12 of the patients body weight moderately decreased, 3 did not change, and 6 patients further increased their weight.(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) The decrease in daily energy expenditure(Barichella *et al.*, 2003, Macia *et al.*, 2004, Montaurier *et al.*, 2007, Perlemoine *et al.*, 2005, Tuite *et al.*, 2005) and the reduction of motor complication such as motor fluctuations and levodopa – induced dyskinesias (Gironell *et al.*, 2002, Ondo *et al.*, 2000) but correlation between the reduction of motor complications and the weight gain was not confirmed in other studies.(Barichella *et al.*, 2003, Macia *et al.*, 2004) The daily energy intake was not altered after surgery in studies on weight gain after STN DBS mechanisms.(Barichella *et al.*, 2003, Macia *et al.*, 2004, Montaurier *et al.*, 2007, Ondo *et al.*, 2000, Perlemoine *et al.*, 2005, Tuite *et al.*, 2005) However, inaccuracy inherent to self-reported food intake

measurement should prompt caution in the interpretation of the results. There are no reports on changes in eating behavior except for the study by Volkmann et al., 2006. In this study on long-term effects of STN DBS on quality of life using the Sickness Impact Profile (SIP) questionnaire(Gilson *et al.*, 1975) in PD a sustained improvement in the Eating category. However the items in this category were rather related to motor aspects of feeding.(Volkmann *et al.*, 2009)

The consequences of DBS therapy induced weight gain have not been assessed with accuracy, but there is clearly an increased incidence of metabolic and cardiovascular disorders. A recent study showed that DBS induced marked metabolic modifications.(Rieu *et al.*, 2011)

1.1.4.3. Possible mechanisms of non-motor complications of the STN DBS

In general, the precise mechanisms of the non-motor complications still remain unclear. The STN DBS effects might not necessarily be direct effects on the associative and limbic circuits, 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. All these factors can possibly affect the results of studies based on pre versus postoperative comparisons.

Moreover the precise mechanism of action of high frequency stimulation is not well defined. Another possible mechanisms involved could be changes in neural firing pattern, or the shift form a pulsatile to steady stimulation.(Voon *et al.*, 2009)

1.2. Emotion, motivation and action

According to the theoretical model of emotion that is founded on basic experiments from both the animal and human research laboratories, 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 latter range from facial and postural expressions to the acts that define behaviors we associate with the notion of pleasure and reward to behaviors we associate with the notion of pain and punishment or aversion; from approach to withdrawal 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 also include the mapping of changes that occur in the cognitive processing style, as well as the evocation of the thoughts that are congruent with the feeling state. 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 adaptive value of feelings comes from amplifying the mental impact of a given situation and increasing the probabilities that comparable situation can be anticipated and planned for in the future so as to avert risk and take advantage of opportunities. 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 (the costs and benefits of action are considered). Regulation is itself of an emotional nature, as it stems from the anticipated emotional consequences of actions for the individual`s many concerns. Those concerns include those about social censure, empathic distress, sympathy, interpersonal relationships, and social harmony. Emotions themselves consist of two separate processes: the changes in motivation and the appraisal processes that trigger them. The appraisal processes, pre-attentive (i.e. automatic, non-conscious) and cognitive (conscious), provide objects and events with emotional value or meaning. The processes causing motivational change are sensitive to the outcomes of the appraisal processes.(Fridja, 2004)

A pleasant stimulus is often called a rewarding stimulus or reward. The actual reward, however, consists in active processes of the brain that reacts to a stimulus rather than the

stimulus itself. Reward is a crucial component for driving incentive-based learning, appropriate responses to stimuli, and the development of goal directed behaviors. Adaptive behvior requires a combination of reward evaluation, associative learning, and the ability to develop appropriate action plans and inhibit inappropriate choices on the basis of earlier experience. Thus, integration of different aspects of reward processing and interaction of reward circuits and brain regions and interaction of reward circuits and brain regions involved in cognition and motor control are essential.(Haber and Knutson, 2010)

Beside the motivational aspects of emotions, emotions have also role in cognition (Zajonc, 1980), decision making (Damasio, 1994), perception (Anderson & Phelps, 2001) and even consciousness (Panskepp, 1998, Damasio, 1999).

1.2.1. Patterns of emotional expression and emotion classification

Patterns of emotional expression are highly varied and can be situated in a continuum of emotional response classification (Table 1.)

Behavioral states	Motivational states	Basic emotions	Moods, background emotions	Social emotions
Approach	Reward	Happiness	Depression	Pride
Withdrawal	Punishment	Fear	Anxiety	Embarrassment
		Anger	Mania	Guilt
		Disgust	Cheerfulness	Shame
		Sadness	Contentment	Maternal love
		(Surprise)	Worry	Sexual love
		(Contempt)		Infatuation
				Admiration
				Jealousy

Table 1. Classification schemes for emotions

The more primitive classes of emotions, (towards the left in the Table 1.), belong to emotional reactions, whereas the more complex classes, (towards the right in the Table 1.), belong to social communication. Typically, researchers working on animals have

adopted a scheme relying on reward and punishment or appetitive and aversive motivational activation, whereas research in humans has often used so-called 'basic' emotions. Finally, psychiatric or social psychological studies have utilized even more complex constructs such as the 'social' emotions, whose neural underpinnings are at present very poorly understood.(Adolphs, 2002)

Theories of how the functional neuroanatomy of emotion operates systematically range from single system models, in which the same neutral system underlies all emotions, to views that propose a combination of some common brain systems across all emotion, allied with separable regions that are dedicated more closely to the processing of certain individual emotions such as fear, anger or disgust (multiple-system models).(Dalgleish, 2004)

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. The appetitive system is activated in contexts that promote survival, including sustenance, procreation, and nurturance, with a basic behavioral repertoire of ingestion, copulation, and caregiving. Conversely, the defensive system is primarily activated in contexts involving threat, with a basic repertoire built on withdrawal, escape, and attack. 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) This dual-system model of emotion has been proposed by many theorists using different terminology; for example, behavioral activation and behavioral inhibition systems(Cloninger, 1987), approach and withdrawal systems(Davidson *et al.*, 1990). Emotions have been also conceptualized in terms of states elicited by positive (rewarding) and negative (punishing) instrumental reinforcers within a two-dimensional space(Rolls, 2004). This motivational view of human emotions has been supported by both psychophysiological and neuroscience research delineating the mediating neural structures and functional circuits and their autonomic and somatic output.(Lang and Bradley, 2010)

Each of the two motivational systems can vary in terms of activation or arousal. That is, arousal is not viewed in this theory as having a separate substrate, but rather as representing intensity of activation (metabolic and neural) of either the appetitive or aversive system, or the coactivation of both systems. 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. To give an example from the observation of animals, if a caged rat is subjected to electric shock on the foot pads, the defense system is engaged. It is then likely either to flee if an exit is available ("fear"), or attack a cagemate if one is present ("anger"). If shocks are repeated randomly and uncontrollably it will first cower helplessly and then become dull and unresponsive ("depression").

Emotions may come in many forms, shaped by genetics and learning to fit the demands of local context, however their fundamental organization is motivational. Thus, their primary description is in terms of affective valence (i.e. appetitive or aversive) and arousal (intensity of activation). Research on affective language and feeling is consistent with this view. The multivariate language 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)

1.2.2. Neural substrates for emotion and motivation

The neural systems involved in the production of emotion and motivation have been identified by functional neuroimaging and neurophysiologic studies and by studies in patients with focal brain lesions and pathology of the autonomic nervous system in humans. Furthermore research in experimental animals provided evidence for functional anatomic connectivity and neural circuits involved in emotions and motivation. Both the cortical and the subcortical regions participate in affective and motivational processes, but cortical and subcortical systems may play very different causal roles. The cortex might mediate conscious experience of emotions and motivation and other psychological processes by hierarchically monitoring and re-representing lower core processes. Cortical causation might be restricted to cognitive aspects of emotion and motivation induction, cognitive decisions based on emotion and motivation, and to voluntary regulation of emotional state via modulation of lower brain structures that more directly cause affective reactions (Bechara et al., 2000, Damasio, 1999, Davidson et al., 2000, Rolls, 1999). By contrast to the damage in the cortical regions that typically does not abolished capacity

for an emotional reaction , the manipulations of subcortical brain structures are highly effective at causing basic affective reactions themselves. (Damasio, 1999, Davidson et al., 2000, Rolls, 1999) (Berridge 1999, Damasio, 1999; LeDoux, 1996; Panskepp, 1998). A competent stimulus, actual or recalled, consciously or non-consciously appraised, is processed in sensory regions and results in the availability of neural signals from which emotions can be triggered. There is a large overlap between both the cortical and the subcortical regions forming a complex network that mediates different aspects of emotional and motivational or reward processes. However, the amygdala has been implicated primarily in emotional processing and the ventral striatum and the ventral tegmental area are the key structure of the reward circuit, which seems to be embedded within the cortico- ventral basal ganglia network (see Figure 1.).(Dalgleish, 2004, Haber and Knutson, 2010, Tamietto and de Gelder, 2010) Moreover, reward does not work in isolation, but its pathways interface with circuits that mediate cognitive function to affect motor planning.

1.2.2.1. Cortical regions involved in the emotional and motivational processing

1.2.2.1.1. The prefrontal cortex

The prefrontal cortex has been implicated in emotion in many ways, but there is no consensus as to its exact functions. It has been proposed that prefrontal cortex (the orbitofrontal region) is involved in learning the emotional and motivational value of stimuli and that prefrontal cortex regions work together with the amygdala to learn and represent relationships between new stimuli (secondary reinforcers) and primary reinforcers such as food, drink and sex. Neurons in the prefrontal cortex can also control and correct reward related and punishment related behavior(Rolls, 2004). According to the somatic marker hypothesis, the prefrontal cortex (especially the ventromedial prefrontal cortex) has been also implicated in processes of human reasoning and decision making based on physiological reactions, such as shifts in autonomic nervous system activity, that do not arise in the body proper but rather in the brain's representation of the body. These reactions provide a signal delineating those current events that have had emotion-related consequences in the past. They influence the

processes of response to stimuli, at multiple levels of operation, some of which occur consciously and some of which occur non-consciously. Examples of the non-conscious action are the undeliberated inhibition of a response learned previously; the introduction of a bias in the selection of an aversive or appetitive mode of behavior, or in the otherwise deliberate evaluation of varied option-outcome scenarios. Examples of the conscious action include the conscious 'qualifying' of certain option-outcome scenarios as dangerous or advantageous.(Damasio, 1996) Patients with lesions of the ventromedial prefrontal cortex have difficulties with situations of uncertainty where the subtle emotional values of multiple stimuli need to be processed (e.g. social situations) (Bechara *et al.*, 1994, Bechara *et al.*, 2000).

Finally, the prefrontal cortex along with the anterior cingulate cortex has been proposed a role in the top-down regulation i.e. that these regions send „bias signals“ to other parts of the brain to guide behavior towards the most adaptive current goals. Often behavioral choices are in danger of being heavily influenced by the immediate affective consequences of a situation (e.g. immediate reward), even though the most adaptive response might be, for example, to delay gratification. It has been suggested that the prefrontal cortex promotes adaptive goals in face of strong competition from behavioral alternatives that are linked to immediate emotional consequences.(Haber and Knutson, 2010)

1.2.2.1.2. Anterior cingulate cortex

The anterior cingulate cortex is considered a key structure of integration of visceral, attentional and emotional information that is crucially involved in the regulation of affect and other forms of top-down control. It has been also suggested that the anterior cingulate cortex is an important neural substrate of conscious emotion experience and of the central representation of autonomic arousal.(Lane *et al.*, 1998) The anterior cingulate cortex has generally been conceptualized in terms of a dorsal “cognitive” subdivision and a more rostral, ventral “affective” subdivision. The affective subdivision of the anterior cingulate cortex is routinely activated in functional imaging studies involving all types of emotional stimuli.(Murphy *et al.*, 2003, Phan *et al.*, 2002) It has been proposed role for monitoring conflicts between the functional state of the organism and any new information that has potential affective or motivation consequences. When such conflicts are detected, the

anterior cingulate cortex projects information about the conflict to areas of the prefrontal cortex where adjudications among response options can occur.(Bush *et al.*, 2000)

1.2.2.2. Subcortical areas involved in the emotional and motivational processing

1.2.2.2.1. The ventral basal ganglia

While the dorsal domain of the basal ganglia is involved in motoric control, the ventral domain appears to be a constellation of multiple functional systems critical for learning and selection of flexible behaviors and of behavioral strategies; for exploration and foraging; for stimulus evaluation; spatial navigation, planning and contingency and reward processing (Humphries and Prescott, 2010). The central concept governing the organization of both the ventral and the dorsal basal ganglia connectivity is the existence of parallel anatomical cortico-basal ganglia-thalamo-cortical loops. (Alexander *et al.*, 1986). These loops –are closed, running in parallel, each originating from a different cortical area, passing through the basal ganglia, and returning to the originating cortical area via thalamus. These loops, however, are also open in the sense that projections from different, but related, cortical areas converge on the same locations in striatum (Alexander *et al.*, 1986, Romanelli *et al.*, 2005). Microscopic channels are discrete parallel loops running within a macroscopic loop. Existing computational models, primarily concerned with dorsal striatum and its associated circuits, use such microscopic channels, each channel representing a different putative action or behavior(Humphries and Prescott, 2010). Anatomically, the channels in striatum and STN are defined by the converging input from topographically related representations in cortex, and the channels in globus pallidus and the output nuclei by their corresponding striatal afferents. There is considerable evidence for extending the concept of these channels to the ventral striatum and its associated circuits.(Humphries and Prescott, 2010)

In addition to the cortico-basal ganglia system, other structures including the amygdala, hippocampus, lateral habenular nucleus, a specific brainstem structures, such as the pedunculopontine nucleus and the raphe nuclei, are key components that regulate the reward circuit (Figure 1.).(Haber and Knutson, 2010, Humphries and Prescott, 2010)

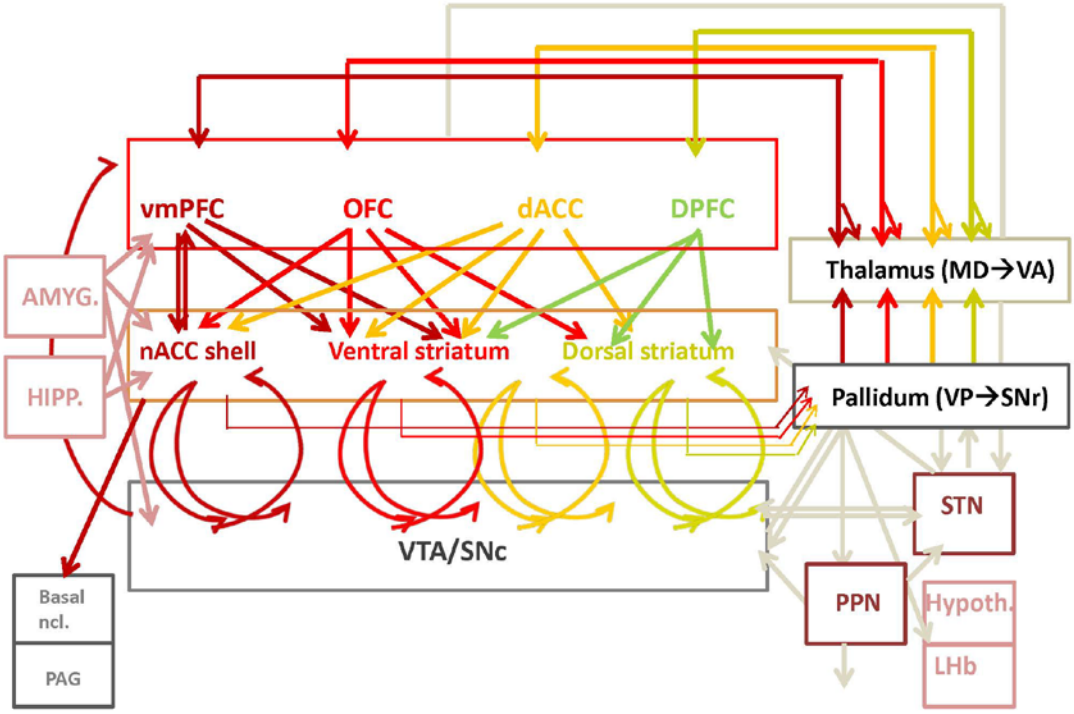

Figure 1. The functional connectivity of the key structures of the reward circuit.

Three networks of integration through cortico-basal ganglia pathways:

1. Fibers from different prefrontal areas converge within subregions of the striatum.

2. Through the organization of striato-nigrostriatal (SNS) projections, the VS can influence the dorsal striatum: Projections from the VTA to the nucleus accumbens shell form a closed reciprocal loop, but also project more laterally to impact on dopamine cells that project to the rest of the ventral striatum, forming the first part of a feed forward loop or spiral. The spiral continues through the striato-nigro-striatal projections through which the ventral striatum impacts cognitive and motor striatal areas through the midbrain dopamine cells.

3. The nonreciprocal cortico-thalamic projection carries information from reward- related regions, through cognitive and motor controls.

Amy=amygdala; dACC=dorsal anterior cingulate cortex; dPFC=dorsal prefrontal cortex; Hipp=hippocampus; hypoth.=hypothalamus; LHb=lateral habenula; MD = medial dorsal nucleus thalami; OFC=orbital frontal cortex; PAG = periaqueductal grey, PPT=pedunculopontine nucleus; SNc=substantia nigra, pars compacta; STN=subthalamic nucleus.; vmPFC=ventral medial prefrontal cortex; VA = ventral anterior nucleus thalami; VP=ventral pallidum; VTA=ventral tegmental area; Red=vmPFC pathways; dark orange=OFC pathways; light orange= dACC pathways; yellow=dPFC pathways; green=output to motor control areas. Adapted after Haber and Knutson, 2010 and Parent and Hazrati, 1995

1.2.2.2.1.1. The ventral striatum

The ventral striatum has been implicated in reward processing and it is activated even by non-consciously perceived omission of expected rewards (Berns *et al.*, 1997). While both the dorsal and ventral striatum receive input from the cortex, thalamus, and brainstem, the ventral striatum alone receives also a dense projection from the amygdala and the hippocampus. The afferent projections from cortical areas mediate different aspects of reward and emotional processing. Around 40 neuron groups can be defined by unique sets of convergent inputs from hippocampal formation, amygdala and prefrontal region. Additionally, the limbic-related thalamic nuclei and the specific thalamic –basal ganglia relay nuclei also project to the ventral striatum. The ventral striatum is placed as a key entry port for processing emotional and motivational information that, in turn, drives basal ganglia action output.(Sesack and Grace, 2010) Although the topographic organization of cortico-striatal projections is well documented, there is also evidence for overlap of these inputs at the single neuron level suggesting functional integration. The striatal neurons form the efferent projections primarily to the ventral pallidum and midbrain (the ventral tegmental area and the substantia nigra).(Parent *et al.*, 1997) In addition, the ventral striatum projects to the pedunculopontine nucleus.(Haber and Knutson, 2010) The nucleus accumbens, predominant part of the ventral striatum, has two major divisions into core and shell regions. The shell has a particularly important function in the circuitry underlying goal-directed behaviors, behavioral sensitization, and changes in affective states. The core- and the shell- based basal ganglia circuits form separate cortico-basal ganglia-thalamo-cortical loops. The shell-based circuits are different from the striato-pallidal pathways in the rest of the basal ganglia. Their target regions of ventral pallidum in turn project widely outside the basal ganglia, to lateral hypothalamus, pedunculopontine nucleus, mediodorsal thalamus and also reciprocate the projection from the shell in a topographic fashion. Furthermore, the shell has direct outputs to structures outside the basal ganglia: to the lateral hypothalamus, to the periacqueductal gray and finally, to the cholinergic nucleus basalis. Through this projection, the reward circuit may have access to a wider region of frontal cortex, than via more confined ventral cortico-basal ganglia circuit.(Haber and Knutson, 2010, Humphries and Prescott, 2010) The activity within the ventral basal ganglia loops is modulated by brainstem dopamine. The striatum has the highest density of dopamine receptors of any

structures in the vertebrate brain and is the main target of the dopaminergic neurons in the ventral tegmental area and substantia nigra pars compacta (Richfield *et al.*, 1989, Richtand *et al.*, 1995).

In humans, the functional imaging studies have shown recruitment of striatal regions during exposures to both primary (i.e., pleasant tastes and sounds) and secondary rewards (i.e., monetary gambles). The event-related fMRI studies demonstrated that different regions of the ventral striatum are recruited during different phases of reward processing. While the nucleus accumbens and medial caudate may respond more robustly during reward anticipation, but the rostroventral putamen in response to reward outcomes.(Haber and Knutson, 2010)

1.2.2.2.1.2. Ventral pallidum

The ventral pallidum is an important component of the reward circuit, its neurons respond specifically during the learning and performance of reward-incentive behaviors. The ventral pallidum receives primarily input from the ventral striatum.(Humphries and Prescott, 2010) In addition, the ventral pallidum also receives a glutamatergic input from the STN and a dopaminergic input from the midbrain. The ventral pallidum projects topographically to the STN, the hypothalamus and to the dopaminergic neurons in the midbrain. Moreover, the ventral pallidum also innervates the pedunculopontine nucleus, the MD thalamic nucleus and both the internal and external segments of the dorsal pallidum and the lateral habenular nucleus. Finally, part of the ventral pallidum projects back to the striatum.(Haber and Knutson, 2010)

1.2.2.2.1.3. Midbrain dopamine neurons

The dopamine neurons have a central function in the reward circuit.(Schultz, 2002) The midbrain dopamine neurons are classically divided into the substantia nigra pars compacta, the ventral tegmental area, and the retrorubral cell groups. The afferent projections involve the striatum, the ventral pallidum, the brainstem (the pedunculopontine nucleus) and the bed nucleus of the stria terminalis, the extended amygdala, the dorsal raphe nucleus. The projections from the colliculus superior suggest the dopamine cells receive a direct sensory projection. The dopamine cells project

massively to the striatum. Midbrain projections from the shell target both the ventral tegmental area and the ventromedial substantia nigra. Projections form the ventral tegmental area to the shell form a ‘closed’, reciprocal loop, but also project more laterally to impact on dopamine cells that project to the rest of the ventral striatum, forming the first part of a feed forward loop or spiral. The spiral continues through the striato-nigro-striatal projections through which the ventral striatum impacts cognitive and motor striatal areas through the midbrain dopamine cells.(Haber and Knutson, 2010)

The dopamine is released from the neurons in substantia nigra pars compacta and from the ventral tegmental area in tonic or phasic fashion. The functional correlates of dopamine are often considered separately for the phasic and the tonic components of dopaminergic neuron firing and corresponding changes in dopamine concentration. The phasic component`s effects are normally interpreted within the framework of dopamine`s role in modulating synaptic plasticity of the cortico-striatal synapses. There are three main hypotheses for the functional correlates of phasic bursts firing.(Humphries and Prescott, 2010) One is the reinforcement learning hypothesis with phasic dopamine signaling reward prediction.(Schultz, 2007) The second is the incentive salience theory (see chapter 1.3.), with phasic dopamine as an ‘incentive salience signal’ - the signal to keep maintaining or repeating the current action, as long as it is worthwhile the signal for ‘wanting’.(Berridge, 2007) The third theory proposed that the phasic dopamine signal acts as a time stamp for the occurrence of any salient stimulus, rewarding or otherwise, so that the conflux of motor commands from cortex and dopamine in the striatum will allow the association between that action and the outcome. The tonic component within the framework of dopamine`s role in modulating short-term excitability of the striatal neurons.(Redgrave and Gurney, 2006) According to general proposals, the tonic dopamine is a controller for the frequency and ease of switching behaviors (Redgrave *et al.*, 1999) or switching actions with regard to average reward rate. (Niv *et al.*, 2007)

In addition to striatal input, the dopamine cells also project widely throughout the cortex. Additionally, there are efferent projections to the hypothalamus, periaqueductal grey, the amygdala and the hippocampus, the STN, the ventral pallidum, the globus pallidus, and the substantia nigra pars reticularis and dopaminergic receptors receptors are found in all of them, including autoreceptors on dopaminergic cells in substantia nigra pars compacta and ventral tegmental area (Smith and Kieval, 2000).

The complexity of dopamine`s actions and receptor distribution in the striatum clearly point to multiple computational roles beyond the foregoing current ideas. Elucidating these roles is a prime area for computational modeling.(Humphries and Prescott, 2010)

1.2.2.2.2. The subthalamic nucleus

The STN forms beside the striatum other input structure of the basal ganglia, receiving input from cortical and thalamic sources. STN has been long considered to be a relay in the motor-related information processing and because of its dysregulation in PD, it has become a target for the surgical treatment of the disease in the 90s, the subthalamotomy and deep brain stimulation (DBS). The scrutiny of its anatomic connectivity later revealed an interesting position at the nexus of motor, associative, and limbic pathways and potentially integrative function of this nucleus is to be considered now.

Evidence on processing of non-motor information within STN has been brought from studies on effects of STN lesions and high frequency DBS in research animals and STN DBS treated PD patients. STN appears to be involved in attentional processes(Baunez and Robbins, 1997, Baunez and Robbins, 1999), an in the inhibitory control and compulsivity(Ballanger *et al.*, 2009, Baunez *et al.*, 1995), possibly via the hyperdirect pathway, which includes cortico-subthalamic connection.(Nambu *et al.*, 2002) Working memory was also found to be impaired in rats after STN lesions and under STN high frequency in PD patients. (Baunez *et al.*, 2001, Hershey *et al.*, 2004)

The STN receives massive afferents from the cortex, the external segment of the globus pallidus, the thalamus, the pedunculopontine nucleus and nucleus dorsalis raphe. The STN efferents project to the pallidal complex, the substantia nigra pars reticularis and to the striatum (the caudate nucleus and the putamen)(see Figure 1.). 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 STN is reciprocally interconnected with the ventral pallidum and neurons in the medial tip of the subthalamic nucleus project to the limbic-related ventral tegmental area and adjacent portions of the substantia nigra pars compacta. Through their projection to the dopaminergic cells in the ventral tegmental area, neurons in the medial tip of the subthalamic nucleus could influence the ascending

mesolimbic dopaminergic pathway directed to the ventral striatum.(Parent and Hazrati, 1995) In monkeys, the role of STN in motivational processing was demonstrated in neurophysiological studies.(Darbaky *et al.*, 2005, Matsumura *et al.*, 1992) 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.*, 2002, Baunez *et al.*, 2005, Baunez *et al.*, 2007, Lardeux *et al.*, 2009, Rouaud *et al.*, Uslaner *et al.*, 2008)

Although some emotional aspects are difficult to record in animals, several measurements of the emotional responses can be used in animal experiments such as skin conductance, cardiac frequency, anxiety, stress and fear conditioning , none of these have been reported after STN lesions or high frequency DBS so far.

Observations from STN DBS treated PD patients suggest that STN is involved in emotional processing (see chapters 1.1.4.2.2. and 1.1.4.2.3.). Neurophysiological studies already gathered some evidence of human STN involvement in emotional processing. Local field potentials were recorded using macroelectrodes from the subthalamic region in patients with PD undergoing bilateral implantation of the STN for DBS while patients viewed pleasant and unpleasant emotionally arousing and neutral pictures. The event-related desynchronization in the local alpha power (8 to 12 Hz) was found for all stimulus categories starting at about 0.5 s after stimulus presentation. A delayed modulation of alpha activity (1 to 2 seconds poststimulus) with larger event-related desynchronization in trials of pleasant and unpleasant stimuli compared with neutral stimuli was found, possibly reflecting the processing or transmission of information related to emotional stimuli.(Kuhn *et al.*, 2005) A significant event-related desynchronization of STN alpha activity with pleasant stimuli that correlated with the individual valence rating of emotionally charged pictures suggested involvement of the human STN in valence-related emotional information processing.(Brucke *et al.*, 2007) The alpha event-related desynchronization to unpleasant pictures correlated significantly with the Beck depression inventory score at 3 months after chronic DBS suggesting a mood –congruent (state-dependent) stimulus processing in the STN of PD patients.(Huebl *et al.*, 2011)

1.2.2.2.3. The brainstem

Several brainstem structures are involved in emotional and motivational processing.(Tamietto and de Gelder, 2010)

Superior colliculus is the earliest post-retinal subcortical structure that responds to coarse emotional stimuli.

The periaqueductal grey and locus coeruleus are implicated in relatively automatic and reflex-like defensive responses (Mobbs *et al.*, 2007). The periaqueductal grey receives visual information from visual colliculus. The locus coeruleus regulates the activity in the anterior cingulate and ventral prefrontal regions by its noradrenergic projections, as well as the activity in the subcortical structures, such as the amygdala, pulvinar and superior colliculus, in response to non-consciously perceived stimuli(Liddell *et al.*, 2005).

1.2.2.2.4. Thalamus

The thalamus has complex connectivity with multiple brain regions. The medial dorsal nucleus projects to the frontal cortex, and is the final link in the reward circuit. These connections are bidirectional, with cortical projections to these thalamic nuclei more extensive than their projections back to the cortex. In addition, there is a nonreciprocal cortical input to the nucleus that is derived from functionally distinct frontal cortical areas. The thalamic relay nuclei seem to integrate information flow from reward and higher cortical 'association' areas of the prefrontal cortex. Both the primary and secondary rewarding and non-rewarding stimuli increase thalamic activation, suggesting that dorsomedial thalamic activation reflects general arousal to a greater extent than value. (Haber and Knutson, 2010). The pulvinar receives direct projections from retina and from the superior colliculus and it is monosynaptically connected to the amygdala. The pulvinar is involved in attentional mechanisms and in responses to salient visual targets and is active during non-conscious perception of emotional stimuli(Tamietto and de Gelder, 2010).

1.2.2.2.5. The amygdala

The amygdala is one of the most important brain regions for emotion, with a key role in processing of faces and other social signals of emotion (particularly involving fear), in emotional conditioning (both the appetitive and the fear conditioning, in which meaningless stimuli come to acquire emotion-inducing properties when they occur in

conjunction with a naturally appetitive or threatening event) and in the consolidation of long-term emotional memories(Dalgleish, 2004). Amygdala has been also associated with the modulation of other cognitive processes, such as visual perception.

The amygdala is involved in both conscious and nonconscious perception of emotional stimuli (unlike the superior colliculus and pulvinar)(Sergerie *et al.*, 2008). This dual role is probably related to the fact that the amygdala is a complex system (it includes up to 12 subnuclei) and receives visual information from different pathways — one originating in the sensory cortex and one originating in subcortical areas(Phelps and LeDoux, 2005). Evidence from functional imaging and behavioral studies demonstrated that the amygdala links the pre-perceptual or pre-attentive sensory processing with emotion (Breiter *et al.*, 1996, Morris *et al.*, 1996). Moreover, there is considerable evidence that the amygdala might be also involved in the process of highlighting of perceptual processing in relation to emotionally salient stimuli and has an important role in reward processing, in part though the interaction between it and ventral striatum form stimulus-reward associations.(Ramirez and Savage, 2007) Amygdalar activation has been observed in contexts involving potential rewards and punishment (Zald, 2003) and decreases with reward devaluation (Gottfried et al., 2003)

1.2.2.2.6. The substantia innominata

The substantia innominata is a sublenticular portion of the basal forebrain and comprises several intermingled neuronal groups that represent an extension of the dorsal amygdala and is activated in response to the arousal of consciously perceived emotional stimuli(Whalen *et al.*, 1994, Whalen *et al.*, 2001).

1.2.2.2.7. The hippocampus

The hippocampus is involved in the contextual evaluation of emotional stimuli and works together with the amygdala in mediating implicit learning and memory consolidation for consciously and non-consciously perceived stimuli (Morris *et al.*, 1998).

1.2.2.2.8. Hypothalamic autonomic centers

The hypothalamus has been implicated in consumptive behaviors and homeostasis (Nakamura and Ono, 1986). Numerous electrical stimulation studies in animals identified hypothalamus as a part of an extensive reward network in the brain, also involving prefrontal cortex, amygdala and ventral striatum (Dalgleish, 2004).

1.3. Reward processing and the incentive motivation concept

K. Berridge and T.E. Robinson postulated an influential theory of drug addiction called incentive sensitization theory (Robinson and Berridge, 1993) According to this theory reward process contains three major psychological components that are mediated by partly dissociable brain neuroanatomical and neurochemical substrates.(Berridge and Kringelbach, 2008)

These components are:

1. Liking: the hedonic impact of a reward or sensory pleasure, it comprises the pleasure elicited reactions that are not necessarily conscious such as facial affective expressions and the conscious experience of pleasure or subjective feeling of niceness.
2. Wanting: motivation for reward, which also includes both the nonconscious incentive salience wanting processes and conscious desires for incentives or cognitive goals.
3. Learning: associations, representations, and predictions about future rewards, which is based on past experiences. Again it includes implicit knowledge as well as associative conditioning and explicit and cognitive predictions.

Berridge and Robinson introduced the apostrophic terms “liking” and “wanting” to refer to non-conscious core processes of affect and motivation (=valenced good/bad reactions) generated by the brain, which influence behavior towards incentives – without necessarily being felt (Robinson and Berridge, 1993; Berridge, 1999). “Liking” and “wanting” are two distinguishable aspects of reward and both together are necessary for full reward and they usually happen together in human life, i.e. the normal reward is both “liked” and “wanted”. When incentive salience is attributed to a reward stimulus representation, it makes that stimulus attractive, attention grabbing, and that stimulus and its associated

reward suddenly become enhanced motivational targets, which are „wanted“ . Hedonic „liking“ by itself is simply a triggered affective state, there need be no object of desire or incentive target, and no motivation for further reward. It is the process of incentive salience attribution that makes a specific associated stimulus or action the object of desire that tags a specific behavior as the rewarded response, and that allows normal pleasure to spur desire for more.(Berridge, 2009)

The mesolimbic dopamine system and its projections to ncl. accumbens and ventral pallidum have been demonstrated to mediate the core of the „wanting“ i.e. incentive salience attribution or attribution of emotional relevance to emotional stimulus such as rewards and their predictive cues but also to aversive stimuli. (Berridge, 2007, Faure *et al.*, 2008, Horvitz, 2000)(Robinson and Berridge, 1998).

The sensory pleasure “liking” seems to depend also especially on the ncl. accumbens and ventral pallidum, however using opioid and endocanabinoid neurotransmission.(Table 2.)

The taste and smell of food and sex are among the most fundamental pleasures and there is evidence for overlap with higher order pleasures (e.g. monetary, artistic, musical, altruistic and transcendent pleasures). All pleasures seem to involve the same hedonic brain systems, even when linked to anticipation and memory.(Kringelbach and Berridge, 2009) The rewarding properties for all pleasures are generated by brain circuits that are distinct from the mediation of other features of the same events (e.g. sensory, cognitive).

There is ample evidence showing the close relationship between the activation of the mesolimbic dopaminergic neurotransmission, motivational "wanting" for food rewards, increase in food intake, and obesity.(Beaver *et al.*, 2006, Berridge, 2009, Davis *et al.*, 2007) This dopamine mediated behavior seems to be also 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.*, 2002, Rouaud *et al.*, Uslaner *et al.*, 2008) However, in STN DBS treated PD patients this aspect of food intake control and weight gain has not been studied so far.

Major categories		Psychological components	Examples of brain circuity
Motivation	Explicit	Wanting Cognitive incentives	OFC, ACC, insular Dopamine
	Implicit	"Wanting" Incentive salience	nAcc, VTA, hypothalamus Dopamine
Pleasure	Explicit	Liking Conscious pleasure	OFC, ACC, insular Opioids, cannabinoids
	Implicit	"Liking" Hedonic impact	Acc shell, VP, PAG, amygd. Opioids, cannabinoids
Learning	Explicit	Learning Cognitive processing	OFC, ACC, vmPFC, insular Ach, dopamine, serotonin
	Implicit	Learning Associative learning	Amygd., hippocampus Ach, dopamine

Table 2. Reward is a complex psychological concept with at least three major subcomponents of motivation or wanting, pleasure liking or affect, and learning. Each of these contains explicit and implicit psychological components that constantly interact and require careful scientific experimentation to tease apart. Explicit processes are consciously experienced (e.g., explicit pleasure or desire), whereas implicit psychological processes are potentially unconscious in the sense that they can operate at a level not always directly accessible to conscious experience (implicit incentive salience, habits, and 'liking' reactions), and must be further translated by other mechanisms into subjective feelings.

ACC = anterior cingulate cortex, amygd. = amygdala., nAcc= nucleus Accumbens, vm PFC = medial prefrontal cortex, OFC = orbitofrontal cortex, PAG= periaqueductal grey, VP = ventral pallidum.

Adapted afterKringelbach and Berridge, 2009.

1.4. Emotion elicitation and assessment

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.

1.4.1. Emotion elicitation

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 large set of standardized emotionally evocative color photographs, which has been proven to activate either appetitive or aversive motivational functions. It includes currently more than 1,000 exemplars of pictures (depicting joyful, sad, fearful, angry, threatening, attractive, dressed and undressed people; houses; objects, landscapes; sports events; photojournalism from wars and disasters; sick patients; mutilated bodies; animals etc.) along with the normative ratings of the pleasure and arousal associated with each picture, obtained from groups of naive subjects. Using these ratings, scientists can select and/or match pictures on the basis of the average reported emotional impact of that picture. Moreover, this collection facilitates the comparison of results across different studies conducted in the same or different laboratory. (Lang and Bradley, 2008) Other types of visually presented emotional stimuli involve standardized emotional film clips and emotional faces.(Ekman, 1976) However, there are other methodologies too. The use of behavioral manipulations of facial expressions and postures, gazing, speech and tone of voice is based on the idea that such voluntary actions can generate other emotional responses such as changes in autonomic nervous system, that are emotion specific or emotional behavior and can be measured. The elicitation of intense or “authentic” emotional responses by these methods in the laboratory is, in general, challenging, however, there are several other strategies that can be used. The dyadic interaction task offers the possibility of studying emotional processes in social contexts. Use of primary reinforcers in the elicitation of emotion and motivational processes can be used to identify brain reward and punishment systems.

1.4.2. Emotion assessment

There are three processes of emotion that can be assessed by different approaches: 1. emotional reactivity and 2. regulation, and 3. emotional understanding.

1.4.2.1. Emotional reactivity and regulation assessment

Emotional reactivity refers to the type magnitude and duration of responses to changes in the internal and external environment that have significance for our goals and wellbeing. Emotional regulation refers to the adjustments in type magnitude, and duration of emotional responses that are made to meet personal, situational, and interpersonal demands. Emotion regulatory processes may be automatic or controlled, conscious or unconscious, and may have effects on the emotion generative process. The emotional reactivity and emotional regulation can be difficult to separate. For example, very small facial expressive and autonomic responses to a highly emotional stimulus in a patient could be caused either by a low level of emotional reactivity or a high level of emotional down-regulation.(Levenson, 2007)

Emotional response can be quantified in terms of changes in emotional expressive behavior and peripheral physiology. There is number of indicators for different emotions that can be analyzed from emotional expressive behavior such as emotion specific facial expression, tone of voice and content of speech. Peripheral physiology involves changes in cardiovascular, electrodermal, respiratory, and somatic systems that can be measures using several laboratory tests (Sequeira *et al.*, 2009). Changes in activation of these systems covary significantly with emotional valence (pleasure ratings) and arousal, as defined by subjective evaluations of the presented stimuli (i.e. pictures with emotional content). Facial muscle activity of the corrugator (“frown”) increases linearly with unpleasantness while activity of the zygomatic (“smile”) muscle increases linearly with pleasantness of the stimulus. Heart rate is also responsive to differences in affective valence with promt deceleration by unpleasant and acceleration by pleasant stimuli. Other evoked response vary with changes in rated arousal regardless of stimulus valence, such as skin conductance activity(Lang *et al.*, 1998).

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. 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, Lang *et al.*, 1990). 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 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.(Davis *et al.*, 2007)

1.4.2.2. Assessment of feelings and emotional understanding

Emotional understanding refers to the recognition of emotions in oneself and others and the knowledge of the reasons they have occurred and their consequences. It takes a number of forms, ranging from the relatively simple (e.g. knowledge about whether or not we or others are experiencing emotion) to more differentiated (e.g., knowledge about the particular emotion or emotions being experienced) to highly complex (e.g., knowledge of cultural norms that apply to emotional expression in the current situation).(Levenson, 2007)

The self-reported emotional experience (feelings) can be measured in several ways. The individuals can describe their emotional responses to the stimulus or rate their emotions. Using the IAPS stimuli, the relationship between evaluative judgments and specific physiological responses has been consistently demonstrated. According to the two dimensional model of emotion, the appetitive and aversive (defensive) systems, that are implemented by neural circuits in the brain, presumably with common outputs to structures that mediate the somatic and autonomic physiological system, account for the hedonic valence. Judgments of hedonic valence indicate which motivational system is engaged. Motivational activation is associated with widespread brain cortical, autonomic, and behavioral activity that varies in its intensity. Judgments of arousal index the intensity of the emotional activation. (Lang and Bradley, 2008, Levenson, 2007)

Changes in activation of the aversive or appetitive motivational system elicited by emotionally charged IAPS pictures and the incentive salience attribution to these stimuli can be expressed in subjective ratings.(Bradley *et al.*, 2001, Phan *et al.*, 2004)

A rating instrument called the self-assessment manikin has been developed for emotion quantification 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)**.** Each dimension is represented by five graphic figures, and participants select any of the figures or between any of the figures making a 9-point scale.(Lang and Bradley, 2008)

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 known to occur 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. AIMS 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

4.1. Materials and methods

Subjects

The study was approved by the local Ethics Committee and all participants gave their informed consent prior to being included in the study. Twenty PD patients treated with bilateral STN DBS for motor fluctuations and/or dyskinesias and eighteen matched controls, all males were included in the study. All the patients fulfilled the UK Brain Bank Criteria for diagnosis of PD. (Hughes *et al.*, 1992)

On the day of the study all participants were screened for cognitive and mood status using the Mini Mental State Examination (Folstein *et al.*, 1975) and the Beck Depression inventory (BDI; Beck et al., 1996).(Beck *et al.*, 1996) The patients and controls demographic variables and disease characteristics are summarized in Table 3. No differences were found for age, MMSE, BDI or education duration between the patients and control group. In the PD group, the mean daily dose of dopaminergic medications (in levodopa equivalents (Kleiner-Fisman *et al.*, 2006) was 550.3±479 mg. Fourteen patients were on levodopa only, two were taking a combination of levodopa with dopamine agonists, two were on dopamine agonist therapy only and two patients were free of dopaminergic medication. Five of the patients were on antidepressant therapy (three on citalopram, one on mirtazapine, one 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 one 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)(Christenson *et al.*, 1994) and all patients who scored in MIDI were examined by a psychiatrist. Only one patient that presented signs of binge eating and punding met the criteria for obsessive-compulsive disorder.(Voon *et al.*, 2009)

		PD Patients	Controls
Age (years)		58.3 ± 6	56.1±7
Education duration (years)		13.8±3	16.9±3
MMSE		28.6±1	29,4±1
BDI		11.8±7	8.4±6
Disease duration (years)		15.7±4	
Time interval after surgery (years)		2.8±2	
DBS STN Parameters	Frequency (Hz)	130.8±3	
	Puls width (us)	76.3±23	
	Amplitude (V)	2.8±0	

Table 3. Parkinson's disease patients and control group – demographic and disease characteristics

Values are expressed as means ± SD

MMSE, Mini Mental State Examination; BDI, Beck Depression Inventory;

DBS STN, Deep Brain Stimulation of the Subthalamic nucleus

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.(Lang and Bradley, 2008) Eighty-four pictures were selected consisting of: i) 21 erotica (erotic females and couples) and ii) 21 food, iii) 21 aversive – victims (mutilations) and threat (human or animal attacks, aimed guns) and iv) 21 neutral content (household objects, buildings, plants. Examples of pictures from different categories are given in Figure 2. 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 two pictures with the same content followed.

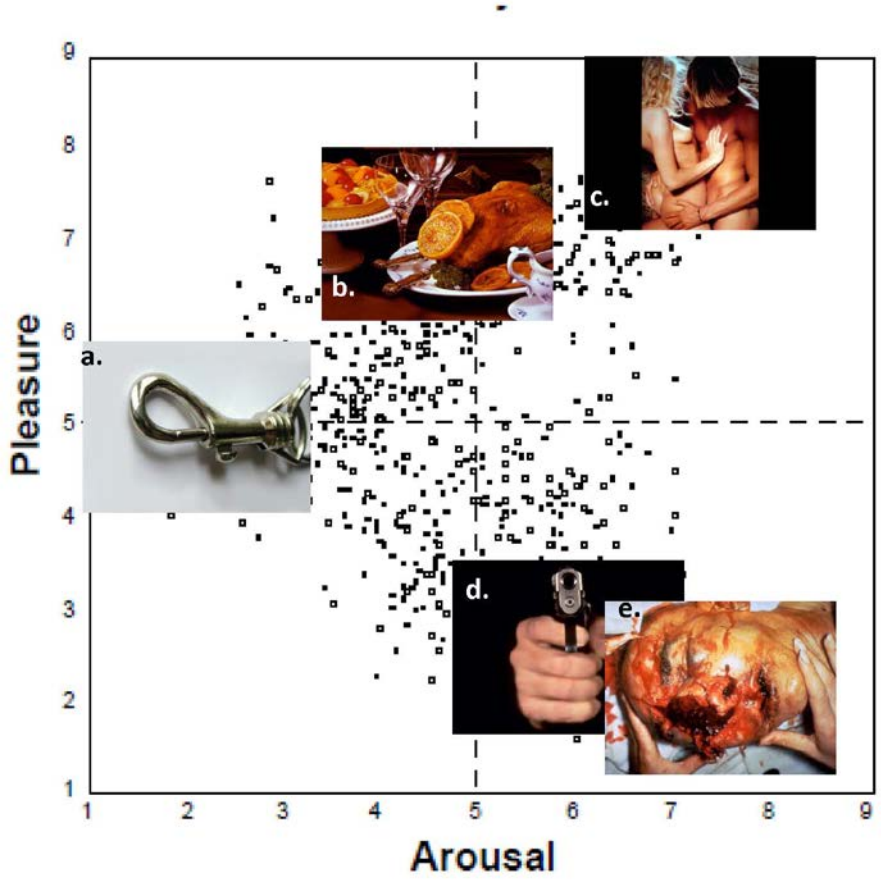

Figure 2. Examples of pictures from the different categories

a. neutral picture; b. food picture; c. erotic picture; d. and e. aversive pictures: d. threat picture, e. victim picture

Pictures are according to their normative ratings superimposed on the boomerang shaped figure that results when each picture of the IAPS is plotted in terms of its normative valence and arousal ratings.(Lang and Bradley, 2008)

The numbers of selected 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: 7402, 7481, 7230, 7320, 7482, 7200, 7350, 7330, 7487, 7220, 7286, 7488, 7289, 7291, 7352, 7283, 7340, 7460, 7280, 7480, 7475;

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, and threat/victim picture 9410

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 a.m. Then they were tested in two 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 6s. Subjects were required to rate each picture separately along the dimension of emotional valence and arousal by self-paced touching the appropriate symbol on two independent visual scales that were presented on the screen after the picture offset. The scales were designed according to the original IAPS scales.(Lang and Bradley, 2008) 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 the IAPS manual. Then they were shown 8 representative pictures for training purposes.

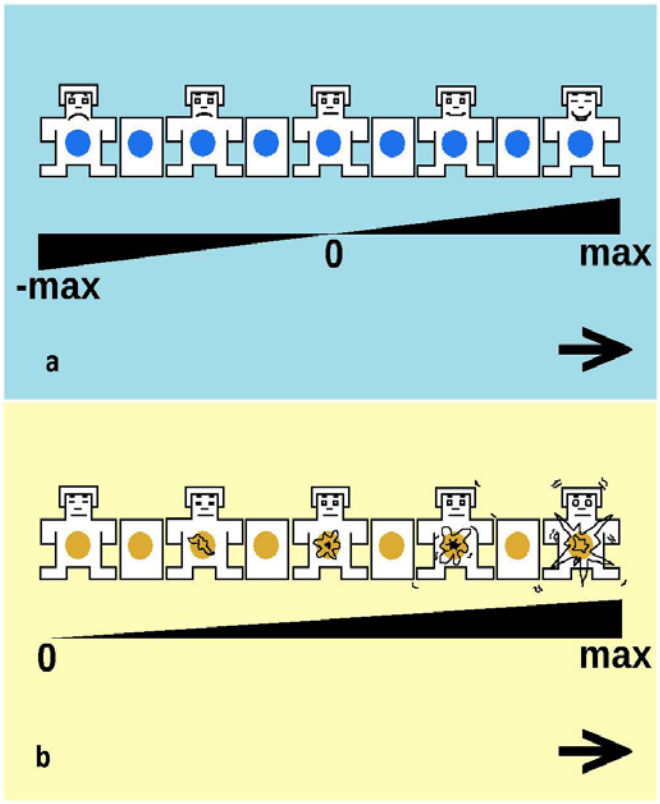

Figure 3. Rating scales

a) Valence (from the left to the right, ranging from most unpleasant to most pleasant)

b) Arousal (from the left to the right, ranging from calm to most arousing)

1-9 scales were designed according to the original scales from the Self Assessment Manikin, which was deviced for emotional ratings of IAPS pictures.(Lang and Bradley, 2008)

4.2. Data analysis

For statistical analysis the SPSS 14.0.1 software (Chicago, IL) was used. As several parameters did not follow the normal distribution, non-parametric 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 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.

4.3.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 ($Z=3.9$, $P<0.0001$).

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 ($\chi^2=7.4$, $P<0.05$ corrected). No differences in valence ratings were found for the other picture categories (Figure 4.).

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 ($Z=2.0$, $P<0.05$). 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 5).
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.

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.

Effect of order on aversive pictures ratings: a post hoc analysis

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).
The results for aversive pictures ratings in patients tested in OFF and ON condition first are summarized in the table 4.
For victims Picture the results were similar. There was a significant between OFF and ON condition difference only in patients tested in OFF condition first: for valence (Z=2.2, P<0.05) and for arousal (Z=2.1, P<0.05).

	AVERSIVE PICTURES					
	VALENCE OFF (mean)	VALENCE ON (mean)	Statistics OFF vs ON difference	AROUSAL OFF (mean)	AROUSAL ON (mean)	Statistics OFF vs ON difference
OFF first (N=12)	2.21	1.95	**Z=2.9, P<0.01**	6.59	7.48	**Z=2.2 P<0.05**
ON first (N=8)	2.15	2.05	Z=2.2, P<0.48	6.98	6.82	Z=0.5 P<0.61

Table 4. The results for aversive pictures valence and arousal ratings in patients tested in OFF and ON condition first. Significant results were found only in group of patients with larger DBS washout period (3 hours vs 1 hour) suggesting there was a DBS aftereffect.

ii) 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<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).

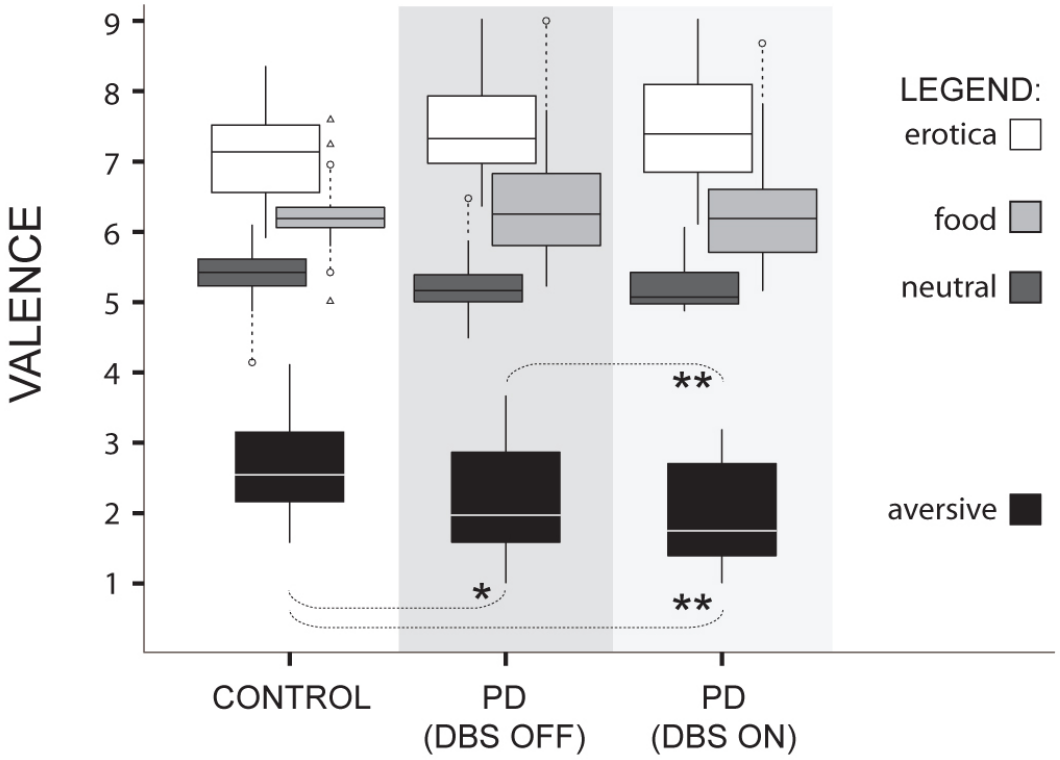

*Figure 4. Valence of selected IAPS pictures of four different categories (erotic, food, neutral, aversive content) as rated by control subjects (N=18) and PD patients (N=20) in conditions with the STN DBS switched OFF and ON. The only difference between conditions/groups of subjects was found for valence of pictures with the aversive content (significance level of post hoc tests: *P<0.05, **P<0.01).*

The box-plot represents: median (horizontal line), interquartile range (length of the box-plot), values within 1.5 interquartile range of the upper/lower quartile (whiskers), ***o*** *– outliers (within 1.5 and 3.0 interquartile range), Δ - extreme values (>3.0 interquartile range); significance level of post hoc tests (*P<0.05, **P<0.01)*

*Figure 5. Valence of two sub-categories 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<0.05, **P<0.01)*

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 appetitive stimuli in the DBS ON condition (erotic: $r=0.66$, $P<0.01$ corrected; food: $r=0.69$, $P<0.01$ corrected) and weakly in the DBS OFF condition (erotic: $r=0.53$, $P<0.05$ 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 ($r=0.59$, $P<0.05$ corrected). (Figure 6.) 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 the body weight changes (see supplementary material). 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).

From correlation analysis we excluded patients (N=5) in whom weight changes were present after introduction of the antidepressants or dopamine agonists before or after the surgery. This included remained patients (N=15) with a well documented, stable body weight after the preoperative introduction of the antidepressants or dopamine agonists and patients in whom this treatment was introduced shortly before testing and in whom no weight change has been detected since then. The positive body weight change correlated positively with arousal ratings of appetitive stimuli in the DBS ON condition (erotic: $r=0.70$, $P<0.01$ corrected; food: $r=0.77$, $P<0.01$ 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 the body weight change 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 ($r=0.64$, $P<0.05$ corrected).

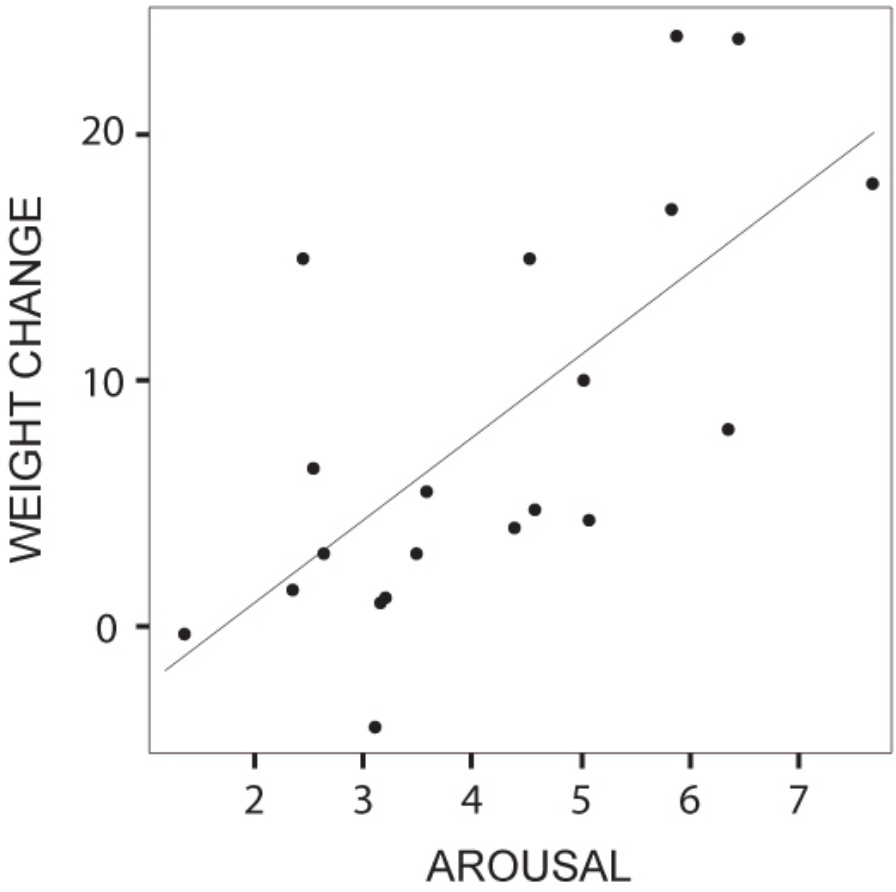

Figure 6. Correlation between the arousal of the pictures with the food content rated by Parkinson's disease patients (N=20) with the STN DBS switched ON and the body weight change before/after STN DBS implantation.

4.4.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 (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 (Liberzon *et al.*, 2003, Phan *et al.*, 2004) and suggested the influence of arousal level on affective and motivational physiological responses.(Bernat *et al.*, 2006, 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 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.(Faure *et al.*, 2008, Horvitz, 2000) Generally, this finding supports a threshold model in which highly arousing and valenced stimuli are needed to detect differences in physiological reactivity between controls and PD patients, whereas less arousing stimuli may not be sufficient to detect this difference.

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. Moreover, the increased motivational relevance attribution to aversive pictures in DBS OFF condition in comparison to controls could not be easily attributed to the neurodegenerative process itself or medication as there is of evidence for impaired incentive salience attribution by dopamine loss (Horvitz, 2002, Chinaglia *et al.*, 1992) or an inhibiting effect of antidepressants on aversive stimuli processing. (McCabe *et al.*, 2009, Rawlings *et al.*, 2010)

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 but without eliciting binge eating.(Baunez *et al.*, 2002, Rouaud *et al.*) 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.(Jech *et al.*, 2001, Johnson *et al.*, 2008, Vitek, 2008) The positron emission tomography (PET) studies failed to show substantial changes in striatal DA concentration due to STN DBS in humans.(Abosch *et al.*, 2003, Hilker *et al.*, 2003, Strafella *et al.*, 2003) However, it has been objected that the small number of residual intact dopaminergic neurons is unable to provide relevant levels of striatal dopamine detectable by the PET scan in advanced PD patients.(Abosch *et al.*, 2003) Recent animal studies using fast scan cyclic voltammetry and amperometry that overcome the analytical limitations of PET and the microdialysis studies found that STN DBS evoked striatal DA release.(Covey and Garris, 2009, Lee *et al.*, 2006, Shon *et al.*, 2010) In animals, STN DBS has been found to increase activity of the dopamine system (Lee *et al.*, 2006, 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 (Groenewegen and Berendse, 1990, Parent and Hazrati, 1995) and ventral pallidum(Parent and Hazrati, 1995, Smith *et al.*, 2009) or by activating directly the mesolimbic dopaminergic projections from ventral tegmental area to nucleus accumbens that are running within the adjacent medial forebrain bundle. (Vitek, 2008, Wise, 2005)

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 comparison and on the body weight of PD patients. (Aronne and Segal, 2003),(Kumru *et al.*, 2006),(Palhagen *et al.*, 2005)

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.

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

5.1. **Materials and Methods**

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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. All patients fulfilled the UK Brain Bank Criteria for the diagnosis of PD(Hughes *et al.*, 1992). The control group was composed of eleven healthy, age-matched subjects.

Before recruitment, all participants were screened for cognitive and mood status using the Mini Mental State Examination (MMSE)(Folstein *et al.*, 1975) and the Beck Depression Inventory (BDI)(Beck *et al.*, 1996). We used a modified version of the Minnesota Impulsive Disorders Interview to rule out impulse control disorders and repetitive behaviors in patients and controls(Christenson *et al.*, 1994).

Demographic and disease-related characteristics of patients and healthy subjects are summarized in Table 5. No differences were detected between patient and control groups in the MMSE-Mini Mental State Examination or BDI-Beck Depression Inventory. *Levodopa equivalent was calculated according Deuschl *et al.*, 2006. Eight patients received levodopa only, two patients received a combination of levodopa and dopamine agonists, one patient received dopamine agonist therapy only, and one patient did not receive dopaminergic medication. One of the control subjects received anxiolytic therapy with buspiron. No other psychotropic medications were taken.

In addition, 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.

		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 (1patient)	
	pulse width (us)	60 (N=9), 90 (N=8), 120 (N=5)	
	amplitude (V)	2.8 (2.3-3.5)	

Table 5. Demographic and disease characteristics of Parkinson´s disease patients and control group

Values expressed as mean (SD) or mean (interval). PD, Parkinson's disease; MMSE, Mini Mental State Examination; BDI, Beck Depression Inventory; STN DBS, deep brain stimulation of the subthalamic nucleus, N= number of electrodes.

Procedure

We selected a total of 84 pictures from the IAPS.(Lang and Bradley, 2008) They were chosen from four categories (21 each): neutral (household objects, buildings, plants), erotic (females and couples), food (sweet and salty) and aversive (victims (mutilations) and threats (human/animal attacks, aimed guns)). Erotic and aversive pictures were valence- and arousal-matched according to normative ratings. (Lang and Bradley, 2008) Three different picture orders were created with maximally two pictures from the same category presented in sequence.

The numbers of IAPS pictures were as follows (the same set of pictures was used as in the first study described in Chapter IV.)

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: 7402, 7481, 7230*, 7320, 7482*, 7200, 7350, 7330*, 7487, 7220, 7286*, 7488*, 7289*, 7291*, 7352, 7283, 7340, 7460, 7280, 7480, 7475;

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, and threat/victim picture 9410*

Pictures assigned with * were presented with startling acoustic stimulus in the study on ABR modulation

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, STN DBS ON and STN DBS OFF using different picture order for each condition. The testing was performed one hour after the stimulators were switched OFF or ON. In each condition, prior to testing, motor subscore of the Unified Parkinson's Disease Rating Scale (UPDRS-III)(Fahn *et al.*, 1987) was performed by a rater blinded to the DBS condition. 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 (Figure 7.).

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 according to the original IAPS scales.(Lang and Bradley, 2008) 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.

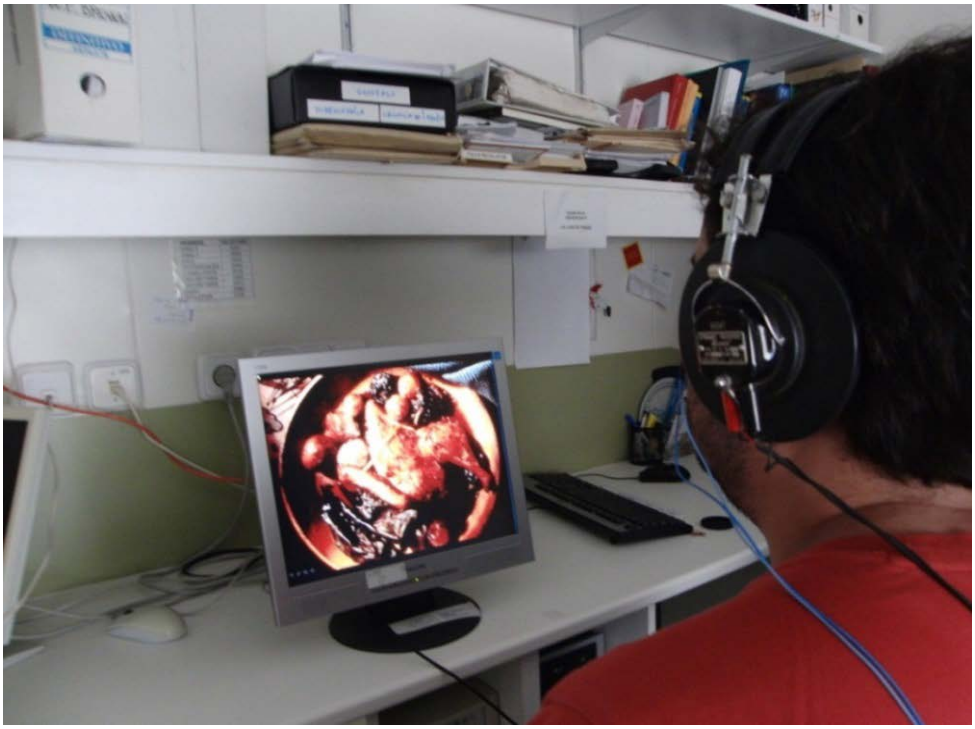

Figure 7. An illustrative photograph of the experimental set up

Series of pictures were presented on a touch sensitive screen. When startling acoustic stimulus (a 50 ms noise burst, 115 dB SPL) was delivered through the headphones (in 30% of pictures from each category) the acoustic blink reflex was recorded from the orbicularis oculi muscles.

Each picture out of 84 was presented for a period of 6 seconds 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 SPL, <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 was performed by custom EVSENG software (J. Wackermann, T. Sieger, Prague, Czech Republic).
Electromyographic (EMG) activity was recorded using Medelec Synergy (Oxford Instruments, Surrey, UK). Frequencies <50 and >1000 Hz were filtered from the raw EMG signal.

The monopolar artifact removal.

Several methods have been used for artifact removal, taking specific characteristics of different recordings (evoked potentials, electroencephalography) into account (Allen *et al.*, 2010, Jech *et al.*, 2006). In the present study, large artifacts related to monopolar STN DBS were removed by subtracting artifact templates in the spectral domain (Figure 8.). ABR signals were transformed into the spectral domain using the Fourier transform. Substantial spectral peaks located at multiples of DBS frequencies were considered potential artifacts, thus matched to artifact template in the form of

$$\frac{\sin(\beta t)}{\beta t}\alpha e^{-i\beta(t+\tau)}$$

,where α, β and τ were scaling parameters fine tuning the amplitude, frequency and phase shift of each artifact, respectively. The values of α, β and τ were found by nonlinear least square optimization. A spectral peak that fitted the scaled artifact template well was considered a genuine artifact, and thus eliminated from the spectra by subtracting the fitted, scaled artifact template from the spectra. Finally, the resulting artifact-free ABR was obtained by taking the inverse Fourier transform of the altered spectra.

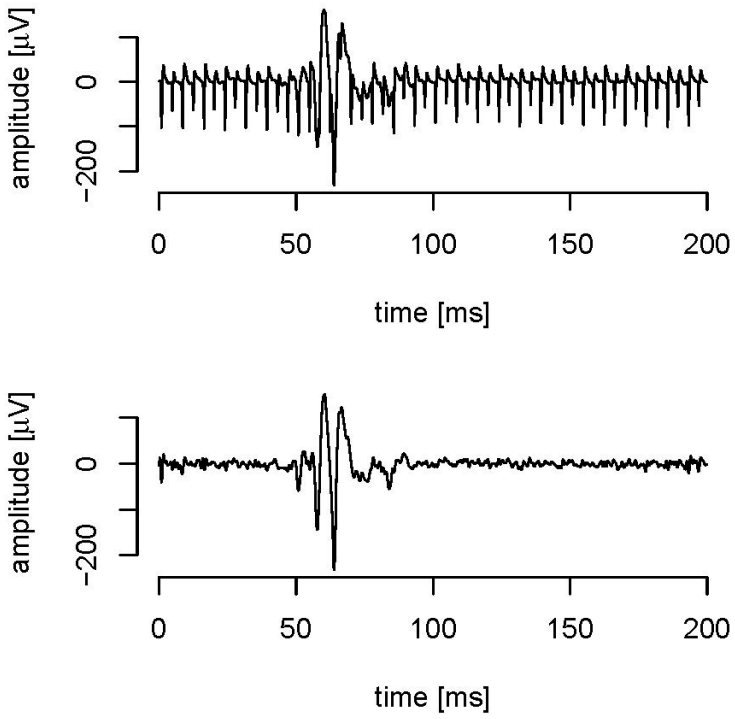

Figure 8. Recording of acoustic blink reflex from the orbicularis oculi muscle in DBS ON condition with an artifact related to monopolar deep brain stimulation of the subthalamic nucleus (top). The same recording after removal of the artifact by means of artifact template removal in spectral domain (bottom).

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 (Brown *et al.*, 1991, Chokroverty *et al.*, 1992, Kofler *et al.*, 2001) 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 were discarded.

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, Levenston *et al.*, 2000).

t-scores equation:

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

5.2.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.

5.3.Results

Clinical observations:

No differences were found for age, MMSE, BDI or education level between the patient and controls. 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 ($T(10)=8.56$, $P<0.001$).

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) and than controls (P<0.01 corrected) (Figure 9). Data on ABR size in all groups and picture categories are summarized in Table 6. The increase in ABR magnitude in the DBS ON relative to the DBS OFF condition was observed in 10 out of 11 patients (Figure 10).

		Neutral	Erotic	Food	Aversive
Healthy subjects	t-scores	36.6 (5.8)	34.8 (4.5)	36.4 (4.8)	37.8 (4.89)
	%		96.2 (9.4)	100.5 (9.6)	104.6 (13.1)
Patients OFF	t-scores	42.4 (3)	39.1 (6.0)	41.1 (6.0)	43.0 (5.6)
	%		91.7 (13.3)	96.2 (12.6)	100.8 (13.9)
Patients ON	t-scores	41.1 (6.1)	45.0 (6.8)	41.2 (8.5)	45.1 (11.4)
	%		110.2 (10.4)	99.7 (9.9)	108.9 (14.3)

Table 6 . Data on ABR size in all groups and picture categories
%= percentage of the ABR at emotionally neutral picture presentation,
SD within parenthesis

The relative change in ABR magnitude from different picture categories with respect to ABR magnitude to neutral pictures.

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

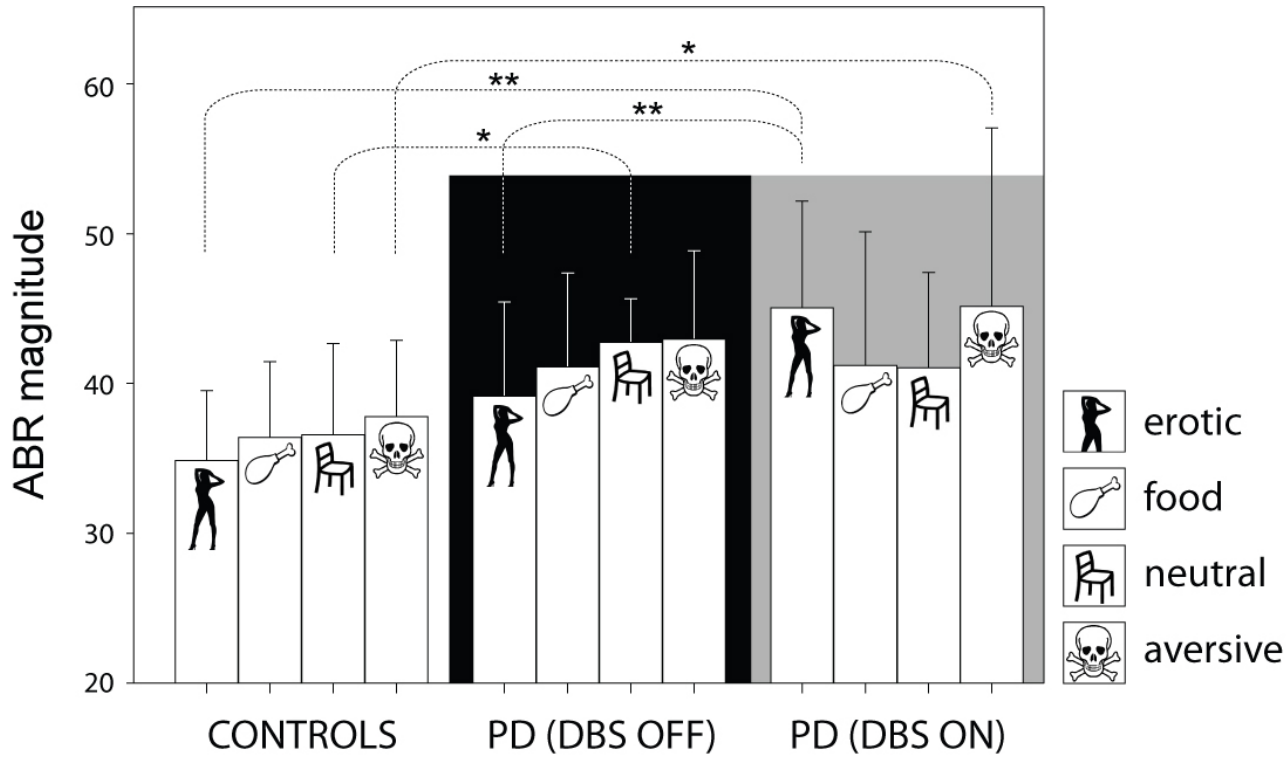

*Figure 9. Magnitude of the blink reflex to an acoustic startle probe (in t-scores) presented during viewing of erotic, food, neutral, and aversive pictures from control subjects (N=11) and Parkinson´s disese patients (N=11) in conditions with deep brain stimulation (DBS) of the subthalamic nucleus OFF 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 were potentiated as if aversive. Corrected significance level *P<0.05, **P<0.01.*

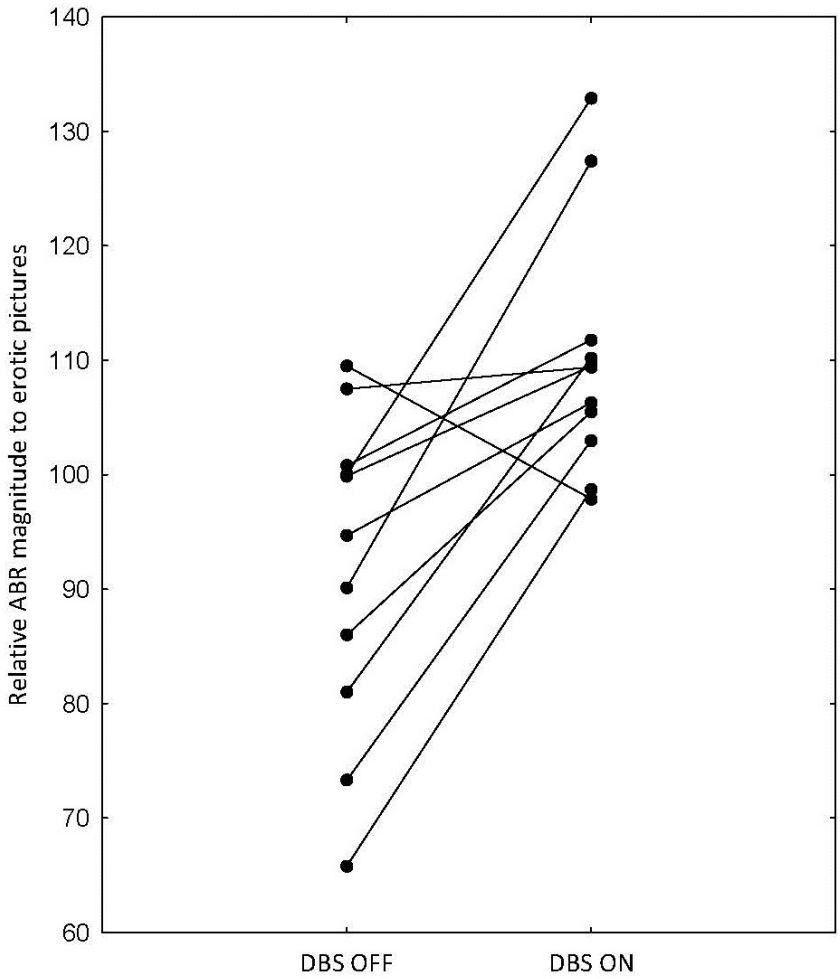

Figure 10. Relative magnitude of the acoustic blink reflex (ABR) in individual Parkinson´s disease patients (N=11) elicited during viewing of erotic pictures in subthalamic deep brain stimulation (STN DBS) OFF and ON conditions. In the STN DBS ON condition there was an increase in ABR magnitude in 10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

Affective ratings:

No significant differences in affective valence and intensity 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, intensity ratings shared the same pattern in all groups and conditions, in which the neutral pictures were rated as the lowest intensity, followed by food pictures, then by erotic pictures, and finally with aversive pictures ($P<0.001$ corrected).

Data on affective ratings in all groups and picture categories are summarized in Table 7.

	Neutral		Erotic		Food		Aversive	
	valence	arousal	valence	arousal	valence	arousal	valence	arousal
Healthy subjects	5.4 (0.3)	2.7 (1.5)	6.9 (0.6)	5.1 (1.4)	6.2 (0.7)	3.8 (1.6)	2.6 (0.8)	5.6 (1.9)
Patients OFF	5.2 (0.3)	3.0 (1.6)	7.4 (0.6)	5.8 (1.7)	6.3 (1.0)	3.8 (1.6)	2.2 (0.7)	6.8 (1.4)
Patients ON	5.2 (0.3)	3.0 (1.6)	7.4 (0.7)	5.1 (2.0)	6.2 (0.9)	3.4 (1.6)	2.1 (0.6)	6.9 (1.3)

Table 7. Data on valence and arousal ratings in all groups and picture categories mean absolute value, SD within parenthesis

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 to 10.9 kg; T=-2.38, 10 df, P<0.05).
Furthermore, 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, i.e., after adjusting with respect to ABR to food pictures in the DBS OFF condition Fr= -0.74, 9 df, P<0.01) (see figure 11). Postoperative weight gain correlated positively with the intensity rating of food pictures (r=0.70, 9 df, P<0.05).

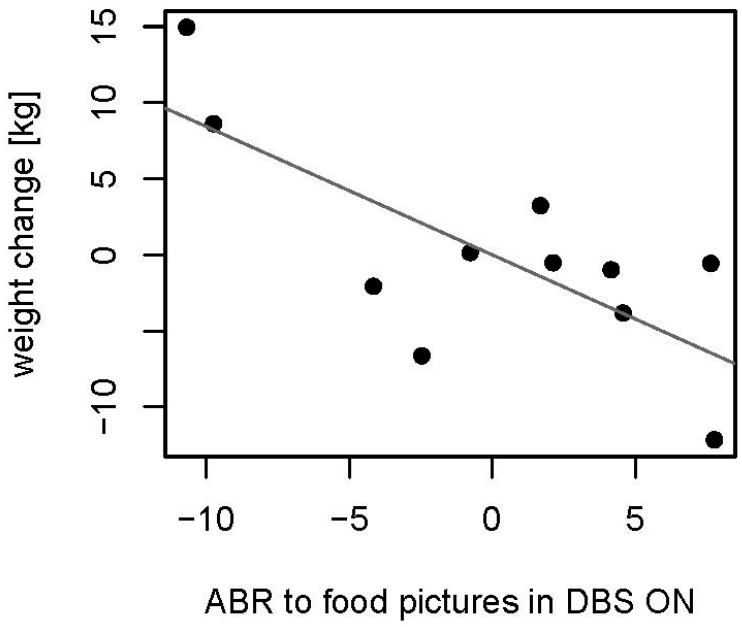

Figure 11. Partial correlation between acoustic blink reflex (ABR) magnitude to pictures of food in Parkinson´s disease patients (N=11) with deep brain stimulation of the subthalamic nucleus (STN DBS) ON, and body weight change after STN DBS implantation (kg), adjusted for ABR to pictures of food with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

5.4.Discussion

In the present study we observed changes in the affective modulation of the ABR due to STN DBS, which suggests that STN DBS modifies the emotional and motivational processing of primary reward cues and aversive stimuli. In previous ABR studies carried out during STN DBS,(Potter *et al.*, 2008) 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. The finding of a larger ABR in PD patients than in controls, regardless of DBS condition can 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.(Bradley *et al.*, 2006) The fact that larger ABR magnitudes were not reported in a previous study on affective modulation of the ABR in off-medicated PD patients,(Miller *et al.*, 2009) 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.(Maetzler *et al.*, 2009) (Sampaio *et al.*)

Affective modulation of the ABR becomes evident during viewing of affect-weighted pictures,(Bradley *et al.*, 2006) with ABR 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) Moreover, ABR potentiation was found in healthy individuals for adventure pictures depicting physically risky sports such as sky diving, which were rated as highly positive stimuli.(Bernat *et al.*, 2006) 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 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 . 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. This finding is consistent with increased motivation for food found in experimental animals after STN DBS(Baunez *et al.*, 2002, Baunez *et al.*, 2005, Baunez *et al.*, 2007, Lardeux *et al.*, 2009, Rouaud *et al.*, Uslaner *et al.*, 2008) and suggests that postoperative weight gain may be related to changes in the processing of food cues. Otherwise no changes in ABR modulation were detected for food cues. According to the subjective rating, food pictures were less intense stimuli. ABR modulation is more pronounced in the context of highly arousing stimuli and is absent for low-arousing stimuli, which only activate these motivational systems weakly (Bernat *et al.*, 2006).

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,(Jech *et al.*, 2001, Vitek, 2008, Winter *et al.*, 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(Ghashghaei *et al.*, 2007, Groenewegen and

Berendse, 1990 , Parent and Hazrati, 1995, Turner *et al.*, 2001, Winter *et al.*, 2008) and the primary startle circuit, and are also known to mediate the affective modulation of the ABR.(Koch, 1999, Koch *et al.*, 1996, Lang *et al.*, 1998) 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) 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 bahaviors including mixed bouts of both positive eating behavior and negative fearful trading in experimental animals.(Faure *et al.*, 2008, O'Donnell *et al.*, 1999, Pennartz *et al.*, 1994, Reynolds and Berridge, 2002, Richard and Berridge, 2011) The STN DBS interactions with the ventral basal ganglia circuits including the non-physiological release of the mesolimbic dopamine(Lee *et al.*, 2006, 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 pedunculo-pontine nucleus and the primary startle circuit as it was demonstrated for prepulse inhibition of the ABR.(Costa *et al.*, 2006)

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

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. In order to explore both aspects of the emotional and motivational processing, the subjective experience and the behavioral response, we examined STN DBS related changes in

1. subjective evaluation of motivational relevance to emotional stimuli, i.e., the incentive salience attribution
2. objective measure of motivational activation to emotional stimuli, i.e., the affective modulation of the startle response

We used an on-off study design, which enables to assess the direct effects of the STN DBS, while controlling for other factors such as changes in postoperative medication, preoperative vulnerability, surgical effects, underlying PD-related factors, and psychosocial effects. Moreover, due to the successful removal of the monopolar DBS related artifact the patients could be studied neurophysiologically in their long-term DBS therapeutic setting, they were adapted to.

1. The present results support our hypothesis that STN DBS modifies the emotional and motivational processing of primary reward cues and aversive stimuli in PD patients.

   Both subjective and 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 likely disrupts physiological inhibition of ABR by appetitive (erotic) cues. These may be experienced as frustrative non-reward (Amsel, 1962) 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.

   In addition, in patients with postoperative weight gain, we found an increased sensitivity to food cues reflected in subjective ratings and also an increased engagement of appetitive motivational system by food cues according to startle modulation measure. This suggests that STN DBS may increase motivation for

food cues, thereby contributing to postoperative weight gain. This may be of practical value for management of this side effect.

2. Our results also support the second hypothesis that the human STN is involved in processing of primary rewards and aversive stimuli. Some evidence for STN role in emotional processing has been already gathered from neurophysiological studies in PD patients, however, the STN involvement in processing of motivationally relevant signals such as food and erotic cues or threatening stimuli has not been studied so far. In line with findings from animal studies, our results suggest that the human STN forms part of the reward circuits and that the STN DBS may potentially influence biological behavior and social interactions.

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VIII. Abbreviations

ABR	Acoustic Blink Reflex
AUC	Area under the Curve
BDI	Beck Depression Inventory
DBS	Deep Brain Stimulation
EMG	Electromyography
fMRI	functional Magnetic Resonance Imaging
IAPS	International Affective Picture System
MMSE	Mini-mental State Examination
PD	Parkinson’s disease
SAS	Startling Acoustic Stimulus
STN	Subthalamic nucleus
UPDRS	Unified Parkinson’s Disease Rating Scale

IX. Supplement I - Publications

(Cumulative impact factor 13.8)

Original articles related to the Thesis:

1. **Serranová 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. V recenzním řízení.

2. **Serranová T**, Jech R, Dusek P, Sieger T, Ruzicka F, Urgosik D, Ruzicka E. Subthalamic nucleus stimulation affects incentive salience attribution in Parkinson's disease. Mov Disord. 2011 Oct;26(12):2260-6. **IF=4.48**

3. Novakova L, Ruzicka E, Jech R, **Serranová T**, Dusek P, Urgosik D. Increase in bodyweight is a non-motor side effect of deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Neuro Endocrinol Lett. 2007;28:21-5. **IF = 1.443**

4. Jech R, Růžička E, Urgošík D, **Serranová T**, Volfová M, Nováková O, Roth J, Dušek P, Mečíř P. Deep brain stimulation of the subthalamic nucleus affects resting EEG and visual evoked potentials in Parkinson's disease. Clin Neurophysiol. 2006 May;117(5):1017-28. **IF = 2.718**

5. Růžička E, Urgošík D, Jech R, **Serranová T**, Volfová M, Roth J, Vymazal J, Mečíř P, Nováková O, Ulmanová O, Brožová H, Dušek P, Špačková N, Liščák R, Vladyka V. Hluboká mozková stimulace v léčbě Parkinsonovy nemoci a třesu: Pražská zkušenost 1998-2003. Čes a Slov Neurol Neurochir. 2004;67(6):423-431**. IF = 0.037**

Other original articles

1. **Serranová T,** Jech R, Marti MJ, Modreanu R, Valldeoriola F, Sieger T, Růžička E, Valls-Solé J. A loud auditory stimulus overcomes voluntary movement limitation in cervical dystonia. PLoS One. V rezenzním řízení.

2. Barraza G, **Serranova T,** Herrero C, Casanova-Mollá J, To-Figueras J, Herranz J, Valls-Solé J.Brainstem dysfunction in variegate porphyria. Přijato k publikaci Muscle and Nerve DOI: 10.1002/mus.23367 **IF: 2.302**

3. **Serranová T**, Valls-Solé J, Muñoz E, Genís D, Jech R, Seeman P. Abnormal corticospinal tract modulation of the soleus H reflex in patients with pure spastic paraparesis. Neurosci Lett. 2008 May 23;437(1):15-9. **IF: 2.085**

4. Roth J, Klempìi J, Jech R, Zidovská J, Uhrová T, Doubek P, Ulmanová O, Brozová H, Volfová M, **Serranová T**, Ruzicka E. Caudate nucleus atrophy in Huntington's disease and its relationship with clinical and genetic parameters. Funct Neurol. 2005 Jul-Sep;20(3):127-30. **IF: 0.681**

5. Kemlink D, Sonka, K, Nevsimalova S, Pretl, M, Benakova M, Zima T, Pantelakis L, **Serranova T**. Familial and sporadic forms of restless legs syndrome. Čes a Slov Neurol Neurochir. 2003;66(6): 387-391. **IF: 0.052**

X. Supplement II. Publications in extenso

1. Serranová T, Jech R, Dusek P, Sieger T, Ruzicka F, Urgosik D, Ruzicka E. Subthalamic nucleus stimulation affects incentive salience attribution in Parkinson's disease.

2. Novakova L, Ruzicka E, Jech R, Serranová T, Dusek P, Urgosik D. Increase in bodyweight is a non-motor side effect of deep brain stimulation of the subthalamic nucleus in Parkinson's disease.

3. Jech R, Růžička E, Urgošík D, Serranová T, Volfová M, Nováková O, Roth J, Dušek P, Mečíř P. Deep brain stimulation of the subthalamic nucleus affects resting EEG and visual evoked potentials in Parkinson's disease.

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.

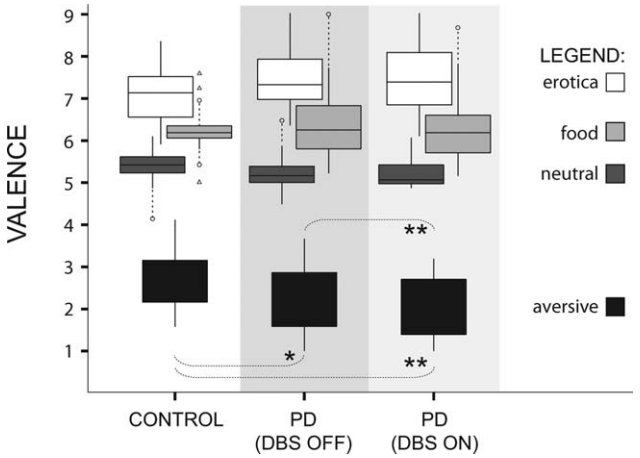

FIG. 1. Valence of selected IAPS pictures of 4 categories (erotic, food, neutral, aversive content) as rated by control subjects (n = 18) and PD patients (n = 20) in conditions with the STN DBS switched OFF and ON. The only difference between conditions/groups of subjects was found for the valence of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

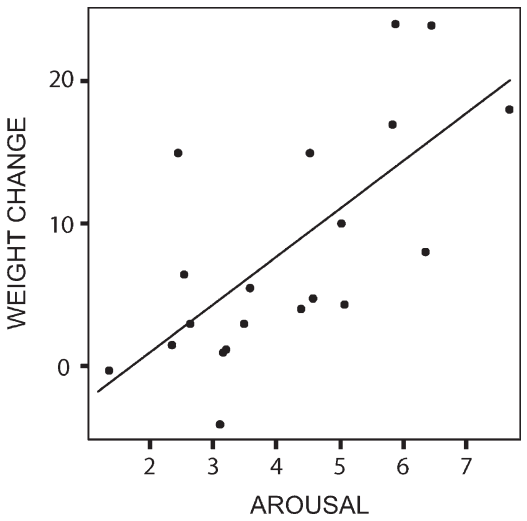

FIG. 3. Correlation between the arousal of the pictures with the food content rated by Parkinson's disease patients (n = 20) with the STN DBS switched ON and body weight change after STN DBS implantation (kg).

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.

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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Increase in body weight is a non-motor side effect of deep brain stimulation of the subthalamic nucleus in Parkinson's disease

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Abstract

Deep brain stimulation of the subthalamic nucleus (DBS STN) is an effective treatment method in advanced Parkinson's disease (PD) providing marked improvement of its major motor symptoms. In addition, non-motor effects have been reported including weight gain in PD patients after DBS STN. Using retrospective survey, we aimed to evaluate weight changes in our patients with advanced PD treated with DBS STN. We inquired 25 PD patients (16 men, 9 women), of mean age 55 (42–65) years, mean PD duration 15 (9–21) years, who previously received bilateral DBS STN. We obtained valid data from 23 patients. In the first survey, 1 to 45 months after DBS, weight gain was found in all patients comparing to pre-DBS period. The mean increase was 9.4 kg (from 1 to 25 kg). The patients' mean body mass index (BMI) increased from 23.7 to 27.0 kg/m^2, i.e. by 3.3 kg/m^2 (+2 to +6.1 kg/m^2). In the repeated survey one year later, in 12 of the patients body weight moderately decreased, 3 did not change, and 6 patients further increased their weight. Possible 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.

Abbreviations

DBS STN	- Deep Brain Stimulation of the subthalamic nucleus
PD	- Parkinson's disease
BMI	- Body Mass Index
UPDRS	- Unified Parkinson Disease Rating Scale
MDS	- Movement Disorder Society
LEDD	- Levodopa Equivalent Daily Dose

Introduction

Bilateral deep brain stimulation of the subthalamic nucleus (DBS STN) is an effective treatment method for selected patients with advanced Parkinson's disease (PD), who can not be optimally controlled by pharmacotherapy. DBS is performed using a stimulating electrode stereotactically implanted into an exactly defined target within the brain, and connected to a stimulator generating high-frequency electrical pulses. It has been sug-

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gested that DBS modifies function of the brain nuclei and circuits and therefore influences motor symptoms of the disease. Beside the effects of DBS STN in PD [11], DBS of the internal segment of the globus pallidus was shown to alleviate both symptoms of PD and different dyskinesias, and DBS of the ventral intermedius thalamic nucleus reduces tremor of various origin [3].

DBS STN effectively influences main motor symptoms of PD (tremor, rigidity, bradykinesia) and as a main therapeutic advantage over pharmacotherapy, it improves late stage motor complications of PD. DBS STN directly alleviates motor fluctuations and indirectly, allowing for reduction of antiparkinsonian medication, suppresses dopaminergic induced dyskinesias.

Beside these largely beneficial outcomes, motor as well as non-motor side effects of DBS have been reported. Non-motor effects include occasional behavioral changes, affective and cognitive disorders. In addition, weight gain has been recently reported as an unexpected consequence of DBS [13,2,9,21]. Also in our PD patients, we noticed weight gain following DBS STN [19]. Therefore, the present study was performed in order to evaluate body weight changes in our patients with advanced PD that were treated with DBS STN.

Material and methods

All 25 patients who received DBS STN between 2000 and 2003 in the Movement Disorders Center, Charles University, Prague, were included in the study. They were 16 men and 9 women, mean age in the time of intervention was 55 years (range 42–65), mean PD duration 14 years (range 9–21).

Repeated retrospective survey was used as a method. The mean interval between DBS implantation and the first survey was 19 months (range 1–45). The subjects were provided with a structured questionnaire (44 questions) regarding their family and personal history focusing on potential presence of metabolic syndrome. Further specific questions concerned body weight changes in the period preceding PD, and in the course of PD, before and after the implantation of DBS. All addressed participants returned the questionnaire.

Body mass index (BMI) was calculated from a person's weight in kilograms divided by height in meters squared (BMI=kg/m^2). Accordingly, patients were divided into 6 groups: underweight (BMI under 18.5), normal weight (BMI from 18.5 to 25), overweight (BMI 25–30), 1st degree obesity (BMI 30–35), 2nd degree obesity (BMI 35–40) and 3rd degree obesity (BMI over 40).

We repeated the survey with the same group twelve months later focusing on body weight and metabolic syndrome signs.

All patients were neurologically evaluated using Unified Parkinson Disease Rating Scale (UPDRS) and MDS scale of dyskinesias within one week before and approximately 1 year after DBS STN implantation. Daily doses of dopaminergic medication were converted to Levodopa Equivalent Daily Dose, LEDD (100 mg of standard levodopa equals 150 mg of CR levodopa, 1 mg pergolide or pramipexole, 10 mg bromocriptine, or 6 mg ropinirole).

Body weight values before and after DBS were compared using paired Student's t-tests. Correlations between clinical parameters and body weight changes were calculated using Spearman's rho coefficient.

Results

Within one year from DBS implantation, 23 out of 25 patients did experience motor improvement including alleviation of motor fluctuations and dyskinesias (detailed results of clinical evaluation were published in [19]). Two patients were excluded from the study of body weight changes. One because of discrepancies between the data provided in the patient's questionnaire, our observation, and the data provided by family members. The other one has had DBS interrupted in the time of the first survey as the stimulator was temporarily withdrawn due to inflammatory complications.

Body weight changes

All 23 patients reported body weight gain after DBS implantation (Table 1, Figure 1). In the first survey, we found an overall mean increase in weight of 9.4 kg (range 1–25 kg), i.e. +13%, p<0.0001. In women, there was an average increase in weight of 12.8 kg (range 6–25 kg), i.e. +21%, p<0.01, and in men, weight increased by 7.6 kg (range 1–20 kg), i.e. +10%, p<0.0001. Comparing mean weight increases in men and women, there was a trend towards difference in genders (p=0.07), In the second survey, 14 subjects lost weight, 3 remained stable, and 6 reported further weight gain compared to the first survey. The mean weight change compared to the first survey was –1.4 kg (range –6 to +11 kg) i.e. –2%, p=0.11; –2.4 kg in men (range –6 to +4 kg) i.e. –3%, p<0.01 and +0.5kg in women (range –6 to +11 kg) i.e. +1%, p=0.79. Comparing the second survey to the values before DBS, there was a mean weight gain of 8 kg (from –4 to +24 kg), p<0.0001. With regard to the information on weight preceding the onset of PD, following DBS, there was a mean change of +13 kg (from –4 to +33 kg) comparing to the lowest weight before PD onset and a mean change of +4 kg (from –9 to +25) comparing to the highest weight the patients ever had before PD onset. In this last comparison, body weight increased in 13, decreased in nine, and two patients were unable to state their highest weight before PD.

No significant correlation was found between changes in UPDRS and MDS scores of dyskinesias and weight changes. Nor did we find any significant correlation between weight changes and the changes in LEDD.

After DBS, all patients increased their BMI. The mean BMI before DBS STN was 23.7 (±standard deviation 2.9). In the first survey, it increased to 27.0 kg/m^2 (±3.6) and in the second survey, it remained nearly unchanged at 26.6 (±3.5) kg/m . Shifts in BMI categories occurred, too.

Comparing to BMI values before DBS, in the first survey two patients increased by two BMI categories, 11 patients shifted by one BMI category (one patient increased from underweight to normal weight, 7 increased from normal weight to overweight, and 3 increased from overweight to the 1st degree of obesity). Ten patients did not change their BMI category. In the second survey, 17 patients did not demonstrate any further changes in their BMI category, 2 patients shifted down 1 category (from the 1st degree of obesity to overweight), and 1 patient shifted up one category from the 1st degree of obesity to the 2nd degree of obesity (Figure 2).

Discussion

In this retrospective study, we found weight gain accompanying motor improvement in all 23 patients evaluated after DBS STN. Therefore, we confirm previous findings of weight increase after DBS STN. Similarly to other reports [13,2,9,21], average weight gain was nearly 10 kg. Surprisingly, women in our study tended to gain more weight than men, while in none of the previous reports such difference between genders was found. Weight gain in our patients did not correlate with any of clinical variables reflecting motor improvement neither with reduction of dopaminergic treatment following DBS STN.

We have to admit that due to the method used (retrospective questionnaire) and different intervals for each patient between the implantation and the time of the first survey, our results are not completely comparable with previous reports. However, in our study, we observed patients for a longer period of time and repeated the same survey on the study group one year later. Thanks to this, beside weight gain following DBS, we found out that at longer intervals, it is possible to observe weight

Table 1. Weight changes after DBS

	Before DBS		After DBS: 1st survey			After DBS: 2nd survey		
	Mean weight (kg)	Range (kg)	Mean weight (kg)	Range (kg)	Mean weight change (1st survey – before DBS) (kg)	Mean weight (kg)	Range (kg)	Mean weight change (2nd survey – 1st survey) (kg)
All	71.0	50–96	80.4	58–105	9.4***	79.0	60–100	–1.4
Men	75.9	60–96	83.5	70–105	7.6***	81.1	66–100	–2.4
Women	61.9	50–79	74.6	58–90	12.8*	75.1	60–90	+0.5

***p<0.0001; *p<0.01

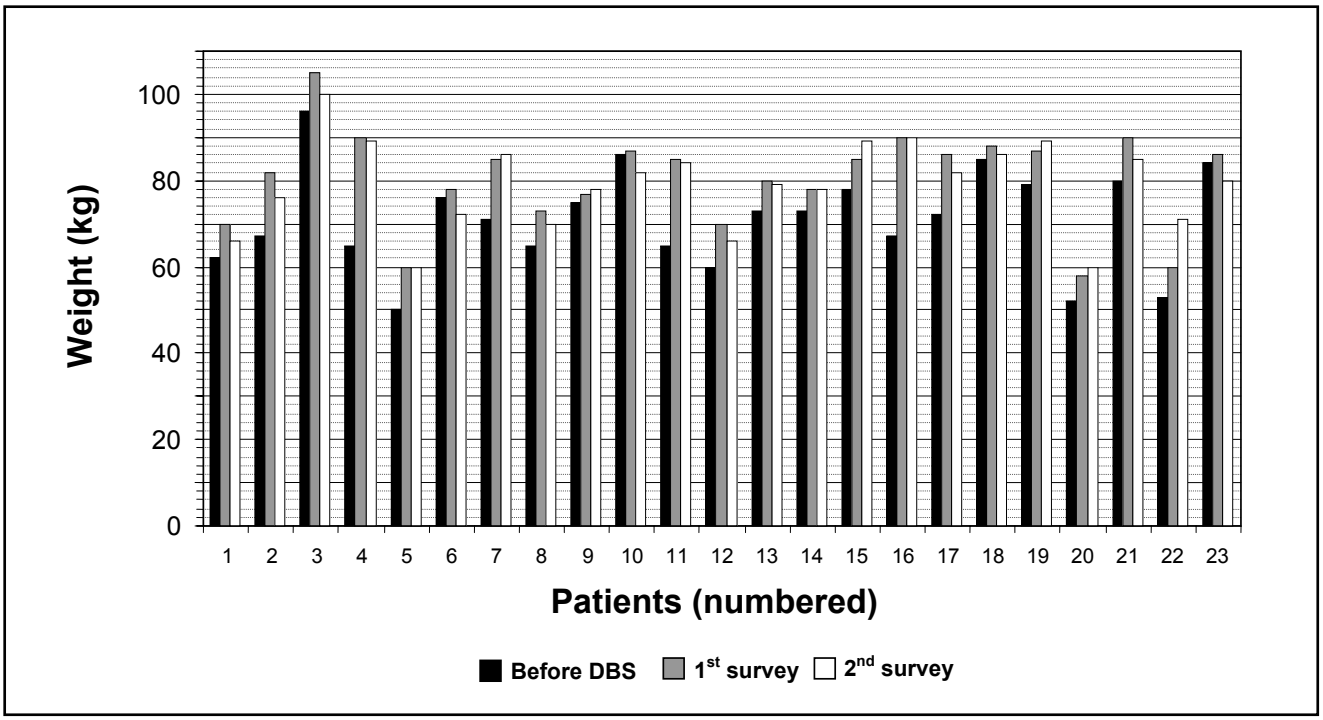

Figure 1. Individual weight changes of the patients before DBS, and after DBS in the first and second survey (kg)

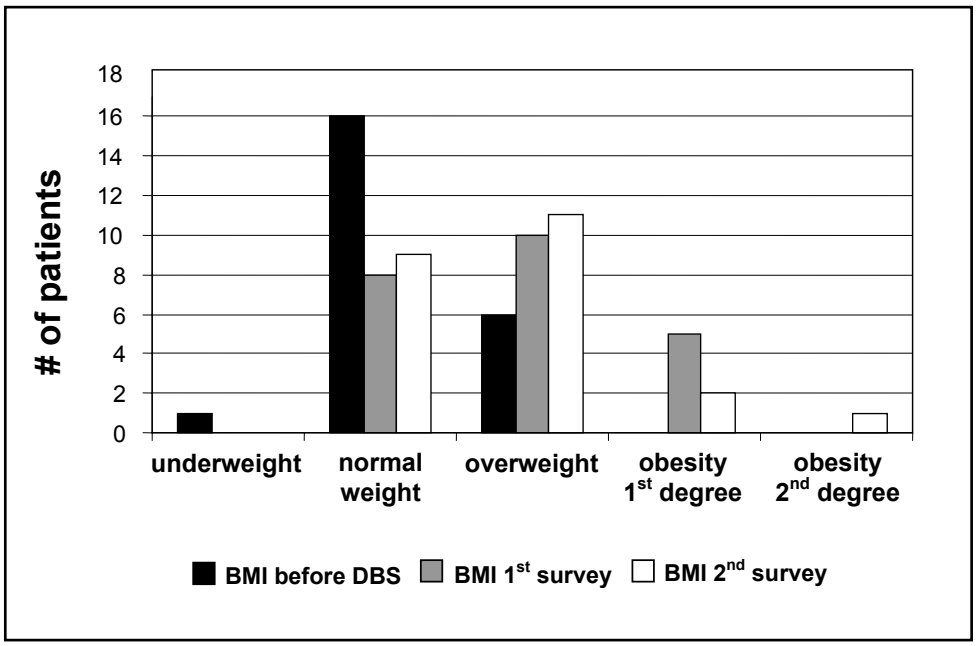

Figure 2. Body Mass Index distribution before DBS, in the first survey and in the second survey. BMI - Body Mass Index

loss reversing the previous weight increase but rarely back to the same level as before DBS. It was unclear how long after the DBS implantation the trend change from increasing to decreasing weight occurred. Possibly, some patients could have already been in a decreasing weight trend when we surveyed them first time, however, they could still report an increase in weight compared to the time before DBS. The weight change interval seems to be very individual. In fact, within 12 months following the first survey, weight increased in three patients with the longest interval as well as in three patients with the shortest interval from the implantation.

In brief, despite different observation methods, the findings from several centers agree in demonstrating weight gain in patients with PD after DBS STN. The mechanism of this weight gain is still unclear and various hypothetical explanations can be suggested.

Firstly, weight gain following DBS STN might reflect a reversal of previous weight loss in PD. Indeed, weight loss has been observed since the early stages of PD and it usually progresses during its course [4,8,15]. According to one study, weight loss in PD patients may begin 2–4 years before the diagnosis is made [7]. One reason for weight loss starting from the beginning of PD may be worsened exploitation of energy from food due to gastrointestinal visceromotor impairment. Accordingly, recent pathologic findings showed involvements of bulbus olfactorius and visceromotor nuclei of the brainstem since the earliest stages of the disease [5]. Also, olfactory dysfunction and motor disability can lead to a decrease of appetite and, in consequence, to a decrease of energetic input [4,1]. However, several studies have reported equal or even higher intake of energy in PD patients compared to healthy subjects [7,20,8]. Surprisingly, according to these studies, energetic input starts to increase when weight begins to decline [4]. The fact that weight loss occurs despite higher intake of energy could mean that it is caused by higher energetic output. This explanation was supported by a couple of studies, which proved that an increase of energetic output was related to severe muscle rigidity [14,10] or dyskinesias, where BMI was negatively correlated with severity of dyskinesias [17]. It was also found that weight loss correlates with the disease severity [4], the degree of hypokinesia [18] or with cognitive decline [12]. Consequently, weight gain can be explained by motor improvement following DBS, especially owing to a reduction in exhausting dyskinesias. Subsequently, the energy output may be reduced, as it was demonstrated in one previous study [13]. Nevertheless, in agreement with our results, the study did not find any correlation between weight gain and the reduction of dyskinesias according to detailed dyskinesia scales [13]. Another study that demonstrated a correlation between weight change and severity of dyskinesias, did so only according to raw UPDRS IV scores that are based on subjective patient evaluation [2].

Secondly, weight gain can be related to changes in medication, especially with regard to a reduction or withdrawal of dopaminergic therapy. It is well known that dopaminergic drugs can cause gastrointestinal discomfort, nausea and vomiting. Therefore, a reduction of dopaminergic drugs might lead to improved alimentation due to an alleviation of the side effects. Nevertheless, neither in our group nor in a previous report [2] patients complained of nausea and vomiting before or after DBS STN. There remains a possibility that dopaminergic therapy can directly influence metabolism and energy consumption. In fact, only a few studies investigated levodopa therapy

in relation to weight in PD patients [18,16]. Palhagen et al. found that patients with an early stage of PD were losing weight even before the initiation of dopaminergic treatment and the loss of weight progressed after levodopa was given [18]. No correlation was found between levodopa dose and weight loss. It was hypothesized that motor improvement induced by levodopa led to changes in energetic input/output ratio. Possible lipolytic or other metabolic effects of levodopa were suggested as well [22]. Consequently, a reduction of levodopa doses would cause weight gain. However, our data do not support this assumption. In accordance to a previous work [2], weight gain did not correlate with LEDD reduction in our patients. In another study, despite a correlation found between LEDD reduction and weight gain, the decreases of LEDD did not correlate with changes in energy expenditure [13].

Finally, weight changes could reflect a direct influence of DBS on autonomous functions and metabolic regulation. The question then would be whether DBS STN specifically normalizes metabolic disturbances induced by PD or it is rather a general effect of stimulation. Despite all the above-mentioned observations, it does not seem that the weight increases following DBS STN in patients with PD reflect just an indirect effect of stimulation related to an improvement of motor disability. In fact, as the patients tend to gain more weight than they ever had, it might reflect a direct metabolic influence of the stimulation rather than just a reversal of pathologic weight loss. In this context, the close anatomic relationship between the subthalamic nucleus and lateral hypothalamus should be taken into account. Hypothalamic pathways and connections of "chemical systems" traverse the medial forebrain bundle in close vicinity to the STN, together with STN connections to the brainstem. Consequently, DBS STN has a chance to influence these pathways as well as adjacent neurons in the lateral hypothalamic area that are involved in feed habits and energy expenditure regulation [6].

In conclusion, DBS STN in PD patients is frequently accompanied by body weight gain. The mechanisms that cause the weight gain are not fully understood. The decrease in energetic output appears as a major contributing factor and may reflect a direct influence of DBS STN on brain systems regulating metabolism and food intake.

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Deep brain stimulation of the subthalamic nucleus affects resting EEG and visual evoked potentials in Parkinson's disease

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Abstract

Objective: We studied changes of the EEG spectral power induced by deep brain stimulation (DBS) of the subthalamic nucleus (STN) in patients with Parkinson's disease (PD). Also analyzed were changes of visual evoked potentials (VEP) with DBS on and off.

Methods: Eleven patients with advanced PD treated with bilateral DBS STN were examined after an overnight withdrawal of L-DOPA and 2 h after switching off the neurostimulators. All underwent clinical examination followed by resting EEG and VEP recordings, a procedure repeated after DBS STN was switched on.

Results: With DBS switched on, the dominant EEG frequency increased from 9.44 ± 1.3 to 9.71 ± 1.3 Hz ($P < 0.01$) while its relative spectral power dropped by 11% on average ($P < 0.05$). Switching on the neurostimulators caused a decrease in the N70/P100 amplitude of the VEP ($P < 0.01$), which inversely correlated with the intensity of DBS (black-and-white pattern: $P < 0.01$; color pattern: $P < 0.05$).

Conclusions: Despite artifacts generated by neurostimulators, the VEP and resting EEG were suitable for the detection of effects related to DBS STN. The acceleration of dominant frequency in the alpha band may be evidence of DBS STN influence on speeding up of intracortical oscillations. The spectral power decrease, seen mainly in the fronto-central region, might reflect a desynchronization in the premotor and motor circuits, though no movement was executed. Similarly, desynchronization of the cortical activity recorded posteriorly may by responsible for the VEP amplitude decrease implying DBS STN-related influence even on the visual system.

Significance: Changes in idling EEG activity observed diffusely over scalp together with involvement of the VEP suggest that the effects of DBS STN reach far beyond the motor system influencing the basic mechanisms of rhythmic cortical oscillations.

Keywords: Deep brain stimulation; DBS; Subthalamic nucleus; STN; EEG; VEP; Parkinson's disease

1. Introduction

While the positive effects that deep brain stimulation (DBS) of the subthalamic nucleus (STN) exerts on motor functions in patients with Parkinson's disease (PD) are well known (see e.g. Krack et al., 2003), the mechanisms of DBS are still poorly understood. DBS appears to inhibit the STN's spontaneous activity, thus directly or indirectly influencing motor circuits and ultimately leading to decrease of rigidity, resting tremor and hypokinesia (Benabid, 2003—review; Lozano et al., 2002—review).

During DBS STN, the execution of movement is accompanied by changes at the subcortical and cortical levels. Beside local changes in the regional blood flow (rCBF) (Ceballos-Baumann et al., 1999; Limousin et al., 1997; Thobois et al., 2002), there are changes in the motor cortex excitability (Cunic et al., 2002; Däuper et al., 2002; Pierantozzi et al., 2002). Hence, DBS affects not only the stimulated nucleus activity but also motor cortex function, probably by involvement in cortico-subcortical oscillations detected by means of event-related desynchronization and synchronization (ERD/ERS) (Brown, 2003—review).

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These oscillations are similarly influenced by dopaminergic medication as well as by DBS STN (Devos et al., 2003, 2004). All these studies have analyzed DBS STN effects solely in relation to the execution of voluntary movements. Quite likely, the cortico-subcortical and cortico-cortical oscillations are also affected while no movement is executed. This is in agreement with the results of a recent study (Silberstein et al., 2005) proving, on the basis of a coherence analysis, DBS STN impact on cortico-cortical coupling of resting EEG activity among a number of brain areas. Consequently, DBS STN may also affect idling oscillations of motor circuits. If this is the case, then also should be affected the μ-rhythm, an equivalent of resting EEG activity of the sensory-motor cortex (Niedermayer and Lopes Da Silva, 1993).

It seems that DBS STN may affect non-motor cortical areas as well. This is corroborated by the observations suggesting that DBS STN cause discrete changes in cognitive functions (Morrison et al., 2004), mood (Herzog et al., 2003) and perhaps even changes in somatosensory or visual perception (Pierantozzi et al., 1999; Priori et al., 2001). If DBS does have such effects, it can be presumed that cortico-subcortical oscillations outside the motor system are affected too. This could concern the visual cortex, which is supplied with an array of rich cortico-subcortical connections (Goebel et al., 2004) and shows an idling activity known as alpha-rhythm. Although visual system involvement is not in the forefront of clinical symptoms, there is considerable evidence of its abnormalities in PD (Bodis-Wollner, 1990—review). Specific findings include prolonged latencies of visual evoked potentials (VEP) elicited by achromatic (Bodis-Wollner and Yahr, 1978; Calzetti et al., 1990; Gottlob et al., 1987; Ikeda et al., 1994) as well as chromatic (Barbato et al., 1994; Büttner et al., 1996) pattern stimuli, usually normalizing in response to dopaminergic treatment (Barbato et al., 1994; Bodis-Wollner et al., 1982). However, it is still unclear whether the mechanisms of visual perception are influenced by DBS STN. For that reason, the resting EEG with DBS bilaterally switched on and off was complemented with VEP recordings in order to explore DBS-related effects on the visual system.

With DBS switched on, EEG and VEP are markedly contaminated with stimulation artifacts. Therefore, part of our study was to learn more about the nature of DBS-related noise and find ways of its elimination. For the spectral power analysis of the DBS-related effects on resting EEG, we chose the alpha band which was the least susceptible to contamination, and in which we assessed the highest peak (the dominant frequency). We also compared DBS impact on the latency/amplitude of VEP elicited by flash, by black-and-white and color pattern reversal stimuli. Selected variables were subsequently correlated with the clinical scores and stimulation parameters.

2. Method

2.1. Patients and examination procedure

Included in the study were 12 patients (7 men, 5 women) with advanced PD and with a 9.9 months history (variance 2–18 months) of bilateral implantation of Medtronic 3389 electrodes placed in the STN and connected to two implanted neurostimulators (Itrel II in 7 patients or Soletra in 5 patients; Medtronic, Minneapolis, MN). At the time of implantation, the patients' mean age was 57.3 ± 6.3 years (mean ± SD). The patients underwent the surgery 13.8 ± 4 years from the first signs of PD on average.

Chronic DBS was set to obtain the optimal clinical effects in individual patients with following parameters: average voltage 2.44 ± 0.7 V (2.38 ± 0.8 V on the right electrode, 2.50 ± 0.8 V on the left). In 6 patients, a frequency of 130 Hz was used bilaterally, in 4 patients 145 Hz was used to stimulate the left STN, and 130 Hz to stimulate the right STN; two patients were stimulated with 145 Hz on both sides. The pulse duration was set at 60, 90, 120 or 150 μs. A description of the patients and DBS parameters is given in Table 1. To serve the purpose of the study, each patient had an average stimulation 'intensity' allocated, corresponding to the mean of arithmetic products of all the parameters from both neurostimulators (*I*-intesity, *u*-voltage, *d*-pulse duration, *f*-frequency): $I=\frac{u_L.d_L.f_L+u_R.d_R.f_R}{2}$

Before launching the examination, the patients received detailed information about the study and then signed a written informed consent. All were examined after an overnight discontinuation of dopaminergic medication (with the last dose of L-DOPA at 9 p.m. of the previous day at the latest). On the day of the examination, both stimulators were switched off at about 6 a.m. At 8:30 a.m., when clinical deterioration was markedly expressed in all cases (medication OFF and DBS OFF condition), motor scoring was performed using Unified Parkinson's disease rating scale, motor part—UPDRS III, whereupon a subscore for tremor (sum of the score from items 20 and 21), a subscore for rigidity (sum of the score from item 22), and a subscore for hypokinesia (sum of the score from items 23–27) were singled out. Approximately at 9:30 a.m., the first recordings of VEP and then EEG were performed. Each patient was lying supine in a semidarkened room, able to follow the computer screen in a mirror over his/her head during VEP, or lying at rest with the eyes closed during EEG registration. Both stimulators were switched on at about 11 a.m. and the recording of the second VEP and EEG started from 11:30 a.m. (medication OFF and DBS ON condition). At about 12:30 p.m., shortly after the end of EEG recording, another UPDRS III examination followed, and finally the patients were restored to their usual dopaminergic treatment.

Table 1
Group of 12 patients with Parkinson's disease (PD) treated by the bilateral DBS STN

Pat.	Sex	Age	Dur.	Preop. complications	UPDRS III		Right DBS STN				Left DBS STN			
					DBS-OFF	DBS-ON								
1	F	54	19	w, OFF-d, s	22	19	BI	0.8 V	60 μs	130 Hz	BI	0.8 V	60 μs	130 Hz
2	F	46	13	w, p-d, OFF-d, s	40	28	BI	1.0 V	60 μs	130 Hz	PS	1.5 V	60 μs	145 Hz
3	F	68	18	w, p-d, s	41	21	PS	2.0 V	120 μs	130 Hz	PS	2.0 V	120 μs	130 Hz
4	M	54	19	w, p-d, bi-d, s	41	35	BI	3.0 V	60 μs	145 Hz	BI	2.0 V	60 μs	145 Hz
5	F	66	6	w, p-d, OFF-d, s	51	41	BI	2.6 V	60 μs	130 Hz	BI	2.5 V	60 μs	130 Hz
6	F	54	12	w, p-d, s	59	11	PS	2.6 V	60 μs	130 Hz	BI	3.0 V	60 μs	145 Hz
7	M	64	13	w, p-d, bi-D, OFF-d, s	30	22	PS	2.5 V	60 μs	130 Hz	PS	2.5 V	60 μs	145 Hz
8	M	62	11	w, p-d, bi-D, OFF-d	28	12	PS	2.8 V	60 μs	145 Hz	BI	3.3 V	150 μs	145 Hz
9	M	56	14	w, e-d, OFF-d,	43	11	PS	3.3 V	120 μs	130 Hz	PS	3.3 V	90 μs	145 Hz
10	M	52	12	w, p-d	42	14	PS	2.2 V	60 μs	130 Hz	BI	3.0 V	120 μs	130 Hz
11	M	52	8	w, bi-d, OFF-d	53	24	PS	2.2 V	60 μs	130 Hz	PS	2.8 V	90 μs	130 Hz
12	M	60	21	w, p-d, be-d	76	24	PS	3.5 V	90 μs	130 Hz	PS	3.3 V	90 μs	130 Hz

dur.—duration of the PD prior surgery; preoperative complications—wearing-off (w), OFF dystonia (OFF-d), sudden OFF/ON phenomenon (s), peak of dose dyskinesias (p-d), biphasic dyskinesias (bi-d), beginning of dose dyskinesias (be-d), end of dose dyskinesias (e-d); UPDRS III—Clinical examination (DBS-OFF) followed at least 11.5 h after overnight withdrawal of dopaminergic medication, and 2.5 h after both neurostimulators were switched off. Clinical examination (DBS-ON) followed about 1.5 h after the two stimulators were switched on; right, left DBS STN—stimulation parameters: bipolar (BI) or pseudounipolar (PS) mode of stimulation, voltage, pulse duration, stimulation frequency.

2.2. Stimulator testing

In one stimulator Itrel II, the output parameters were directly measured for the purpose of assessing the DBS-generated contamination frequencies. The stimulator was set at 2 V, 120 μs pulse duration and a frequency of 130 or 145 Hz. The measurement proceeded at 1 kΩ resistance using an HP 34401 A digital multimeter (Hewlett-Packard, Palo Alto, CA) with a declared accuracy of ± 3 mHz at 100 Hz.

2.3. EEG and VEP

An EEG system Brainscope (M&I, Czech Republic) was employed for the recording. An electrode cap was used with Ag/AgCl electrodes arranged in 10–20 system. To make sure that there was no electrode displacement between the first and second recordings, the electrode cap was left on the patient's head during all examinations.

EEG was sampled with a frequency of 250 Hz/channel in the 0.015–75 Hz band in derivations Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, T5, T6, P3, P4, O1, O2, Fz, Cz and Pz relative to the reference electrode placed on the left mastoid. In each derivation, the signal was converted to the common reference and subsequently transformed by discrete fast Fourier transformation (fft) analysis in the 0–125 Hz band with a discrimination of 0.0119 Hz. An 84 s artifact-free segment of the recording was selected for analysis. This was followed by an analysis of artifacts resulting from DBS. In order to distinguish artifacts from brain activity, the time-related development of the spectra with a step of 2 s and a discrimination of 0.5 Hz was established for each derivation. All contaminating frequencies from DBS and the power mains were then removed with notch-filters. Recordings made with DBS switched off were filtered in the same way. For group analysis, the absolute spectra were converted to relative spectra: for each patient and each derivation of the recording made with DBS off we first calculated the normalization constant defined as mean absolute power in the 4–16 Hz band. The absolute spectrum was then transformed into the relative spectrum so as to make the normalization constant of each derivation equal to 100% relative power. To calculate the relative spectra with DBS switched on, we used the same normalization constants as with DBS off. The dominant frequency and its relative power were measured in all derivations. In each derivation, the highest peak in the alpha band was chosen as the dominant frequency except in patient no. 11, whose dominant peak was in the subalpha band (with DBS off: 7.2 Hz). For further analysis, the original EEG signal was converted to longitudinal bipolar derivations C3–F3, C4–F4, Cz–Fz, Pz–Cz, O1–P3 and O2–P4. This signal, too, was transformed by means of discrete fft, notch-filtered and converted to relative spectra. Here, too, the dominant frequencies were assessed.

VEP was elicited using a monitor with a screen of a relative size of 28×21 degrees of the visual field. Three types of stimuli were used: (a) BW-VEP: stimulation with a pattern reversal of black-and-white checkerboard stimulus of $40'$ size and 1.3 Hz reversal frequency. The black/white contrast reached 100% (white brightness 32 cd/m^2, black brightness 0 cd/m^2); (b) C-VEP: stimulation with a pattern reversal of color checkerboard stimulus of $40'$ size and 1.3 Hz reversal frequency with a blue square reversing into a yellow one, a green square into a red one, and vice versa. The color co-ordinates according to the 1931CIE chromacity diagram were as follows: yellow $x=0.406$, $y=0.525$; blue $x=0.155$, $y=0.078$; red $x=0.607$, $y=0.358$; green $x=0.290$, $y=0.616$. The color areas brightness was isoluminant—14 cd/m^2; (c) F-VEP: stimulation with a white flash of 32 cd/m^2 brightness, repeat frequency of

1.3 Hz, and 5 ms flash duration. Parameters of visual stimuli were measured with a LumaColor photometer (Tektronix, OR) with J1803 and J1810 sensors.

VEP were sampled with a frequency of 1000 Hz/channel in the 0.015–75 Hz band in derivations Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, T5, T6, O1, O2, Fz, Cz, Pz and Oz relative to the left mastoid. Also related to this reference were records from 4 Ag/AgCl electrodes placed above the upper and below the lower eyelids and at the internal and external canthi of the left eye. The signal from each derivation was then recalculated to the common reference and to the 3 bipolar derivations O1–Fz, Oz–Fz and O2–Fz. Contamination of the signal from DBS was then checked on using fft analysis in the 0–500 Hz band and 0.0091 Hz discrimination in a record of 190 s duration. The time-related development of the power spectra was rated at 1 s intervals using 1 Hz frequency discrimination. The harmonic multiples of contaminating frequencies were eliminated by notch-filters, and the data was transformed back into EEG signal. At least 120 epochs of the signal lasting 200 ms before and 400 ms after the stimulus were averaged. Epochs contaminated by motion artifacts were removed prior averaging manually. For reproducibility check, each VEP recording was performed twice. BW-VEPs and C-VEPs were assessed in terms of the latencies of waves N70, P100, N140 and of the inter-peak amplitude N70/P100. In the F-VEP, a second positive peak was found in the interval of 90–190 ms. Its amplitude was rated relative to the previous negative peak.

The EEG signal was processed by our own program created in the MATLAB 6.13 environment (MathWorks, Nattick, MA). VEP was processed using an EPanalyzer 2.7 (Nebuželský&Jech, Czech Republic). The EEG of patient no. 6 was contaminated by a large DC-shift, and the VEP of patient no. 4 by major oculomotor artifacts. Hence, both were excluded from subsequent analyses so finally 11 patients were included in each of the separate EEG and VEP analyses. Three-dimensional maps were displayed using the EMSE 42 (Source Signal Imaging, San Diego, CA). For statistical analysis, the SPSS 11.5 (SPSS Inc., Chicago, IL) was used performing the Kolmogorov–Smirnov, general linear model (GLM) with repetition, analysis of covariance (ANCOVA), the Wilcoxon signed rank and Spearman's or Pearson's correlation tests. The results of 1st-level statistics were corrected for multiple comparisons using the Bonferroni correction.

3. Results

3.1. Clinical parameters

After DBS was switched on, motor impairment was markedly improved with the UPDRS III motor score decreasing from 43.8 ± 15 (mean $\pm$ SD) to 23.3 ± 12 (Wilcoxon, $Z = 2.86$, $P < 0.01$) (see Table 1).

3.2. Stimulator frequency

Measurements revealed a discrepancy between the frequencies set on stimulator Itrel II and those measured at its output. With the frequency set at 130 Hz, the real stimulation rate of 128.025 Hz was found. With the frequency set at 145 Hz the real value was 146.314 Hz.

3.3. DBS artifacts

Interference due to artifacts when DBS was on was seen in all patients. Regardless of the derivation, there were harmonic multiples of the 18.29 Hz frequency expressed throughout the band from 0 to 125 Hz (up to 6 peaks in the signal with a sampling of 250 Hz), and 0 to 300 Hz (up to 16 peaks in the signal with a sampling of 1000 Hz) (see Fig. 1a and b). Peaks of 128.03 and 146.32 Hz were found in all records and, as a rule, they reached the maximal power among all of the artifact peaks. Harmonic multiples of the 69.79 frequency were also seen all through the band in many records, reaching the maximal power at 139.59 Hz. Another expected contamination came from the mains frequency (50 Hz), though this was seen in only some of the patients. Unlike DBS artifacts, however, it was present already while the stimulation was off (see Fig. 1c). In contrast to brain activity, artifacts arising from DBS and the power mains were constant as evidenced by the presence of vertical lines in the graph showing the time-related development of the power spectra (see Fig. 1b). All the harmonic multiples of frequencies 18.29, 67.79 and 50 Hz were subsequently eliminated from the records by narrow-band notch-filters (width ± 0.1 Hz).

3.4. EEG

With DBS switched on, the relative power of the dominant frequency in all derivations decreased by an average of 11% (DBS OFF: 2809 ± 1420; DBS ON: 2508 ± 1310, GLM with repetition, factor 'DBS', $F = 7.82$, $P < 0.05$) (see Figs. 2 and 3). While the factor 'derivation' was significant ($F = 2.63$, $P < 0.001$), the interaction 'derivation $\times$ DBS' was not ($F = 0.86$, $P < 0.63$). Post-hoc comparison of the relative power in each of the derivations showed that with DBS ON there was a significant decrease in derivations Fz, F4, F8, Cz, C4, P3, T5 ($P < 0.05$ uncorrected) and T4 ($P < 0.01$ uncorrected) (see Fig. 4a).

Further, with DBS switched on, the dominant frequency increased non-significantly (DBS OFF: 9.48 ± 1.1; DBS ON: 9.58 ± 1.1, GLM with repetition, factor 'DBS', $F = 2.30$, $P < 0.16$). After EEG conversion into bipolar longitudinal derivations, the dominant frequency increase reached the threshold of significance (DBS OFF: 9.44 ± 1.3; DBS ON: 9.71 ± 1.3, GLM with repetition, factor 'DBS', $F = 13.4$, $P < 0.01$) (see Table 2). Neither the factor 'derivation' ($F = 0.43$, $P < 0.81$) nor the interaction 'derivation $\times$ DBS' ($F = 0.48$, $P < 0.78$) were found significant. Subsequent comparison of the dominant frequency in each

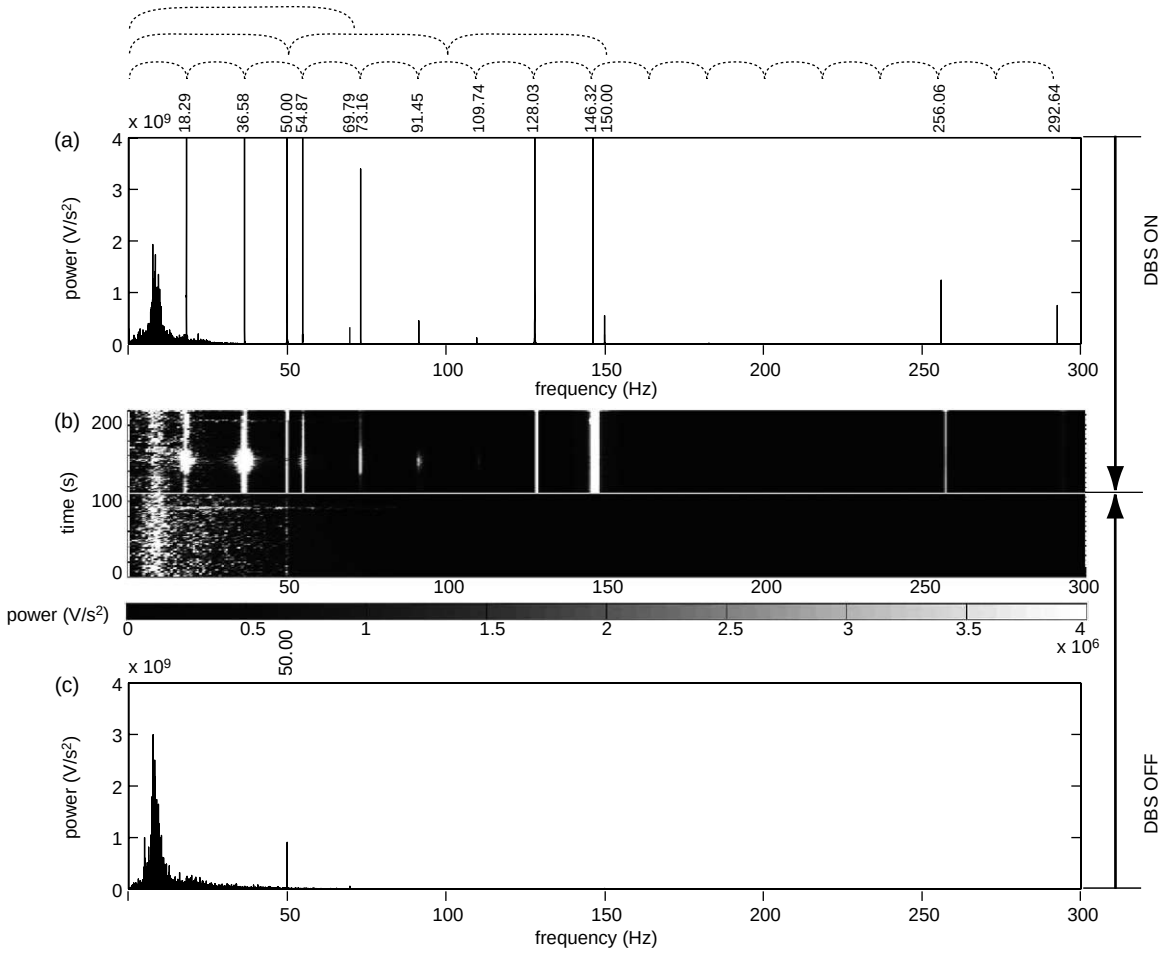

Fig. 1. An example of contaminating artifacts from DBS STN in PD patient no. 9 in derivation P4-avg.ref. in EEG sampled at 1 kHz. Parameters of stimulation: DBS STN on the right: 130 Hz, 120 μs, 3.3 V; DBS STN on the left: 145 Hz, 90 μs, 3,3 V; pseudounipolar setting: (a) absolute power spectrum with DBS STN ON bilaterally. Beside brain activity dominant in the alpha band (left), artifacts were registered as harmonic multiples of the mains (50 Hz) and neurostimulator frequencies (18.29 and 69.79 Hz), (graph discrimination: 0.0091 Hz); (b) time-related development of the power spectrum with DBS bilaterally OFF (lower half of graph) and ON (upper half). Unlike the brain activity, which is distributed dispersely, artifacts give rise to vertical lines. While lines from neurostimulation are present solely with DBS switched ON, the main frequency line (50 Hz) is present in both the ON and OFF states (time-related development by 1 s, graph discrimination: 1 Hz); (c) absolute power spectrum with DBS STN switched OFF bilaterally. All that is noticeable throughout the spectrum is the brain activity and the electric mains artifact (graph discrimination: 0.0091 Hz).

of the bipolar derivations showed that with DBS on there was a significant frequency increase in derivations Cz–Fz, C4–F4, O2–P4 ($P<0.05$ uncorrected) and C3–F3, O1–P3 ($P<0.01$ uncorrected) (see Fig. 4b).

The average dominant frequency from all the pseudounipolar derivations correlated inversely with the UPDRS III subscore of rigidity ($\rho=-0.50$, $P<0.05$) regardless of whether DBS was on or off (see Fig. 5). With respect to a high inter-lead correlation of frequencies, an inverse correlation between the dominant frequency and the score of rigidity was found in 16 out of 19 derivations ($P<0.05$ uncorrected).

3.5. VEP

3.5.1. BW-VEP

With DBS switched on, 3 bipolar derivations (O1–Fz, Oz–Fz and O2–Fz) showed no change of the N70, P100 or N140 latencies (multivariate GLM with repetition, factor 'DBS': $F=1.2$, $P<0.36$, factor 'derivation': $F=3.0$, $P<0.13$) (see Table 3). What was noted with DBS ON was a lowering of the N70/P100 amplitude in all 3 bipolar derivations (ANCOVA, factor 'DBS': $F=10.8$, $P<0.01$, factor 'derivation': $F=0.1$, $P<0.90$) (see Fig. 6a, Table 4). The factor 'intensity' of DBS (covariate) was found significant ($F=25.1$, $P<0.001$) with the N70/P100 amplitude decreasing in proportion to increasing intensity ($r=-0.84$, $P<0.01$) (see Fig. 7).

3.5.2. C-VEP

As regards the latencies of N70, P100 or N140, no significant difference was found between DBS ON and OFF (multivariate GLM with repetition, factor 'DBS': $F=1.1$, $P<0.39$, factor 'derivation': $F=3.4$, $P<0.08$) (see Table 3). With DBS switched on, the bipolar derivations showed a significant decrease of the N70/P100 amplitude (ANCOVA, factor 'DBS': $F=9.4$, $P<0.01$, factor

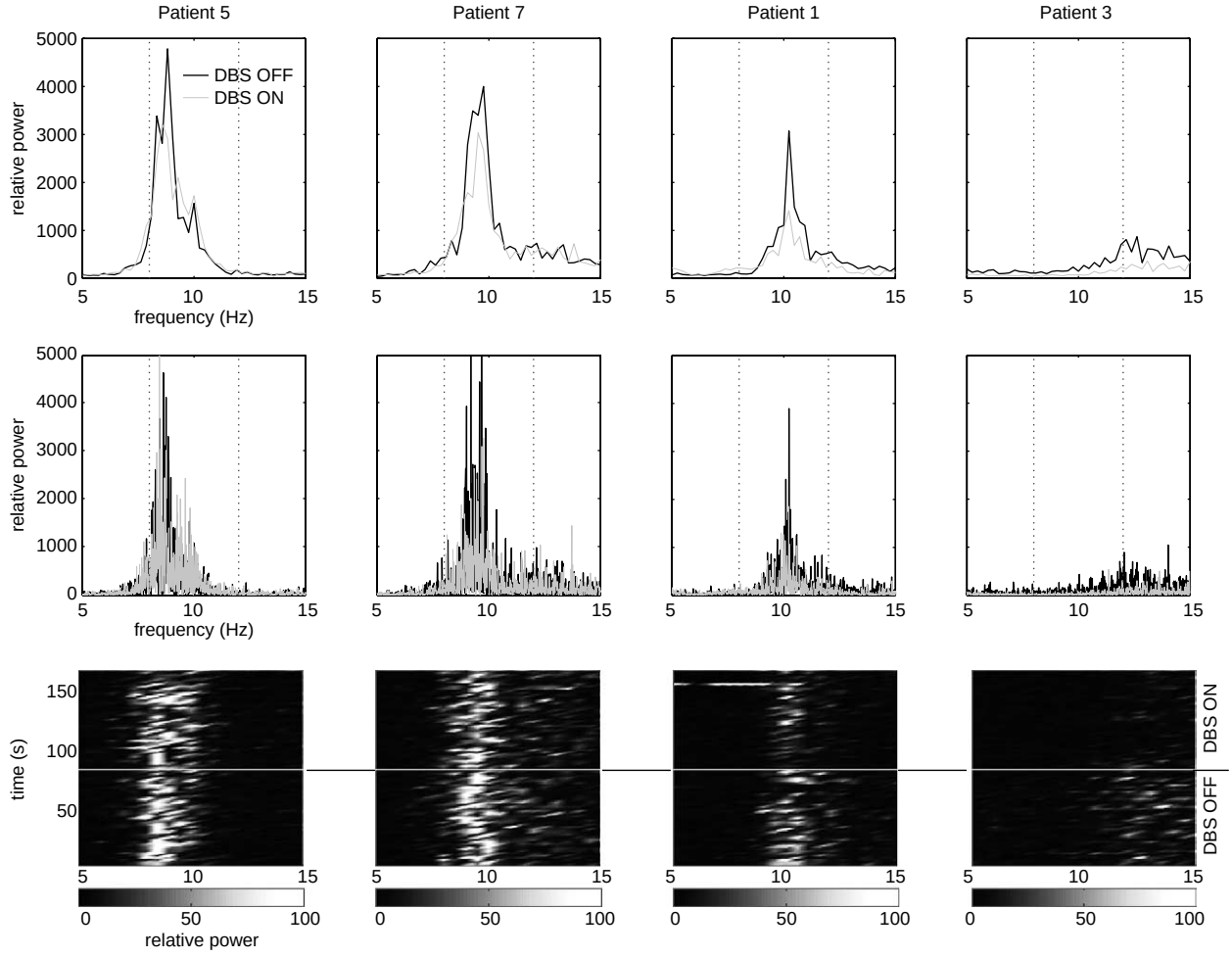

Fig. 2. Comparison of relative power spectra with DBS STN bilaterally switched OFF (black line) and ON (gray line) in 4 patients with Parkinson's disease in derivation F4-avg.ref. in EEG sampled at 250 Hz: (a) relative power with a discrimination of 0.2381 Hz; and (b) with a discrimination of 0.0119 Hz representing a decrease in the dominant frequency power with DBS STN in the ON mode; (c) time-related development of the power spectra with DBS switched OFF (lower half) and ON (upper half of the graph) developed in epochs of 2 s each with 0.5 Hz discrimination. The change in the power was not due to an artifact from neurostimulation as follows from the absence of spectral lines in the 5–15 Hz band. Graphs arranged vertically invariably correspond to the identical EEG record.

'derivation': $F=0.1$, $P<0.89$) (see Fig. 6b, Table 4). The factor 'intensity' of DBS (covariate) was significant ($F=16.9$, $P<0.001$) and the N70/P100 amplitude inversely correlated with the DBS intensity ($r=-0.70$, $P<0.05$).

3.5.3. F-VEP

The latencies of the N2 and P2 peaks were unaffected by DBS (multivariate GLM with repetition, factor 'DBS': $F=0.04$, $P<0.96$, factor 'derivation': $F=2.0$, $P<0.19$). The same applied to the N2/P2 amplitude (ANCOVA, factor 'DBS': $F=0.03$, $P<0.86$, factor 'derivation': $F=0.002$, $P<0.99$, factor 'intensity'—covariate: $F=0.001$, $P<0.98$) (see Tables 2 and 3, Fig. 6c).

4. Discussion

DBS caused artifacts, which often exceeded the EEG signal as such. While the power of artifacts differed between derivations the share of contaminating frequencies was the same in all the patients. The records showed a predominance of the 18.29 Hz and 69.79 Hz frequencies occurring in their harmonic multiples (see Fig. 1). However, the stimulator was set at the frequencies of 130 and 145 Hz, respectively. Surprisingly, these never appeared in any EEG/VEP record. Independent measurements of the Itrel II neurostimulator eventually revealed that the manufacturer-declared frequencies differed from those recorded at the output. Real frequencies were 128.025 and 146.314 Hz, respectively, i.e. 7 or 8 times the contaminating frequency of 18.29 Hz observed in all our EEG/VEP records. This is because the neurostimulator design prevents changing the frequency continuously, but only in frequency multiples of the resonance circuits. This explains also why it was impossible to tell from the record which of the patients had been stimulated with which frequency, as all the harmonics were present in the record simultaneously regardless of the DBS frequency actually used.

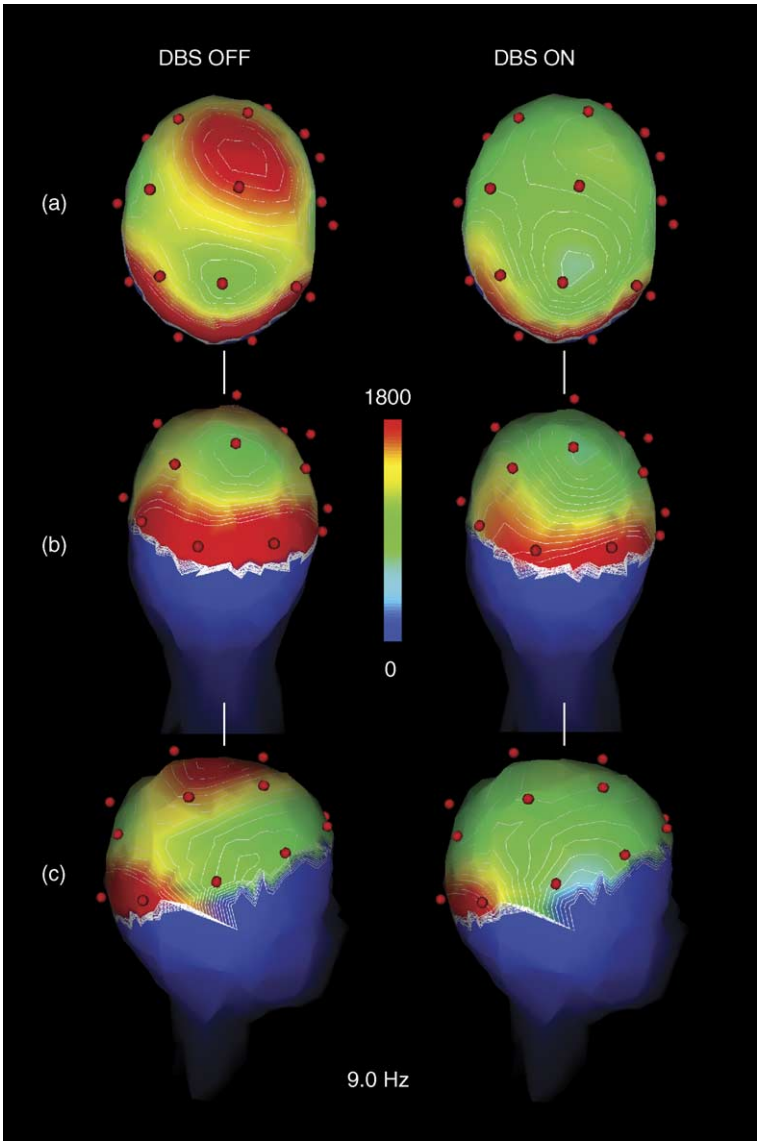

Fig. 3. Average map of relative power at 9 Hz—group average of 11 patients examined with the DBS STN bilaterally switched OFF (left column) and ON (right column). A map of relative power with a preponderance of higher power in the occipito-temporal and fronto-central regions viewed (a) from above, (b) from the rear, and (c) from the right side. Reduction of relative power became apparent after DBS STN was switched ON.

On the graphs showing time-related power spectra, the stimulation artifacts—unlike the biological signal—were well identifiable as vertical straight lines (see Fig. 1b) while none of the contaminating frequency harmonics interfered with the delta to alpha bands. All the signal changes observed around the dominant frequency are then likely to have been related to the DBS biological effects rather than to some other kind of EEG artifacts.

The clinical effects of DBS STN were positive in all of the patients as evidenced by the UPDRS III motor score mean improvement by nearly one half, which is in agreement with previous observations (Herzog et al., 2003; Krack et al., 2003; Østergaard et al., 2002). Main result of the present study is that the DBS STN induces detectable changes in VEP and resting EEG. Against expectations, the EEG activity was affected not only over the motor regions; there were frequency and spectral power changes over a large part of the scalp. This might suggest a direct or indirect DBS influence over fundamental mechanisms of intracortical and cortico-subcortical oscillations. Indeed, it appears that a functional projection between the STN and the motor cortex does exist according to the studies showing synchronous oscillations recorded by an implanted electrode and scalp EEG in the beta, gamma and alpha bands (Marsden et al., 2001; Williams et al., 2002). With DBS switched on, we noted an acceleration of the dominant frequency in the alpha band generated mainly temporo-parieto-occipitally but also a faster μ-rhythm generated fronto-centrally (see Table 2). This was an increase representing an average change of 0.27 Hz, albeit significant

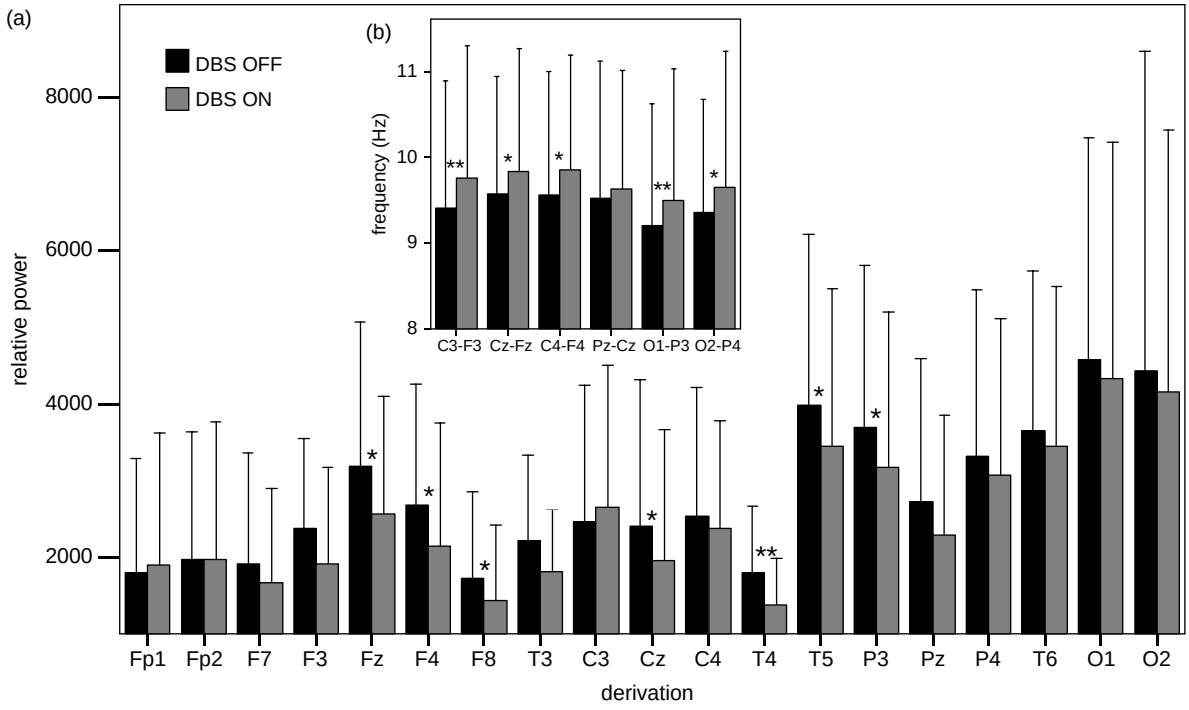

Fig. 4. Comparison of the dominant frequency and its relative power with DBS STN switched OFF (black) and bilaterally ON (gray)—group analysis of 11 patients with Parkinson's disease: (a) after DBS STN was switched ON, the relative power of the dominant frequency decreased in nearly all the derivations (common reference used); (b) with DBS STN switched ON, the dominant frequency showed an increase (bipolar longitudinal derivations). Post-hoc statistics: $^{**}P<0.01$ and $^{*}P<0.05$ uncorrected.

only in rating the signal in bipolar derivations as these appear to be more susceptible to local changes than common reference derivations (see Fig. 4b).

The physiological origin of acceleration in the dominant frequency remains unclear, as does the relevance of the rhythmic idling activity of the brain. Despite some chronotopographical differences, the occipital alpha and rolandic μ-rhythm appear to share the same mechanisms (multiple cortical generators with rich cortico-cortical and subcortical afferentation) which are under strong impact of sensory stimuli (Kuhlman, 1978). The alpha and μ-rhythm frequencies exhibit considerable interindividual and intraindividual differences even in healthy subjects. While the alpha-rhythm gradual acceleration is often associated with brain maturation, short-term acceleration depends upon vigilance, emotional tension and obviously also on the circadian or menstrual cycle phases (Niedermayer and Lopes Da Silva, 1993). In advanced age, it tends to slow down (Busse and Obrist, 1963), a feature uncorroborated by other authors (Duffy et al., 1984). However, background rhythm deceleration and occurrence of slow frequencies have repeatedly been found in patients with PD (England et al., 1959; Stephens et al., 1979; Yeager et al., 1966). Beside PD patients with cognitive function involvement, this slowing down was especially noted in those with

Table 2
Mean dominant frequency (Hz) ±SD in bipolar longitudinal derivations with DBS STN bilaterally switched OFF and ON in 11 patients with PD

	DBS OFF	DBS ON	*F*	*P*
Frequency[1]	9.44±1.3	9.71±1.3	13.4	0.01
Frequency[2] F–C	9.52±1.4	9.82±1.4	8.7	0.05
Frequency[3] O–P	9.28±1.3	9.58±1.5	9.8	0.05

Frequency[1]—mean dominant frequency in derivations C3–F3, Cz–Fz, C4–F4, Pz–Cz, O1–P3, O2–P4. Frequency[2] F–C (μ-rhythm)—mean dominant frequency in fronto-central derivations C3–F3, Cz–Fz, C4–F4. Frequency[3] O–P (alpha-rhythm)—mean dominant frequency in occipito-parietal derivations O1–P3, O2–P4.

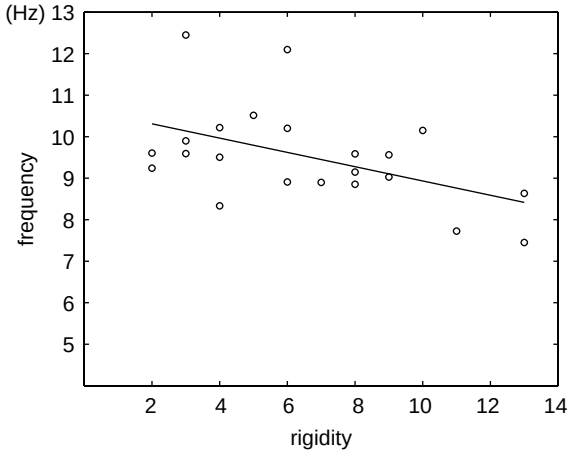

Fig. 5. Dominant frequency and rigidity. Rigidity subscore increase coincided with dominant frequency decline (average frequencies from all derivations relative to avg. ref. recorded with DBS STN off and on) ($P<0.05$).

Table 3
BW-VEP, C-VEP and F-VEP latencies with DBS STN switched OFF and ON (11 patients with PD)

	DBS OFF	DBS ON	DBS OFF/ON	
			F	*P*
BW-VEP:				
N70	77±8	75±7	4.1	0.071
P100	111±11	111±11	0.3	0.61
N140	142±17	144±17	0.4	0.52
C-VEP:				
N70	74±12	73±15	0.0	0.99
P100	113±13	112±12	0.9	0.37
N140	150±21	149±21	0.9	0.37
F-VEP:				
N2	120±31	120±32	0.08	0.78
P2	150±33	150±32	0.01	0.92

The mean latencies (ms) ± (SD) from 3 bipolar derivations O1–Fz, Oz–Fz a O2–Fz are given.

a pronounced motor deficit (Neufeld et al., 1988). In our study, we made similar conclusions since we found that in patients with lesser rigidity there was a higher dominant frequency than in those with greater rigidity (see Fig. 5). Additionally, the improvement of rigidity induced by DBS STN correlated with increase in dominant frequency. The DBS STN-related acceleration in the alpha band followed by clinical improvement might therefore reflect normalization of the abnormally slowed idling activity of the cortex. Although the pathophysiological mechanisms of rigidity are not fully understood (Wichmann and DeLong, 2004), our observation may additionally suggest some cortical involvement in its development. This is also in agreement with changes in cortico-cortical coherences of resting EEG as were found to correlate with the UPDRS III motor score in patients treated by DBS STN (Silberstein et al., 2005).

Decrease in the dominant frequency power induced by switching on DBS of the STN was found in both bipolar and common reference derivations. The relative power dropped diffusely all over the scalp by an average of 11% (see Fig. 4a). This decrease was the most apparent in the fronto-central region (see Fig. 3). The reason for the predominance of change in this area may lie in the DBS STN priority impact on the motor cortex function. This is supported by findings of DBS-related increase in an initially decreased intracortical inhibition (Cunic et al., 2002; Däuper et al., 2002; Pierantozzi et al., 2002) and local reduction of regional blood flow in the primary motor cortex (Ceballos-Baumann et al., 1999; Limousin et al., 1997; Thobois et al., 2002).

However, our findings could be caused by the two frontally located burr holes, through which the leads pass to the electrodes. Defects in the cranium are often accompanied by increased signal amplitude (Niedermayer and Lopes Da Silva, 1993). Despite being covered with a plastic lid, the holes may have caused local improvement in the signal/noise ratio but they cannot have been responsible for the decrease of the spectral power with the DBS switched on. Obviously, the power decrease was not an artifact caused by neurostimulation either. If that were the case we would expect the power to rise and there would be vertical lines in the graphs representing time-related development of the spectral power (see Fig. 2c).

Nevertheless, the decrease itself in the dominant frequency power can be interpreted differently. It may have been a case of DBS inhibition effect on the cerebral cortex as much as a case of stimulation effect interfering with cortico-subcortical oscillation and thereby causing its desynchronization and consequently a power decrease.

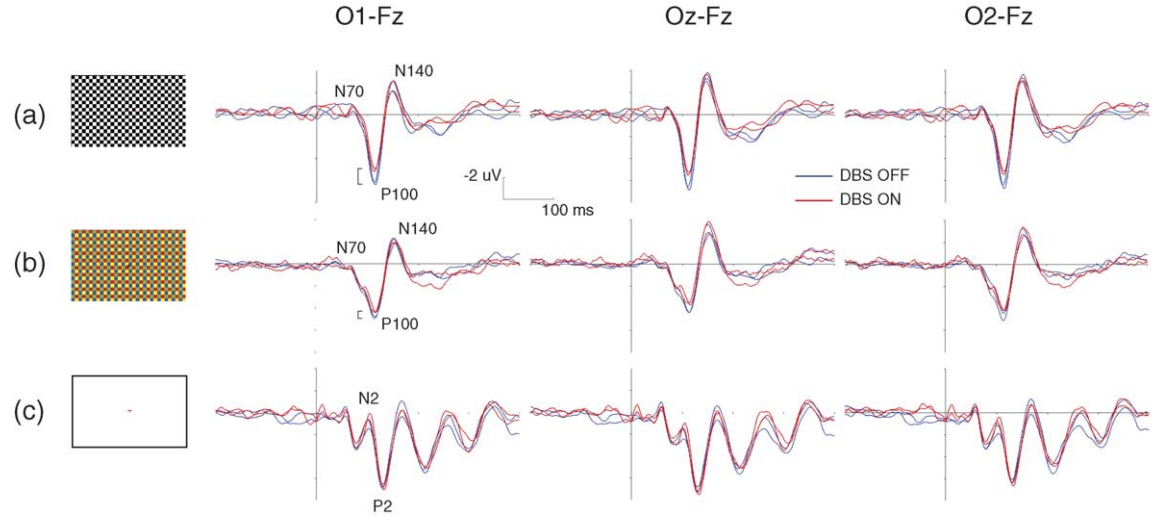

Fig. 6. Group-averaged curves: (a) BW-VEP; (b) C-VEP; and (c) F-VEP from 11 patients with Parkinson's disease examined twice with DBS STN switched OFF (blue line) and twice in the ON state (red line). (a) On stimulation with a black-and-white pattern there was a distinctive difference in the VEP amplitude in all bipolar derivations O1–Fz, Oz–Fz and O2–Fz; (b) on stimulation with a color pattern the difference in the VEP amplitude was less expressed; and (c) on stimulation with a flash, there was no apparent difference.

Table 4
BW-VEP, C-VEP and F-VEP amplitudes with DBS STN switched OFF and ON (11 patients with PD)

	DBS OFF	DBS ON	DBS ON/OFF		Intensity of DBS		Derivation	
			F	*P*	*F*	*P*	*F*	*P*
BW-VEP:								
N70/P100	8.9±4.2	7.4±3.8	10.8	0.01	25.1	0.001	0.1	0.90
C-VEP:								
N70/P100	6.2±3.6	5.6±3.2	9.4	0.01	16.9	0.001	0.1	0.89
F-VEP:								
N2/P2	6.6±3.9	6.9±4.0	0.03	0.86	0.001	0.98	0.002	0.99

The mean amplitudes (μV)±(SD) from 3 bipolar derivations O1–Fz, Oz–Fz and O2–Fz are given.

Alpha and μ-rhythms are usually regarded as idling activities known to become desynchronized during vision, attention focusing or during the preparation and execution of voluntary movements (Niedermayer and Lopes Da Silva, 1993). However, attenuation of those rhythms also depends on dopaminergic mechanisms since withdrawal of anti-parkinsonian medication was found to suppress the alpha and beta-rhythms during the execution of movement to a lesser degree than in response to L-DOPA (Brown and Marsden, 1999; Wang et al., 1999). The DBS STN effect on the dominant frequency power as we observed it was similar.

There was a similarity between EEG and VEP results. DBS STN caused an amplitude decrease in BW-VEP and C-VEP similarly as it produced a decrease in the relative power of the dominant EEG alpha-rhythm recorded over posterior regions. Visual functions in PD, particularly VEP, have been studied repeatedly (Bodis-Wollner, 1990—review). Many authors described delay of the P100 latency in VEP elicited by the black-and-white pattern reversal using stimuli of a lower contrast and higher spatial frequency (Bodis-Wollner and Yahr, 1978; Calzetti et al., 1990; Delalande et al., 1998; Onofrj et al., 1986). Treatment with L-DOPA usually leads to normalization, i.e. to VEP latency shortening (Bodis-Wollner et al., 1982; Onofrj et al., 1986). Its amplitude usually did not differ from that in healthy persons, nor is it influenced by dopaminergic treatment either (Bodis-Wollner, 1990—review), but with the progression of PD, the P100 amplitude decreases (Ikeda et al., 1994). P100 latency prolongation was also observed in PD patients using color pattern reversal stimulation (Büttner et al., 1996). Subsequent administration of L-DOPA induced an even more pronounced shortening of its latency than when a black-and-white stimulus was used (Barbato et al., 1994).

However, with DBS switched on, we observed none of the expected P100 latency shortening typical for dopaminergic treatment. Latency shortening could also have been expected because of the occipital acceleration of the alpha-rhythm. As anticipated, the latency of N70 BW-VEP tended to be shorter, but this change did not reach the significance threshold perhaps due to higher variance or relatively low number of subjects. Instead, with DBS switched on, we found a significant lowering of the N70/P100 amplitude (see Fig. 6). Using a stimulus 15′ and 30′ in size, Priori et al. (2001) made a similar conclusion; 1 day after DBS was switched off, they observed an increase in the VEP amplitude despite they refrained from discontinuing ordinary antiparkinsonian medication. It is still questionable whether or not the amplitude lowering was an artifact due to DBS, possibly accounting for the signal/noise ratio decrease. That, however, would happen only if the noise would contain frequencies interfering with the band of VEP. As already mentioned, the noise from DBS was regular and constant, which enabled us to identify it and then to filter it out. Therefore, it seems then that the VEP changes observed are not an artifact and that DBS and dopaminergic medication may influence the visual system by different mechanisms. Since DBS STN does not enhance the synthesis of endogenous dopamine (Hilker et al., 2003; Strafella et al., 2003), different VEP changes in response to L-DOPA as distinct from DBS STN are not surprising.

The observed decrease in the N70/P100 amplitude was even more significant when the stimulation parameters of both stimulators were taken into account. Higher amplitude and longer pulse duration are known to lead to greater clinical effects (Krack et al., 2002; Moro et al., 2002). The

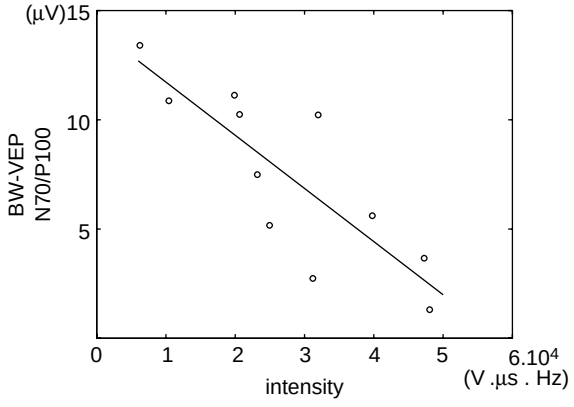

Fig. 7. BW-VEP N70/P100 amplitude relative to DBS STN stimulation intensity in 11 patients with Parkinson's disease. Increase of intensity (defined as average of arithmetical product of voltage, pulse duration and frequency from both neurostimulators) was accompanied by N70/P100 amplitude decrease in VEP elicited by black-and-white stimulus ($P<0.01$).

dependence on frequency is more complex, but within the range of 50–185 Hz, raising the frequency also makes for clinical improvement (Moro et al., 2002). While the voltage on the two stimulators in our patients was within the range of 0.8–3.5 V, only 4 different pulse lengths and two different frequencies were used for stimulation (Table 1). This prevented us from rating the effect on the VEP amplitude of each of the parameters of stimulation separately. Hence, for the purpose of our study the stimulation 'intensity' was understood to mean the arithmetical product of all 3 parameters of the stimulator settings. In a simplified form, the 'intensity' value expressed the voltage with regard to pulse duration and stimulation frequency. A higher 'intensity' was accompanied by a lower N70/P100 amplitude, and vice versa (see Fig. 7). It was as if a higher 'intensity' inhibited or desynchronized the primary visual cortex function more. A lesser though still significant amplitude lowering, with the DBS on, was noted also in response to stimulation with a color pattern of the same temporal and spatial frequency. It was only when stimulation with a flash was used that we failed to prove DBS STN effects on VEP (see Fig. 6c). While this may have been due to the different sensitivity of the visual system, given different parameters of visual stimulation, it may also have been related to a greater variability of the F-VEP (Ikeda et al., 1994).

We proved that even major contamination with stimulation artifacts was not an obstacle for assessment EEG/VEP records because the problem can be solved by selective filtration of the DBS harmonics. As we hypothesized, DBS of the STN does influence cortical activity. Moreover, DBS-related changes in the resting EEG were observed not only over the motor areas as we had expected but also over large areas of the scalp. Consequently, beside the effects on stimulated nucleus and the basal ganglia circuitry, DBS seems to affect basic mechanisms of cortico-subcortical oscillations. Acceleration of the dominant alpha frequency and decrease in its spectral power, detected also over the visual areas, were accompanied by VEP amplitude decreases. This supports the notion that the effects of DBS STN may reach far beyond the motor system.

Acknowledgements

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