Cognitive and emotional effects of Deep Brain Stimulation of the Subthalamic Nucleus in patients with Parkinson´s disease

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List of Abbreviations

ANOVA	analysis of variance
CM	centromedian nucleus of thalamus
DBS	deep brain stimulation
DLPC	dorsolateral prefrontal cortex
ER	error rate
FA	false alarm
GABA	gamma-aminobutyric acid
GPe	external segment of the globus pallidus
GPi	internal segment of the globus pallidus
HC	healthy controls
ICB	impulsive control behavior
IFC	inferior frontal cortex
L-Dopa	levodopa
LDT	lexical decision task
LED	L-Dopa equivalent daily dose
LH	lateral habenula
M	mean
ME	main effect
mg	milligram
ms	millisecond
OCD	obsessive-compulsive disease
OFC	orbitofrontal cortex
PD	Parkinson´s disease
PF	parafascicular nucleus of the thalamus
PPN	pedunculopontine nucleus

RA	response accuracy
RMET	Reading the Mind in the Eyes Task
RT	reaction times
SC	superior colliculus
SD	standard deviation
SE	standard error
SMA	supplementary motor area
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulate
SOA	stimulus onset asynchrony
STN	subthalamic nucleus
ToM	Theory of Mind
UPDRS	United Parkinson´s disease rating scale
V	Volt
VA	ventral anterior nucleus of thalamus
VL	ventrolateral nucleus of thalamus

Abstract

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become an effective and secure option for treatment of Parkinson´s disease (PD). Its effect on improving motor impairments following dopaminergic depletion in the substantia nigra has been variously shown. The influence of STN-DBS on concomitant non-motor symptoms has also reached more and more of attention, since these may have the potential to affect subjectively perceived quality of life in patients. Behavioral, affective and cognitive changes in patients after STN-DBS have thus been considerably studied in recent years. The present thesis aimed to investigate STN-DBS modulations on different cognitive and emotional functions in PD patients. The STN is supposed to hold a crucial role in action selection and reward processing as well as in perceptual decision-making. The first thesis project investigated whether stimulation of the STN influences the patients´ selective ability to act for anticipated reward or loss, or whether DBS changes action selection independent from motivational valence. Behavioral results demonstrate the impact of STN-DBS on motivational action control in PD by selectively improving action execution when rewards are anticipated. Thus, STN-DBS establishes a reliable congruency between action and reward anticipation.

The second project investigated whether STN-DBS in PD patients influences decision-making under difficult, high-risk decisions. Results show that stimulation of the STN affected perceptual decision-making depending on the difficulty of decisions and as a function of baseline impulsivity in patients. DBS of the STN selectively affected the tendency to stick with a default option on difficult decisions and increased accuracy of responses.

Finally, I conducted an experimental setting to assess STN-DBS impact on implicit and explicit processing of emotional semantic and facial stimuli in an affective priming paradigm. I found that even reduced facial information is sufficient to induce automatic implicit emotional processing and can lead to classical and inverse priming effects in healthy control participants, but also in non-stimulated PD patients. In these patients, specific altered processing of the emotions happiness and disgust was detected. The experimental setting was finally applied in stimulation-treated PD patients. STN-DBS affected explicit more than implicit processing, indicating basal ganglia-thalamocortical regulations on explicit, and only attenuated on implicit

emotion processing. Profound diminishing effects on response accuracy for disgust-connoted stimulus material, but also an ameliorating effect on fear stimuli could be demonstrated under stimulation.

Taken together, this PhD thesis demonstrates that STN-DBS improved action selection under reward anticipation, facilitated decision-making under difficult decisions, and finally, influenced particularly explicit, but also implicit emotional processing. The results provide causal evidence for the potential of STN-DBS to influence cognitive and emotional aspects in patients and to have considerable impacts on quality of life besides improved motor functioning.

Zusammenfassung

Die Tiefe Hirnstimulation (THS) des Nucleus Subthalamicus (STN) wird als effektives und sicheres Mittel in der Behandlung des Morbus Parkinson (PD) angesehen. Die Effekte in der Verbesserung der motorischen Beeinträchtigungen, welche aus dem dopaminergen Abbau in der Substantia nigra resultieren, konnten vielfach gezeigt werden. Auch dem Einfluss von STN-THS auf begleitende nicht-motorische Symptome kommt mehr und mehr Bedeutung zu, da diese die subjektiv erlebte Lebensqualität der Patienten erheblich reduzieren können. In den letzten Jahren sind daher verstärkt Verhaltens-, affektive und kognitive Veränderungen durch STN-THS auf Patienten geprüft worden. Die vorliegende Arbeit untersuchte die STN-THS Auswirkungen auf verschiedene kognitive und emotionale Funktionen in PD Patienten. Dem STN wird eine wesentliche Rolle bei der Handlungsauswahl und der Belohnungsverarbeitung, ebenso wie bei der perzeptuellen Entscheidungsfindung zugesprochen. Die erste Studie untersuchte, ob die STN Stimulation die Fähigkeit beeinflusst, selektiv für antizipierte Belohnungen oder Verluste zu handeln, oder ob die THS die Handlungsauswahl unabhängig von motivationaler Valenz moduliert. Verhaltensergebnisse deuten auf eine Wirkung von STN-THS auf die motivationale Handlungskontrolle bei Patienten hin, indem selektiv nur jene Handlungsausführungen verbessert werden, die mit einer Belohnung einhergehen. STN-THS generiert damit eine zuverlässige Verbindung zwischen Handlung und antizipierter Belohnung.

Das zweite Projekt untersuchte, inwieweit STN-THS in PD Patienten die Entscheidungsfindung bei schwierigen, riskanten Entscheidungen beeinflusst. Ergebnisse zeigen, dass die Stimulation des STN auf die wahrnehmungsbezogene Entscheidungsfindung in Abhängigkeit von der Schwierigkeit der zu treffenden Entscheidung und als Funktion der Baseline-Impulsivität der Patienten Einfluss nimmt. Sie wirkt selektiv auf die Verhaltenstendenz ein, bei schwierigen Entscheidungen bei einer voreingestellten Auswahl zu bleiben, und erhöht die Antwortgenauigkeit.

Schließlich wurde ein experimentelles Setting erstellt, um die Wirkung von STN-THS auf die implizite und explizite Verarbeitung von emotionalen semantischen und Gesichts-Stimuli in einem affektiven Priming Paradigma zu untersuchen. Es konnte gezeigt werden, dass selbst begrenzte Gesichtsreize ausreichend sind, um automatische implizite Emotionsverarbeitung zu induzieren, und dass diese

reduzierte Information zu klassischen und inversen Priming Effekten in gesunden Kontrollpersonen führen kann, jedoch ebenso in nicht-stimulierten PD Patienten. Bei den Patienten wurde eine veränderte Verarbeitung der Emotionen Freude und Ekel beobachtet. Der Versuchsaufbau wurde abschließend bei THS-behandelten Patienten ausgeübt. STN-THS beeinflusste die explizite Emotionsverarbeitung mehr als die implizite; dieses Ergebnis verweist somit auf eine Basalganglien-thalamokortikal induzierte Wirkung auf die explizite, und nur abgeschwächt auf die implizite Emotionsverarbeitung. Eine erheblich verminderte Antwortgenauigkeit für Ekel-assoziiertes Stimulusmaterial sowie eine Verbesserung der Diskrimination von Angst-bezogenen Stimuli konnten unter Stimulation nachgewiesen werden.

Zusammenfassend demonstriert diese Dissertation, dass STN-THS die Handlungskontrolle und -auswahl unter Belohnungsantizipation verbessert, die Entscheidungsfindung bei erschwerten Entscheidungen erleichtert, und schließlich insbesondere die explizite, aber auch implizite Emotionsverarbeitung beeinflusst. Die Ergebnisse verweisen direkt auf das Potential von STN-THS, kognitive und emotionale Aspekte bei PD Patienten zu verändern und sich damit zugleich erheblich auf die Lebensqualität – neben den motorischen Verbesserungen – auszuwirken.

1. Introduction

PD is a neurodegenerative disease associated with motor disturbances. DBS of the STN has reached more and more importance and relevance in the treatment of PD within the last years. Today, it is considered as method of choice next to standard drug treatment. Since the 1960s, PD is commonly treated with levodopa (L-Dopa). Usually, the L-Dopa therapy shows satisfying results with respect to motor improvements, but in about half of the patients the so-called „long term L-Dopa syndrome“ with distinct reductions of medication effects („wearing off“), fluctuations and dyskinesias can be observed, that diminish quality of life in a considerable way and sometimes gain more relevance in daily living than the motor disturbances themselves (Chaudhuri & Schapira, 2009). These drug-induced side effects are hardly or even no longer treatable after several years.

After the first scientific publication addressing DBS in PD patients was published (Benabid et al., 1987), the method reached an increasingly important role and has become an effective treatment method in PD over the last 20 years. Meanwhile, long-time studies constitute DBS as a secure and reliable standard therapy in the treatment of movement disorders. It alleviates tremor, rigidity, bradykinesia and L-Dopa-induced dyskinesia. The effectiveness of bilateral DBS of the STN on motor symptoms in patients with advanced PD is generally accepted (Hickey & Stacy, 2016). The STN is assumed to play an important role not only in motor functioning, but also in other behavioral, affective and cognitive aspects due to its functional role, position and interconnection within the basal ganglia loops. For several years, research thus aimed at examining these additional impacts of the STN on behavioral or emotional levels. The aim of the present thesis was to systematically investigate the influence of STN-DBS on different aspects of action control, decision-making and emotion processing in PD patients.

In the introductory theoretical section, I will first describe clinical symptoms of PD with references to epidemiology and neuropathology (Chapter 1.1). Afterwards, I will give a theoretical overview of structure and functioning of the basal ganglia, the basal ganglia-thalamocortical loops and their interconnecting projections and pathways (Chapter 1.2). I will describe structure and functional role of the STN as the crucial neurological area in PD treatment (Chapter 1.3). Afterwards, I will

introduce DBS of the STN as method of choice for PD therapy, its indication and functional principle, before highlighting some previous empirical findings of STN-DBS´ influence on cognitive, behavioral and affective issues (Chapter 1.4). Finally, my own studies on cognitive and emotional effects of STN-DBS in PD patients will follow (Chapters 2-6), before discussing them conclusively (Chapter 7).

1.1 Parkinson´s disease

Idiopathic PD is a chronic, slowly proceeding neurodegenerative disease with motor and non-motor symptoms elicited by a loss of dopaminergic neurons in the substantia nigra and other brain regions. The degeneration is accompanied by a pathogenetic fibrillisation of the unstructured soluble protein alpha-synuclein as well as the formation of Lewy bodies and neurofibrillary tangles in nigral regions, limbic and brainstem nuclei and neocortical regions (Braak et al., 2003; Kalaitzakis et al., 2009). James Parkinson provided the first detailed description of the disease in his monograph "An Essay on the Shaking Palsy" (Parkinson, 1817).

PD is characterized by four cardinal motor symptoms (Braak et al., 2003; Litvan et al., 2003) :

(I) *Bradykinesia*, which refers to a slowing of voluntary movements that cannot be attributed to a paralysis, at first commonly manifested in little and accurate tasks like writing, buttoning or shaving;
(II) *Resting tremor*, meaning the involuntary rhythmic oscillation of body parts, most typically limbs or jaws, that is reduced or disappears during the execution of voluntary movements, but is enhanced under emotional tension or mental activities;
(III) *Rigor (or rigidity)*, stiffness, referring to an increased muscle resistance during the passive movements of body parts;
and
(IV) *Postural instability*, meaning difficulties in maintaining an adequate body posture during standing and walking, with a risk of falling. Postural instability commonly occurs in the later stages of the disease.

The diagnosis of PD requires the presence of bradykinesia, in addition with at least one of the remaining three cardinal symptoms, as well as good response to L-Dopa (Litvan et al., 2003). Further motor symptoms include akinesia (absence of normal unconscious movements, e.g. arm swings during walking), hypomimia (paucity of normal face expressions), freezing of gait (suddenly occurring, several seconds lasting blockades of movements) or micrographia (decreased size and also speed of writing) among others.

Non-motor features include psychiatric symptoms like depression, anxiety, apathy, hallucinations or drug addictions during the course of the disease. Sensory and vegetative signs comprise constipation, hypotension, hyposmia, diffuse pain, dysaesthesias, sleep disorders like excessive daytime sleepiness or insomnia, and sexual disorders among others. Moreover, cognitive impairments are an important category of non-motor PD symptoms. More than the half of the patients are affected by Mild Cognitive Impairment in the first five years after diagnosis, which can be a precursor of dementia (Williams-Gray et al., 2007). About 20-30% of PD patients are diagnosed with dementia at some point during the disease progression. Further cognitive impairments often described in PD patients are perseverations, deficits in executive functions like planning or decreased cognitive flexibility, deficits in learning and memory, attention shifting or visuospatial functions . These non-motor symptoms contribute to a significant worsening of quality of life in patients (Morgante et al., 2000; Braak et al., 2003; Lim et al., 2010; Kehagia et al., 2010).

The prevalence of PD in the German population older than 60 years is about one percent and it increases up to two to three percent in people older than 70 years. PD is thus one of the most frequent neurodegenerative diseases in Germany. The manifestation of the disease commonly starts between the 50^{th} and 60^{th} year of age. Disease onset before the age of 40 is found in only 10% of the patients and is usually associated with a familiar-genetic form of PD. In comparison to women, men are 1.5 to 2 times more frequently affected by PD, but this gender difference diminishes with ongoing age (De Lau & Breteler, 2006, Elbaz et al., 2002).

Ageing processes, genetic factors, environmental influences as well as endogenous mechanisms are supposed to play an important role in the pathogenesis of PD (Lotharius & Brundin, 2002).

1.2 Neuropathology of PD

The following section gives an overview of PD-relevant subcortical areas and their connections within the basal ganglia and cortical projection areas, as well as neuropathological changes in PD.

The key mechanism in PD refers to the degeneration of dopamine-producing neurons in the substantia nigra pars compacta (SNc). The SNc is centrally involved in various circuits of the extrapyramidal system and has regulatory functions. Dopaminergic neurons project from the SNc via the medial forebrain bundle to the striatum and pass signals that influence the control and modulation of motor impulses and sequences. The PD-inherent neuron loss can be adjusted by upregulating postsynaptic dopamine receptors and a compensatory neurotransmitter synthesis for a certain time period. However, neurodegeneration is already far advanced when the diagnosis PD is made. It is estimated that when patients first seek medical treatment for emerging motor symptoms, already 60% of dopaminergic neurons in the SNc have degenerated and almost 80% of the striatal dopamine is lost (Leplow, 2007; Hornykiewicz, 1982).

The lack of dopamine eventually leads to a decrease of the activating effect of the basal ganglia on the cerebral cortex. The basal ganglia are a group of subcortical nuclei comprising the striatum (caudate nucleus, putamen), the nucleus accumbens, the SNc and substantia nigra pars reticulata (SNr), the STN and the globus pallidus (internal and external segment, GPi and GPe) (Albin, Young & Penney, 1989). The striatum is considered the major input structure to the basal ganglia (Wichmann & DeLong, 2016) which are essentially involved in the processing of cognitive and affective behavior. This becomes apparent by the intense connections between basal ganglia and the thalamus as well as the frontal cortex. The basal ganglia can be divided into a dorsal system, which is engaged in motor, and a ventral system, that participates in affective processing. This functional-topographic distribution is preserved throughout all basal ganglia nuclei (Parent & Hazrati, 1995a).

1.2.1 Basal ganglia-thalamocortical circuitry

Neuronal processing in the basal ganglia primarily occurs in parallel functional circuits. Alexander and colleagues (Alexander, DeLong & Strick, 1986; Alexander and Crutcher, 1990) proposed five specific cortico-striato-thalamocortical loops: the motor and oculomotor circuit, two associative loops of higher functioning (the dorsolateral prefrontal and lateral orbitofrontral loop) as well as the limbic anterior cingulate circuit. These loops transmit information within the basal ganglia elements in a partially closed and sequentially arranged way (Alexander, DeLong & Strick, 1986; Parent and Hazrati 1995a; Middleton and Strick, 2000). These circuits form the pathways through which higher and lower regions of the brain communicate with the basal ganglia.

Each loop originates from specific parts of the cortex, is processed in specific thalamic nuclei and projects back to at least one cortical input area (Alexander and Crutcher, 1990; Parent and Hazrati, 1995a; Temel et al., 2005). The two *associative circuits* stem from the dorsolateral prefrontal cortex (DLPC) and lateral orbitofrontal cortex (OFC), respectively. From here, these circuits are directed to the caudate nucleus, further on to the dorsomedial part of the GPi, to the rostral region of the SNr and to the anterior parts of the GPe. The GPi and SNr project to nuclei of the thalamus, while the thalamocortical pathway leads back to the DLPC and the lateral orbitofrontal circuit back to the lateral OFC. In the *limbic circuit*, projections from limbic and paralimbic cortices, the hippocampus and the amygdala are primarily concentrated at the level of the ventral striatum, which projects to the ventral pallidum. From here the limbic circuit is directed to the thalamus. This circuit is closed by a thalamocortical pathway to the anterior cingulated area and medial orbitofrontal cortex. The cortical input to the *motor circuit* mainly originates from the primary motor, premotor and somatosensory areas. This glutamatergic input is largely directed to the putamen, which projects topographically to the motor parts of the GPe and GPi and the SNr. From the GPe, a pathway projects to the STN. The STN mainly projects to the GPi and SNr. This motor loop is closed by means of the thalamic projection to the cortical areas (see *Figure 1*).

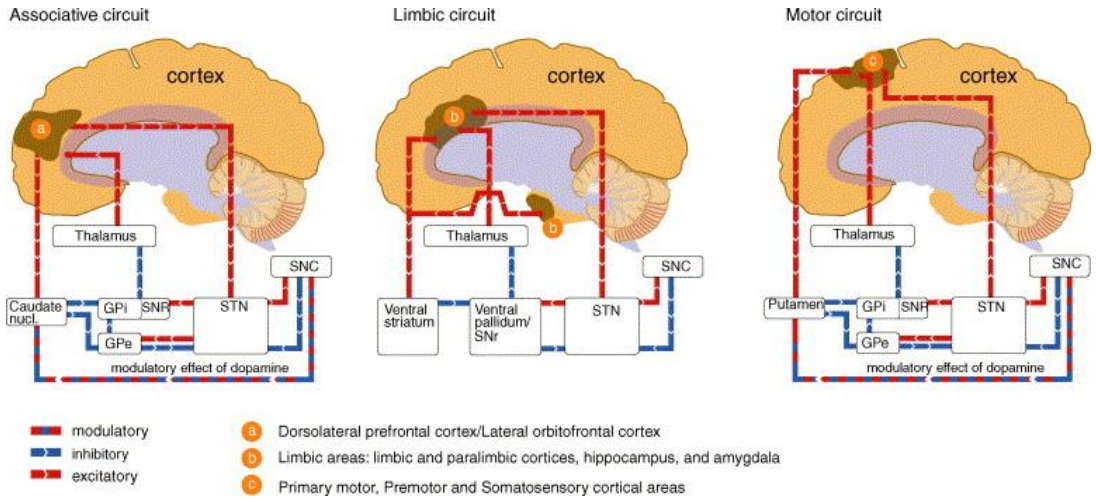

Figure 1. Schematic illustration of the basal ganglia-thalamocortical associative, limbic and motor circuits (taken from Temel et al., 2005)

Basically, the major output regions of the basal ganglia are the GPi and the SNr, which project to the thalamus and to the brainstem (Obeso et al., 2000). The monosynaptic striatal projection to GPi/SNr is called the *direct* pathway, while the projection linking the striatum to the GPi/SNr by way of GPe and the STN is referred to as the *indirect* pathway. Activation of the direct pathway facilitates movement while activation of the indirect pathway reduces movements (Bateup et al., 2010; Freeze et al., 2013). The STN is anatomically connected with both the direct, through its projection to the GPi and SNr, and the indirect pathway, through its projection to the GPe.

Finally, the so-called *hyperdirect* pathway links frontal cortical areas directly to the GPi/SNr via topographic projections to the corresponding functional areas of the STN (Nambu et al., 1996). Projections to the STN are of special importance since the STN is the only basal ganglia nucleus that has excitatory influence, while all other connections are inhibitory. An activation of the indirect pathway thus results in an enhanced inhibition of the thalamo-cortical transfer, which leads to an inhibition of movements. As a consequence, the basal ganglia serve as a kind of filter for possible movements and actions by enhancing those motor programs that fit best to the current situation.

1.2.2 The neurodegenerative process in PD

In PD, due to dopamine depletion, an imbalance between direct and indirect pathway in favor of the inhibitory indirect pathway occurs. The loss of dopaminergic nigrostriatal connections leads to the disinhibition of direct projections from the striatum to the GPi with a successive increase of neuronal activity in the GPi. Simultaneously, the inhibition of striatal neurons in the GPe enhances, so that the activity of STN neurons is not sufficiently inhibited through the GPe. As a consequence of this activity increase in the STN, the hyperactivity in the GPi accelerates, which represents the most important output structure within the basal ganglia loop. Due to the hyperactive GPi, inhibition on thalamocortical projections by the internal pallidum occurs, which is even boosted by a reduced function of the direct pathway. These shifts of activity and inhibition manifest as hypokinesia and thus depict a cause for at least a part of the clinical motor symptoms of PD (see *Figure 2*). Due to its simplicity and explicatory value this model is still very prominent in PD literature, although it cannot explain the complete clinical picture of the disease. More recent concepts further emphasize abnormally high neural firing and synchronization signals in the basal ganglia as well as in cortical structures in PD patients (DeLong & Wichmann, 2009; Hammond et al., 2007).

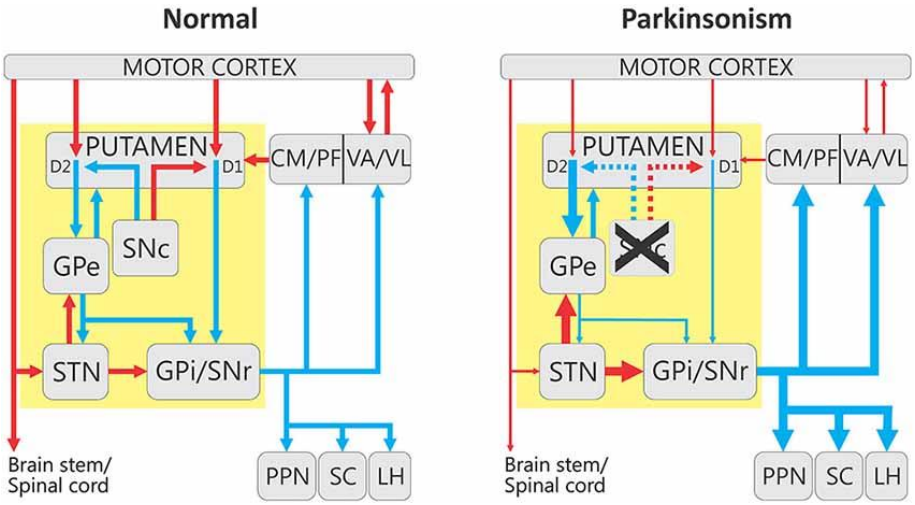

Figure 2. Fire rate changes in the basal ganglia-thalamo-cortical motor circuit in PD. The left side shows circuits in the "normal" healthy state, the right side shows overall changes in activity in PD. Blue arrows indicate inhibitory, red arrows excitatory connections, while the thickness of the arrows corresponds to their presumed activity. (taken from Galvan et al., 2015)

1.3 Structure and connectivity of the Subthalamic Nucleus

Due to its exceptional position within each of the aforementioned circuits (Section 1.2.1), the STN stands a central role in the basal ganglia physiology and is pathologically as well as therapeutically of great importance. The STN is a small, lenticular nucleus located ventral to the thalamus, dorsal to the SNc and medial to the internal capsule. The STN receives and projects to a number of different regions inside and outside the basal ganglia. The main afferents arise from the cortex (glutamatergic), GPe (GABAergic), parafascicular nucleus (glutamatergic) and centromedian nucleus (glutamatergic) of the thalamus, SNc (dopaminergic), pedunculopontine nucleus (cholinergic and glutamatergic) and the dorsal raphe nucleus (Hamani et al., 2004; Parent and Hazrati, 1995b; Orieux et al., 2000). In turn, STN efferents (glutamate-mediated neurotransmissions) are predominantly directed to GPi, GPe, SNr, SNc and the pedunculopontine nucleus (Hamani et al., 2004; Parent and Hazrati, 1995b). The studies of Parent and Hazrati (1995a;b) identified three functionally different subareas of the STN (see *Figure 3*). The biggest subarea contains sensomotor afferences and efferences and is located in the dorsolateral STN. Cognitive-associative connections are situated foremost in the ventral STN. The limbic subarea is located at the medio-ventral tip of the STN. Mallet et al. (2007) suggested gradual transitions between the single subareas rather than strict divisions.

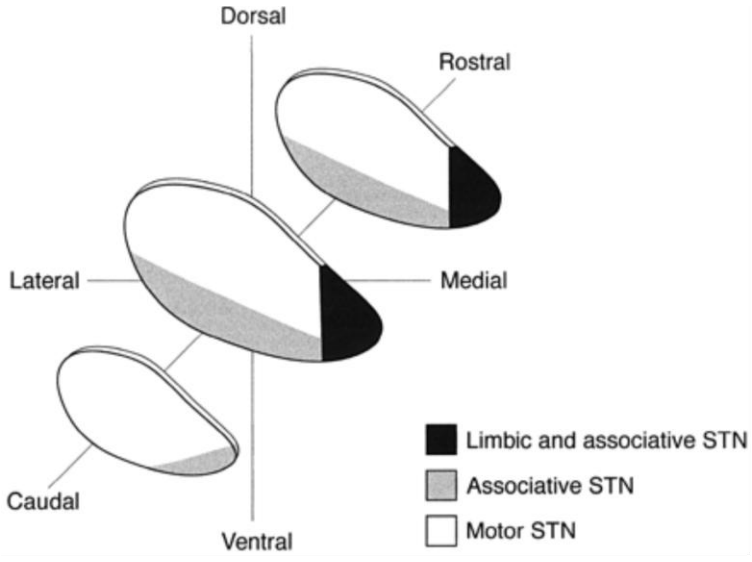

Figure 3. Schematic representation of the intrinsic organization of the STN according to the tripartite functional subdivision of the basal ganglia. (taken from Hamani et al., 2004)

Through its projections to the GPi and SNr as well as to the GPe, the STN is anatomically connected with both the direct and the indirect pathways. It is thus integrated in cognitive and other high-level processes which are anatomically and functionally represented by the two *associative* basal ganglia-thalamocortical loops. Hence, the STN can regulate information processing within the basal ganglia at different layers: at the level of an intermediate station (connections with GPe) and at the level of the basal ganglia output (connections with GPi/SNr). In fact, the STN may be critical for action selection processes to prevent premature responding, so that all potential responses are considered before facilitating the most appropriate one (Frank, 2006). It is thus involved in the selection and inhibition of actions as well as in a general flexibility of instrumental behavior.

Motivational as well as emotional processes are represented by the basal ganglia-thalamocortical *limbic* circuit that contains connections between limbic and paralimbic cortices, the hippocampus and the amygdala with the ventral striatum (Alexander & Crutcher, 1990; Parent & Hazrati, 1995a). The STN has an important role within this loop since it is directly connected with the output region of this circuit and is thus crucially involved in the processing of different emotional stimuli.

As for motor performance, it is represented by the basal ganglia-thalamocortical *motor* circuit by means of the direct and indirect pathway. The STN is anatomically connected with both and is thus a principal regulator of the motor circuit output towards the thalamic nuclei (Plenz & Kital, 1999). After passing the specific regions of the thalamus, the motor circuit is closed by the projection to the supplementary motor area (SMA), the pre-motor areas and the primary motor cortex (Alexander & Crutcher, 1990).

In sum, there is substantial anatomical and physiological evidence that the STN is critically involved in motor control as well as different cognitive and emotional processes.

1.4 Deep Brain Stimulation of the Subthalamic Nucleus

1.4.1 Indication and functional principle of DBS

The aim of therapy in PD is to alleviate disease symptoms, to improve quality of life and to stop or at least to slow down the disease progression. For a long time, L-Dopa was presumed to be method of choice in the treatment of PD. Compared to other active substances, it is superior in effectiveness for bradykinesia, rigor and tremor (Krauss & Volkmann, 2004). But the clinical effect of L-Dopa changes in the course of treatment over several years. Dyskinesias and fluctuations of effectiveness may occur, as well as late motor complications and maybe even psychic disturbances like hallucinations or delusions ("L-Dopa long-term syndrome").

Thus, despite best possible drug treatment, it is often not possible to maintain the initial improvements of motor functions in patients with ongoing disease duration. Also side effects of drug treatments contribute to the loss of effectiveness, reduce well-being of patients and let alternative treatments appear necessary and desirable.

After DBS was firstly introduced in the 1990s, it rapidly became the preferred treatment in advanced PD. Especially in patients with intractable tremor, motor fluctuations or dyskinesias, DBS is now commonly applied. It is particularly indicated in cases in which motor complications and/or medication intolerance have led to an unacceptable decline in quality of life (Deuschl et al., 2006; Weaver et al., 2009). It is further indicated in patients with fluctuations, in patients endangered of developing psychotic formations and in patients without unstable or untreated medical conditions including depression and dementia. The patient must be capable to emotionally, cognitively and physically manage the surgery, the handling of DBS itself and the regular post-operative cares (Houeto et al., 2006).

DBS offers several advantages. For one, the functioning of the technique is reversible (by switching it ON or OFF) and individually adaptable (with reference to stimulation parameters like DBS contacts, voltage or frequency). Significant improvements of motor symptoms in PD have been continuously observed, plus, L-Dopa medication, which is often accompanied by side effects, can be reduced under stimulation.

DBS in its current form is a symptomatic treatment which does not alter the progression of the disease itself. Moreover, it does not influence the non-L-Dopa

responsive motor and non-motor aspects of PD like freezing of gait and balance problems (Wichmann & DeLong, 2016).

DBS therapy consists of chronic local electrical stimulation of discrete brain targets through an implanted wire bundle electrode with multiple contacts and a small implanted subcutaneous, externally programmable pulse generator. The primary targets for DBS in PD are specific regions of the STN, GPi or the ventral striatum. During DBS surgery, electrodes are stereotactically placed into the brain, guided by neuroimaging and/or electrophysiological recording. These electrodes contain four separate contacts, spaced 0.5– 1.5 mm apart along their distal end. An internal pulse generator, which is similar to a cardiac pacemaker, is simultaneously or subsequently implanted, usually in the subclavicular region, and connected to the electrode (Bronstein et al., 2011). In bilateral DBS, two independent single-channel stimulators or a single dual-channel stimulator can be used. Multi-site DBS lead implantations can be done during single surgical sessions or as staged procedures. Different aspects of the stimulation can be controlled via telemetric adjustments of the pulse generator, including the choice of electrode contacts, the stimulation voltage or current, the width of the stimulation pulses, and the frequency of stimulation. The stimulation parameters vary between patients, stimulation targets and specific disorders, but typically, pulses are delivered at 60–185 Hz, with an amplitude of less than 4 V, and a pulse width between 60 and 200 μs (Wichmann & DeLong, 2016; Elias et al., 2007; Hristova et al., 2000).

The mechanism underlying DBS in PD and other motor disturbances remain controversial. When the procedure was first applied, it was believed that DBS works similar to lesioning procedures like pallido- or thamalotomy, by inactivating the stimulated tissue. Here, stimulation-induced depolarization blocks, referring to the cell depolarization with an abolishment of spontaneous action potentials, or the local release of inhibitory transmitters were postulated (Kringelbach et al., 2007; Beurrier et al., 2001). However, multiple electrophysiological recording studies in primates and human patients have demonstrated that STN-DBS has multiple effects on cell bodies and the excitation of fibers (afferent and efferent projections from targeted regions; Kringelbach et al., 2007; Temel et al., 2007). Furthermore, stimulation parameters as for instance pulse duration strongly determine which tissue elements (cell bodies or axons) are stimulated. Recent investigations postulate that the mechanisms involved in DBS seem to be far more complex than previously

anticipated. Instead of simple excitations of fibers and inhibitions of cells, neural regions that are influenced by DBS might reach novel dynamic states over time and might be characterized by altered ionic currents, nonsynaptic mechanisms, excessive extracellular levels of neurotransmitters and ions as well as microenvironmental changes that favor the development of plasticity (Hamani et al., 2017; Florence et al., 2016; Hamani & Temel, 2012).

1.4.2 Effects of STN-DBS in PD patients

In the following section, I will sum up some previous research results of STN-DBS effects on motor and especially non-motor aspects in PD patients.

Motor effects

The beneficial effects of STN-DBS on motor functions as bradykinesia, rigidity, tremor have extensively been shown in animal studies as well as in human patients. In parkinsonian rodents and primates, STN lesions or high-frequency stimulation mitigate motor deficits (Bergman et al., 1990; Benazzouz et al., 1993; Wichmann et al., 1994; Darbaky et al., 2003; Hamani et al., 2004). In humans, the stimulation of the STN leads to improvements of the cardinal symptoms rigidity, tremor and akinesia and – following these improvements – to a considerable decline of restrictions in daily routines (Deuschl et al., 2006; Krack et al., 2003; Ballanger et al., 2009; Houeto et al., 2006; Limousin et al., 1998). These motor effects were shown to be constant over time (Krack et al., 2003; Herzog et al., 2003; Visser-Vandewalle et al., 2005). One year after surgery, patients showed improvements of 66%, and still 54% of motor enhancement five years post-operatively, with special improvement (70-75%) of rigidity and tremor (Krack et al., 2003).

Neuropsychiatric effects

Several studies investigated neuropsychiatric changes in patients after STN-DBS. Results range from findings of no significant neuropsychiatric changes after stimulation to the proposal that affective disorders were the most frequent side effects of DBS. Precisely, impacts on affect and emotion, foremost depression or

depressive mood, were frequently observed (Couto et al., 2014; Houeto et al., 2002; Vingerhoets et al., 2002; Thobois et al., 2002). Romito et al. (2002) indicated a frequency of post-operative depressive disorders with 25%. Anxiety or apathy were described as further possible side effects of stimulation (Abbes et al., 2018; Houvenaghel et al., 2015; Martinez-Fernandez et al., 2016). In fact, apathy after STN-DBS could even cancel out the benefits of motor improvements in terms of perceived quality of life. Importantly, results are heterogeneous and vary from improvement to deterioration of neuropsychiatric aspects under STN-DBS.

Other investigations showed that stimulation of the STN could improve sleep disorders, which are frequently observed in PD patients, by increasing sleep quality, improving nocturnal mobility and decreasing wakes after sleep onset (Amara, 2011; Deuschl et al., 2006).

Clinical studies further suggest that STN-DBS may be associated with enhanced motivated impulsivity (Ballanger et al., 2009; Frank et al., 2007; Hälbig et al., 2009; Weaver et al., 2009; Bronstein et al., 2011; Rothlind et al., 2015), but again, results are heterogeneous. Lim et al. (2009) summarized that dopamine dysregulation syndromes and impulse control disorders as common side effects after stimulation (Zhang et al., 2014, Janssen et al., 2014) "may persist, worsen or develop after DBS surgery, few also improved".

Abbes et al. (2018) showed decreased impulse control disorders and neuropsychiatric fluctuations in patients in the long term. A few other reports did not find any negative effect of stimulation on the behavioral performance in PD patients (Ardouin et al., 1999; Jahanshahi et al., 2000; Schneider et al., 2003). Actually, the question remains to what extent certain factors that are described as side effects following DBS are present even before surgery and might not have been assessed (or could not be measured) pre-operative. In a retrospective study, Houeto and colleagues (2002) described pre-surgical psychic and behavioral disorders that were concealed by patients due to fear of exclusion from DBS.

Neuropsychological effects

Much attention is paid to cognitive changes induced by STN stimulation. In patients who showed clear symptoms of dementia before surgery, STN-DBS led to a clinical deterioration of cognitive abilities (Limousin et al., 1998), which is why beginning dementia is classified as a clear exclusion criteria for DBS (Ardouin et al., 1999).

In general, STN-DBS is considered as relatively safe concerning cognitive alterations in patients after surgery, since it is associated with only minimal or no changes of patients´ performance on the neuropsychological level (Jahanshahi et al., 2000; Krack et al., 2002). Some studies showed declines in executive and memory tasks or a general cognitive decline after DBS (Xi et al., 2015; Jahanshahi et al, 2000; Fasano et al., 2010; Saint-Cyr et al., 2000), while others were able to show improved cognitive outcomes following stimulation in these domains (Foki et al., 2018; Alegret et al., 2001; Freund et al., 2009). Further investigations report no neuropsychological changes in specific executive, memory or attention tasks (Demeter et al., 2017; Zangaglia et al., 2009; Perozzo et al., 2001). These differences in outcome measures of DBS may be partly ascribed to different diagnostic approaches and measurements.

However, deficits in semantic and phonematic verbal fluency after STN-DBS were constantly described in several studies (Demeter et al., 2017; Foley et al., 2017; Houvenaghel et al., 2015; Jahanshahi et al., 2000). The precise cognitive mechanism underlying this deterioration is still unclear, but studies suggest reduced motivation, linguistic skills, executive functioning as well as reduced generativity and processing speed after DBS.

As a conclusion, due to interference with the basal ganglia-thalamocortical associative circuits, different aspects of cognitive functioning might or might not decline after STN-DBS. Here, also other (pre-surgical) factors as disease progression rate and speed, age at onset and gender of patients amongst others, but also influences that can be ascribed to the surgical intervention itself might play crucial roles in neuropsychological outcome after stimulation. At any rate, cognitive impairments in terms of executive deficits, memory or attentional deficits as well as neurobehavioral changes after stimulation can have an important role in establishing the functional outcome of patients.

Cognitive and behavioral effects

Cognitive dysfunctions are approved as frequent and relevant non-motor features of PD and are associated with a degeneration of the basal ganglia-thalamocortical cognitive loop, but DBS may modulate these cognitive disruptions. Previous reports indicate that bilateral STN stimulation in PD patients worsened dual-task function of cognitive-motor performance when moving from a single-task to dual-task paradigm.

The loss of performance in both tasks was exaggerated with increasing task difficulty (Alberts et al., 2008). Greenhouse et al. (2013) showed a normalization in response switching in patients under STN-DBS and proposed differential effects of STN stimulation depending on stimulation electrode location. The authors found that stimulation of the ventral contacts but not of the dorsal contacts normalized the behavioral pattern compared to controls. Wojtecki et al. (2011) provided evidence for a frequency-specific modulatory effect of STN-DBS on the cognitive representation of time intervals in PD patients.

A considerable focus of interest lies on influences of STN-DBS on action selection, reward processing and response conflicts in patients, due to the role of the STN in flexible motivated behavior and action control (Frank et al., 2007; Chowdhury et al., 2013; Schroeder et al., 2002; Guitart-Masip et al., 2012; 2014). The crucial role the STN holds in cognitive processes as information processing and action selection by eliciting a "global nogo signal" over premature responding has been reported in Section 1.3, page 10. Stimulation of the STN might interfere with this processing. In accordance, Ballanger et al. (2009) observed impaired response inhibition under STN-DBS in PD patients during a "go-nogo" task. DBS of the STN is generally associated with enhanced impulsivity of patients when it is ON. However, it improves the reactive inhibition of impulsive actions that interfere with goal-directed behavior, and especially the dorsal STN circuitries have been shown to be crucial for modulating the reactive inhibitory control of motor actions (van Wouwe et al., 2017). Moreover, STN-DBS affected the cognitive processes involved in reward processing and conflict responses. It facilitated the expression of incentive actions, increased impulsive action selection in an incentive context (Houvenaghel et al. 2016) and boosted the incentive effect of promised rewards (Palminteri et al., 2013). STN-DBS thus influences the flexibility of instrumental behavior in the face of a motivational outcome. However, flexible behavior still underlies so-called "Pavlovian congruencies" that favor actions leading to rewards and inhibit actions that lead to losses or punishments. It is yet unknown whether STN-DBS selectively influences those Pavlovian-congruent actions, i.e. reinforces rewarded actions and inhibits punished actions, or if stimulation generally improves actions regardless of valence and reason (reward vs. punishment). This question will be investigated in Chapter 2 of this thesis.

A continuative and broad field of interest is set in the influence of STN-DBS on decision-making in patients. Making decisions is a complex and highly relevant function in everyday life and refers to strategic, executive functioning. Studies propose a beneficial effect of STN-DBS on decision-making under risk in PD patients by influencing the ability to make advantageous decisions in risky decisions (Boller et al., 2014), as well as a positive influence of stimulation on active feedback learning for decisions in conflict situations (Meissner et al., 2016; van Wouwe et al., 2011). However, studies also emphasize the role of patients´ impulsivity in the experimental settings. As already mentioned above, STN-DBS is said to increase impulsivity in patients (Ballanger et al., 2009; Frank et al., 2007). It was suggested that the STN sends global "nogo" signals in decision-making to evaluate different options before acting. DBS would disturb this function, leading to impulsive behavior (Frank, 2006). The STN is also supposed to play a crucial role in overcoming a behavioral status quo bias in difficult decisions, i.e. the tendency to stay with a default option. The possible STN-DBS modulation of perceptual decision-making when a choice is set by default in dependence from patients´ impulsivity is topic of Chapter 3.

Emotional effects

STN-DBS was variously observed to influence emotion perception in PD patients. This impact has been shown in different stimulus modalities (facial, vocal or semantic processing of emotions), instructions and in a variety of emotional cues (Enrici et al., 2017; McIntosh et al., 2015; Schneider et al., 2003; Berney et al., 2007; Péron et al., 2010; Serranová et al., 2011; Geday et al., 2006).

To date, research focusing on the effects of STN-DBS on emotion processing and recognition demonstrated unsteady results. Some studies showed no changes of recognition of emotional stimuli (faces and prosody) under stimulation (McIntosh et al., 2015; Albuquerque et al., 2014; Schneider et al., 2003; Berney et al., 2007), while other publications described slight worsening in the discrimination of emotional facial stimuli under DBS (Péron et al., 2010; Geday et al., 2006; Serranová et al., 2011). Especially the recognition of negative emotions as for instance fear or disgust displayed in faces are affected and diminished under DBS. In contrast, other studies could demonstrate a beneficial influence of STN-DBS on the discrimination of emotional prosody by facilitating reactions on highly conflicting stimulus material

(Brück et al., 2011), and could show DBS influence on the processing of emotional semantic stimuli by eliciting semantic priming under DBS (Castner et al., 2007). However, emotion processing refers to the automatic implicit as well as to the conscious explicit processing, and both functions may underlie different cognitive-emotional processes which have been only sparsely investigated yet.

The STN holds a central role in cognitive as well as emotional processing due to its central position in the basal ganglia-thalamocortical circuitry. While explicit emotional processing was proposed to be influenced by stimulation of the STN and its subcortical connections, emotional assessment per se (i.e. the implicit emotional processing) would not be affected by stimulation (Geday et al., 2006). STN-DBS might thus have different consequences for implicit and explicit processing. So far, only Castner and colleagues (2007) investigated the impact of DBS on those two different aspects of emotional processing, but focused on semantic stimuli only. The influence of STN-DBS on implicit and explicit emotional processing on reduced facial stimuli (eyes) in PD patients has not been investigated yet and will be topic of Chapter 6, with the introduction of two pre-studies that are reported in Chapters 4 and 5.

1.5 Objectives and specific aims

This PhD project aims at investigating how DBS of the STN modulates different cognitive and emotional functions in patients with PD. Particularly, I am interested in the DBS-dependent influence on action selection under anticipation of rewards and punishments (Project A) as well as in the impact of DBS on decision-making under difficult pre-set choices (Project B). A third aim consists in investigating the influence of STN-DBS on implicit and explicit emotional processing by presenting emotional semantic and facial stimuli (Project C). For this, the thesis provides two pre-studies on healthy participants (Study C1) and PD patients without DBS (Study C2) and the investigation on the final group of stimulation-treated PD patients (Study C3); see an overview of the experimental settings in *Table 1*.

1.5.1 Specific aim of Project A

This project examines the influence of STN-DBS on the motivational regulation of action control and reward processing in PD patients.

STN functioning is associated with flexible, goal-directed instrumental behavior which yet underlies hard-wired, "Pavlovian congruencies" that favor rewarded actions over inhibiting those actions leading to punishments (Guitart-Masip et al., 2012). DBS of the STN might selectively influence the flexibility of instrumental behavior in the face of motivational outcome. Thus, in the first project, PD patients performed a valenced go/nogo task (Guitart-Masip et al., 2011) whose contingencies explicitly decouple valence and action, with and without STN stimulation, and results were compared with an age- and gender-matched control group of healthy participants.

<u>Hypothesis A:</u>

Based on findings of behavioral congruencies that favor actions leading to rewards over those leading to losses, I expect STN-DBS to selectively increase the execution of "go"-actions to obtain rewards when compared to actions to avoid losses.

1.5.2 Specific aim of Project B

This project investigates the impact of STN-DBS on perceptual decision-making in PD patients in difficult and high-risk status quo choices, depending on the individual baseline impulsivity.

When faced with difficult decisions, people tend to stay with the default option. Neurophysiological evidence suggest an important role of the STN in overcoming this so-called status quo bias that often leads to suboptimal choice behavior (Fleming et al., 2010; Yu et al., 2010). The STN is supposed to provide a "nogo" signal that raises response thresholds when making decisions to prevent unwanted impulsive responses (Frank, 2006), and STN stimulation might interfere with this function. Project B investigates the effects of STN-DBS on difficult perceptual decision-making ("tennis line judgment" paradigm by Fleming et al., 2010) in PD patients, depending on the individual baseline impulsivity that was assessed by applying the Eriksen flanker task (Eriksen & Eriksen, 1974).

Hypothesis B:
I hypothesize that STN-DBS will selectively affect the answering mode in decision-making depending on the difficulty of decisions, leading to increased status quo bias.

1.5.3 Specific aims of Project C, Studies 1-3

1) The first study investigates if reduced facial emotional information is sufficient to induce implicit emotional processing in healthy participants.

2) The second study examines implicit and explicit emotional processing in PD patients in a lexical decision task coupled with an affective priming paradigm, using semantic and reduced facial emotional stimuli.

3) The third study investigates DBS-dependent influences on implicit and explicit emotional processing in an affective priming paradigm with reduced facial emotional stimuli.

Processing of emotional stimuli happens as automatic implicit and explicit processing, which refers to conscious action and stimulus discrimination under deliberate control. Implicit processing of emotions can be measured by affective priming paradigms; resulting priming effects between two combined stimuli (prime and target) allow for conclusions about the automatic emotional processing that is triggered by the prime. Among a variety of investigations with different primes, targets and tasks, evidence for reduced facial information (for instance eyes) acting as primes is lacking and will thus be addressed in Study C1.

Non-stimulated PD patients have been shown to be impaired in explicit emotion recognition, especially for negative connoted emotional stimuli, while implicit emotional processing has been hardly measured in PD. Moreover, studies using reduced emotional facial information (eyes) for implicit and explicit processing are missing. This will be aim of Study C2.

Finally, in PD patients with STN-DBS, implicit as well as explicit emotional processing has not been systematically investigated yet. However, it has been proposed that while explicit emotional processing would be targeted by STN stimulation, implicit processing would not be affected by DBS (Geday et al., 2006). Capturing possible selective influences of STN-DBS on both emotional processing types in patients is desirable and will be topic of Study C3.

<u>Hypothesis C1)</u>

Even reduced emotional information in human eyes is sufficient to influence automatic emotional responses in terms of affective priming effects.

<u>Hypothesis C2)</u>

I expect PD patients to show worse results in implicit and explicit emotion processing when compared to healthy participants. But despite their known explicit emotional processing deficits, PD patients are supposed to be still responsive to implicit emotion.

Hypothesis C3)

In STN-DBS-treated patients, I expect unaffected implicit processing by stimulation, but altered behavioral results in explicit emotional processing when DBS is ON.

Table 1. Experimental design overview

Project	Sample	Control group	Paradigm
A	16 PD patients with STN-DBS	16 healthy participants (age- and gender matched)	Go-NoGo paradigm (adapted from Guitart-Masip et al., 2011)
B	18 PD patients with STN-DBS	-	Eriksen Flanker Go-NoGo paradigm, "tennis line judgment" paradigm (Fleming et al., 2010)
C Study C1)	16 healthy participants	-	Affective priming paradigm with lexical decision task
Study C2)	16 PD patients	16 healthy participants (age- and gender matched)	Affective priming paradigm with lexical decision task
Study C3)	14 PD patients with STN-DBS	-	Affective priming paradigm with lexical decision task

PROJECT A

2. Effects of STN-DBS on action selection and reward anticipation in PD patients

Specific aim:

This project examines the influence of STN-DBS on the motivational regulation of action control and reward processing in PD patients.

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Abstract

DBS of the STN is an effective treatment for motor impairments in PD but its effect on the motivational regulation of action control is still not fully understood. I investigated whether DBS of the STN influences the ability of PD patients to act for anticipated reward or loss, or whether DBS improves action execution independent of motivational valence. 16 PD patients (12 male, mean age = 58.5 ± 10.17 years) treated with bilateral STN-DBS and an age- and gender-matched group of healthy controls (HC) performed a go/nogo task whose contingencies explicitly decouple valence and action. Patients were tested with (ON) and without (OFF) active STN stimulation. For HC, there was a benefit in performing rewarded actions when compared to actions that avoided punishment. PD patients showed such a benefit reliably only when STN stimulation was ON. In fact, the relative behavioral benefit for go for reward over go to avoid losing was stronger in the PD patients under DBS ON than in HC. In PD patients, rather than generally improving motor functions

independent of motivational valence, modulation of the STN by DBS improves action execution specifically when rewards are anticipated. Thus, STN-DBS establishes a reliable congruency between action and reward ("Pavlovian congruency") and remarkably enhances it over the level observed in HC.

2.1 Introduction

DBS of the STN has become a standard and effective treatment in advanced PD. Although the mechanisms of DBS are still not sufficiently clarified, it is assumed that the high-frequency stimulation leads to a functional inhibition of the hyperactive STN and thereby reduces the inhibitory influence of the basal ganglia nuclei on thalamo-cortical projections (Limousin et al., 1998) which - in consequence - leads to an overall improvement in motor functions.

While STN-DBS can lead to considerable motor improvements (Limousin et al., 1998; Ballanger et al., 2009), its effects on the motivational regulation of action control are still unclear and there is evidence to suggest that STN-DBS could influence the flexibility of instrumental behavior in the face of a motivational outcome. Goal-directed instrumental action control ideally entails the flexibility to deploy or withhold actions independent of whether the goal is to obtain reward or to avoid loss (Guitart-Masip et al., 2014). However, this flexibility is constrained by seemingly hard-wired congruencies (so-called "Pavlovian congruencies") that favor the performance of actions that lead to rewards and the inhibition of actions that lead to losses (Guitart-Masip et al., 2012). This asymmetry in choices is mirrored by the direct and indirect pathways of the striatum that reinforce rewarded actions or inhibit punished actions, respectively (Frank et al., 2004) and is modulated by dopamine (Guitart-Masip et al., 2012; 2014; Salamone et al., 2005; Berridge et al., 1998). It has been suggested that the STN acts by increasing the decision-threshold of actions encoded within the basal ganglia systems (Frank, 2006) when control over preponderant actions needs to be exerted (Fleming et al. 2010). Therefore, one possibility is that STN-DBS selectively releases the brake over Pavlovian congruent actions preferentially computed in the striatum. Alternatively, STN-DBS will improve performance of any action regardless of Pavlovian congruency between action and reward.

In the present study, I tested between these two alternatives. To that end, I adapted the go/nogo action/loss (or valenced go/nogo) paradigm (Guitart-Masip et al., 2011; 2012) to a simplified format that can be performed by PD patients. Patients were instructed to make actions to obtain rewards, to make actions to avoid losses, to withhold actions to obtain rewards and to withhold actions to avoid losses. Patients were tested in two conditions, with the STN-DBS being ON and OFF. I hypothesize

that if STN-DBS selectively releases the brake over Pavlovian congruent actions, DBS ON will increase the advantage of performing instructed go actions to obtain rewards when compared to make actions to avoid losses. Consequentially, DBS ON would have no effect on nogo trials since this activation through DBS only targets actions.

2.2 Methods

Participants

The study included 16 patients with PD (12 male (75%), mean age= 58.5 ± 10.17 years; 13 right handed) with bilateral DBS of the STN. Patients were recruited from the Departments of Neurology and Stereotactic Neurosurgery at the University of Magdeburg and the diagnosis of PD was confirmed by a neurologist specialized in movement disorders. The mean duration since DBS operation was 27.63 ± 24.51 months. Demographic and disease characteristics of each patient can be seen in *Table 2.* All patients remained on their prescribed dopaminergic medication in conjunction with DBS and were tested during the ON state of their medication cycle. All patients had chosen DBS surgery because their medications were no longer providing optimal control over their motor symptoms. DBS parameters in the sample at the time of testing were as follows: *voltage* [right: median=2.8, range 1.0-5.8; left: median=2.5; range 2.0-5.5], *frequency* [right: median=130, range 60-200; left: median=130; range 60-200] and *pulse width* [right: median=60; range 60-130; left: median=60; range 60-130].

Electrodes were placed bilaterally in the STN of all patients. The surgical procedure for STN-DBS utilized standard stereotactic techniques with microelectrode recordings for electrophysiological localization and has been described previously (Elias et al., 2007). The HC group consisted of 16 age- and gender-matched participants (mean age 58.38 ±10.14 years, 12 male). None of the patients and controls fulfilled neuropsychological criteria for dementia or showed clinically relevant levels of depression at the time of testing. Further exclusion criteria were: history of neurological condition other than PD (for patients), any psychiatric condition known to compromise executive cognitive functioning (e.g. schizophrenia, bipolar affective disorder, mood disorders) or any untreated or unstable medical

conditions. Also, patients only participated when they were able to execute simple finger movements to press a button when STN-DBS was OFF.

All patients and HC participated voluntarily and could quit the test at any time. Written informed consent was obtained from all patients and HC participating in the study and the experiment was approved by the local ethics committee (University of Magdeburg, Germany).

Table 2. Demographic and disease characteristics in PD patients.

Patient #	Age [years]	Gender	Disease duration [years]	assessment post surgery [months]	LED [mg/d]	DBS contacts	DBS voltage [V], frequency [Hz], pulse width [µs]
1	60	F	23	12	528	10- G+ / 2- G+	3.0 V, 130 Hz, 60 µs/ 4.0 V, 130 Hz, 60 µs
2	72	M	10	66	1829	1- G+ / 6- G+	5.8 V, 130 Hz, 60 µs/ 2.0 V, 130 Hz, 90 µs
3	53	M	9	13	813	C+ 3- / C+ 11-	2.8 V, 130 Hz, 90 µs/ 2.0 V, 130 Hz, 90 µs
4	75	F	8	12	0	C+ 10- / C+ 2-	3.5 V, 130 Hz, 60 µs/ 4.0 V, 130 Hz, 60 µs
5	52	F	17	62	1664	2- G+ / 6- G+	3.2 V, 60 Hz, 90 µs/ 3.0 V, 60 Hz, 90 µs
6	68	M	11	52	157	3- G+ / 5- 7+	5.0 V, 130 Hz, 60 µs/ 3.5 V, 130 Hz, 60 µs
7	52	M	14	29	482	3- G+ / 10- 11+	1.0 V, 180 Hz, 60 µs/ 5.5 V, 180 Hz, 60 µs,
8	55	M	32	13	838	2- 1+ / 10- 11+	2.8 V, 130 Hz, 90 µs/ 2.2 V, 130 Hz, 90 µs
9	68	M		51	500	3+ 2- / 7+ 6-	4.0 V, 130 Hz, 130 µs/ 4.0 V, 130 Hz, 130 µs
10	57	M	11	9	480	2- G+ / 11- G+	1.1 V, 60 Hz, 60 µs/ 3.6 V, 60 Hz, 60 µs
11	66	M	17	61	728	2- G+ / 4- 6+	2.0 V, 130 Hz, 60 µs/ 3.5 V, 130 Hz, 60 µs
12	64	F	10	49	0	1- G+ / 6- G+	2.0 V, 130 Hz, 60 µs/ 2.5 V, 130 Hz, 60 µs
13	39	M	5	4	187	3- G+ / 11- G+	2.3 V, 130 Hz, 60 µs/ 2.1 V, 130 Hz, 60 µs
14	59	M	4	3	250	G+ 3- / G+ 11-	2.0 V, 130 Hz, 60 µs/ 2.0 V, 130 Hz, 60 µs
15	41	M	14	3	100	3- G+ / 10- G+	3.5 V, 200 Hz, 60 µs / 2.0 V, 200 Hz, 60 µs
16	55	M	9	3	0	2- G+ / 10- G+	2.0 V, 130 Hz, 60 µs/ 2.5 V, 130 Hz, 60 µs

LED=L-Dopa equivalent daily dose in mg.

Stimuli

The experimental paradigm was generated and carried out with Presentation software (Neurobehavioral Systems, Inc.). The paradigm was adapted from Guitart-Masip et al. (2011) (see *Figure 4*) to simplify it for patient use.

On each trial, patients first saw an iconic cue: green or red signs (O or X) combined with different € symbols (see *Figure 4*). There were four trial types depending on the cues presented at the beginning of the trial: 1) "go to win": A green circle combined with a € sign indicated that a reward could be obtained by action (button press); 2) "go to avoid losing": a green cross combined with a crossed-out € sign indicated that a punishment could be avoided by action (button press); 3) "no-go to win": a red circle combined with a € sign indicated that reward could be gained by withholding an action (button press); 4) "no-go to avoid losing": a red cross combined with a crossed-out € sign indicated that a loss could be avoided by withholding action. Half of the trials (160) were go cues, the other half no-go cues.

The button press had to be made in response to a target (a black circle appearing either on the right or the left side from a fixation cross) subsequently presented within a time period of 250 - 2000ms after the cue. Participants had to indicate the side (left or right) of the circle with a press on the corresponding mouse-button within 1000ms with their preferred hand. After the response, a fixation mark appeared that was followed by a feedback indicating whether the response was correct (green upward arrow) or wrong (red downward arrow) or if a punishment was avoided (yellow horizontal bar). For each correct answer the patient won 0.08 €, for each wrong answer 0.08 € were subtracted. The gains and losses for each trial were added to a total; at the end of the experiment the entire amount was paid to the participant.

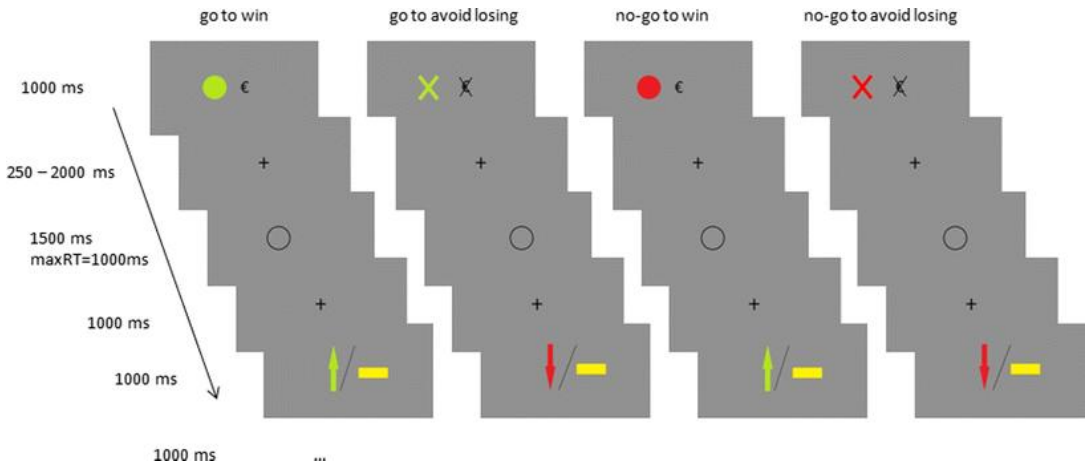

Figure 4. Experimental design: On each trial, one of four different cues was presented that indicated the required reaction to the coupling of action (press or do not press a button) and valence (win or lose) to a target, followed by a black circle appearing either on the right or left side of a fixation cross. In go trials, patients had to press a right or left button of a computer mouse according to the direction of the target with their preferred hand. In nogo trials, patients had to withhold a response. Feedback was given in terms of a green upward arrow (correct reaction, win of € 0.08), a red downward arrow (wrong reaction, loss of € 0.08) or a yellow horizontal bar (absence of win or loss) after presentation of the black circle and a delay of 1000ms. 320 trials were presented in a randomized matter in four blocks of each 80 trials.

Experimental Procedure

The experiment and the process of switching the stimulator ON or OFF were explained to the patients and confirmation of consent was affirmed. The values and response contingencies associated with each cue were fully explicit. Patients were seated in front of a computer screen, looked at a fixation cross in the middle of the screen and had to press either the left or the right button on a computer mouse with their preferred hand. During one session, 320 trials were presented in four runs with a short break (2-3 minutes maximum) after each 80 trials. Cues were displayed in a random manner, i.e. 80 trials were assigned to each of the four trial types ("go to win", "go to avoid losing", "nogo to win" and "nogo to avoid losing"). The randomization was carried out by Presentation.

One test session (320 trials) lasted about 40 minutes; the first session was preceded by a training of 15 minutes. In the training patients were instructed to the

functionality of the answering buttons, the cues were introduced and explained, and patients could practice the go/ nogo procedure in three parts (1. presentation of and responding to the circle on either the left or right side, 2. explanation of the iconic cues and afterwards training of go/ nogo trials with combined written instructions underneath the pictures, 3. training of go/ nogo trials without written instructions).

The order of the ON/OFF testing was randomized across patients. Between both sessions, a break of one hour was integrated after the DBS stimulator was switched ON or OFF, respectively, to assure a complete remission of the DBS effect. This ensured that motor symptoms had largely subsided after inducing stimulation and that the increase in motor symptoms had reasonably stabilized after terminating stimulation (Hristova et al., 2000; Lopiano et al., 2003). Before the start of the second session, participants were reminded of the four different cue pictures and their outcomes.

2.3 Results

Successful trials

For the analysis of behavioral data the percentage of successful trials (correct on time button press responses for all conditions) were analyzed (see *Figure 5)*. For the HC the two-way repeated-measures analysis of variance (ANOVA) with the factors *action* (go/no-go) and *valence* (win/avoid losing) revealed a significant main effect (ME) of the factor *action* [$F(1,15)=10.18$; $p<0.01$] as well as a significant *action* x *valence* interaction [$F(1,15)=4.84$; $p<0.05$]. Thus, HC performed better in no-go trials than in go trials (ME *action*) and the choice of action was modulated by the anticipation of reward; replicating former results in a version of this task in which participants were instructed on task contingencies before testing (Guitart-Masip et al., 2011; 2012).

For the comparison of HC and PD patients under DBS OFF, the three-way repeated-measures ANOVA with the factors *action* (go/nogo), *valence* (win/avoid losing) and *group* (PD/HC) revealed significant main effects of the factors *action* [$F(1,15)=9.49$; $p<0.01$] and *group* [$F(1,15)=6.24$; $p<0.05$] as well as a significant *group* x *action* interaction [$F(1,15)=6.01$; $p<0.05$]. Thus, whereas PD patients with DBS-OFF

performed generally worse than HC (ME *group*), both groups performed worse in actively executing a response than in omitting one, which resulted in less successful go trials than nogo trials (ME *action*). Furthermore, this effect of action selection was stronger in PD patients under DBS OFF (*group* x *action*).

For the comparison of HC and PD patients under DBS ON, the ANOVA revealed significant MEs of the factors *action* [$F(1,15)=8.46$; $p<0.01$], *valence* [$F(1,15)=5.38$; $p<0.05$] and *group* [$F(1,15)=5.95$; $p<0.05$], a significant *action* x *valence* – [$F(1,15)=18.41$; $p<0.001$], a significant *group* x *action* – [$F(1,15)=5.08$; $p<0.05$], a significant *group* x *valence* – [$F(1,15)=8.07$; $p<0.01$], and a significant *group* x *action* x *valence* interaction [$F(1,15)=6.97$; $p<0.05$]. Thus, PD patients under DBS ON performed generally worse than HC (ME *group*). However, both groups performed worse in actively executing a response than in omitting one, which results in less successful go trials than nogo trials (ME *action*), and finally, both groups performed better when anticipating a reward than a loss (ME *valence*). The effects of action selection (*group* x *action*) as well as the effect of valence anticipation were stronger in PD patients with DBS ON (*group* x *valence*). Furthermore, in HC as well as PD with DBS ON the choice of action was modulated by the anticipation of reward (*action* x *valence*). Importantly, this interaction was considerably stronger in STN-DBS ON (*group* x *action* x *valence*).

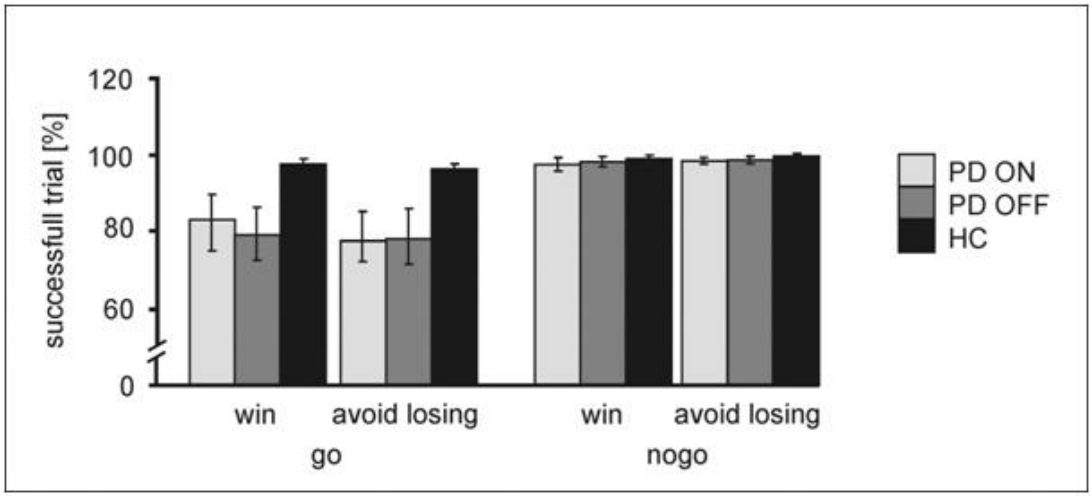

Figure 5. The percentage of successful trials, i.e. the trials that were answered in a correct way (button presses in go trials, no responses in nogo trials), was assessed. Light grey bars indicate results when DBS was ON, dark grey bars show results when DBS was OFF, black bars show results of the HC group. All bars show M ± SE. *** $p<0.001$

To further elucidate the observed STN stimulation effect on the *valence* x *action* interaction - i.e. the behavioral benefit for initiating a response when anticipating a reward over the response initiation when anticipating to avoid a punishment (Pavlovian congruency effect; Guitart-Masip, 2011) - I subsequently calculated and directly compared "*Pavlovian congruency gain indexes*" by subtracting values of avoid losing-trials from win-trials (see *Figure 6*).

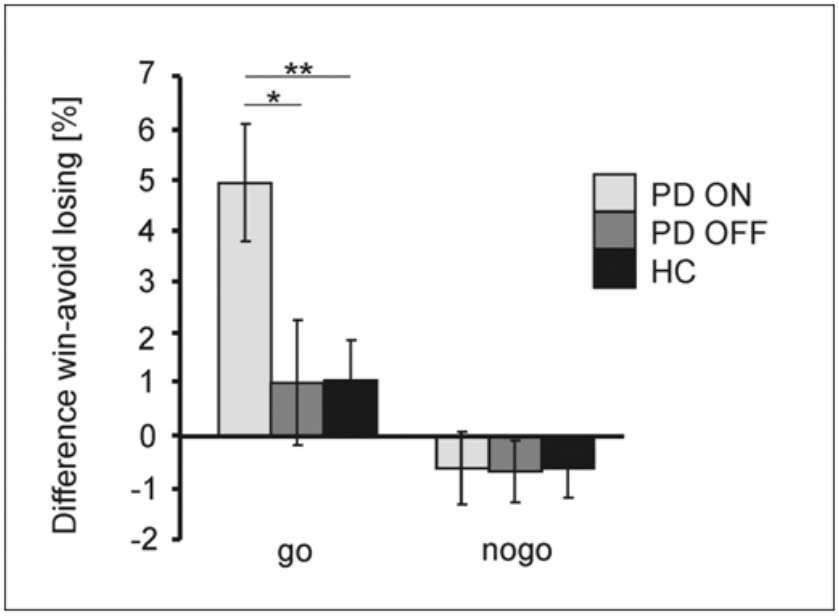

Figure 6. For successful trials, the behavioral benefit for the reward-related gain as the difference between go to win and go to avoid losing trials (left) and between nogo to win and nogo to avoid losing trials (right) was assessed. These two scores represent the interaction between action and valence in choice accuracy (difference value of win – lose). Light grey bars indicate results for DBS ON, dark grey bars for DBS OFF and black bars show the difference values for HC. All bars show M ± SE.

Here, PD patients under DBS ON showed the largest reward related gain in go-trials when compared to DBS OFF [T(15)=2.37; p=0.031] and to HC [T(14)=3.03; p=0.008]. No differences for gain in go trials were visible between PD patients with DBS OFF and HC [T(15)=-0.05; p=0.96]. For nogo trials, no differences were observed between all three groups [DBS ON vs. DBS OFF: T(15)=0.12; p=0.91; DBS ON vs. HC: T(15)=0.0; p=1.0); DBS OFF vs. HC: T(15)=-0.09; p=0.93]. Subsequently, the patients´ differential parameters were correlated with the individual daily L-Dopa equivalent dose (LED; in mg). Neither under DBS ON (r=.29, p=0.27) nor in the OFF condition (r=-.03, p=0.91) the Pavlovian congruency effect (i.e. the benefit for initiating a response when anticipating a reward over the response initiation when anticipating to avoid a punishment) was modulated by the dopaminergic medication.

Reaction times

For the comparison of RT in the go trials between HC and PD patients under DBS ON and OFF, the separate ANOVAs with the factors *valence* (win/avoid losing) and *group* (PD patients DBS ON or OFF/ HC) revealed a significant ME for the factor *group* only [HC/DBS ON [F(1,15)=10.36; p=0.006]; HC/DBS OFF [F(1,15)=14.89; p=0.002]]. HC were faster compared to PD patients when DBS was ON (go to win: T(14)=3.33; p=0.005; go to avoid losing: T(14)=2.79; p=0.014) and OFF (go to win: T(14)=3.52; p=0.003); go to avoid losing: T(14)=3.65; p=0.002). Neither HC nor PD differed in their RT for go to win versus go to avoid losing trials HC: [T(15)=-1.42; p=0.18], DBS ON: [T(15)=-0.56; p=0.59], DBS OFF: [T(15)=-0.76; p=0.46].

Further variables

To investigate possible modulatory effects of dopamine agonists on task performance I correlated the Pavlovian congruency effect under DBS ON with the daily amount of dopamine agonist medication (in mg), but found no significant relation (r=-0.27; p=0.31). Also, a direct comparison of patients with (n=9) and without (n=7) dopamine agonist medication showed no significant difference in the Pavlovian congruency effect [T(14)=-1.33; p=0.2].

I also tested for gender differences in the outcome of DBS modulation in terms of the Pavlovian congruency effect and compared male with female patients. Neither under DBS ON (r=.15, p=0.58) nor in the OFF condition (r=-.12, p=0.5) the Pavlovian congruency effect was modulated by gender. Furthermore, directly comparing Pavlovian congruency values between female and male patients revealed neither for DBS ON [T(14)=-0.58, p=0.57] nor in the DBS OFF condition [T(14)=-0.69, p=0.50] a statistical significant result.

Finally, I tested for possible confounds due to patients´ age, disease duration and post-surgery assessment time on the Pavlovian congruency effect. Neither age (r=-.28, p=0.29), disease duration (r=.36, p=0.19) nor post-surgery assessment time (r=-.002, p=0.96) correlated with the Pavlovian congruency effect under DBS ON.

2.4 Discussion

As in a previous study with healthy old adults (Chowdhury et al., 2013), the HC took advantage of a Pavlovian congruency between action and reward; they showed a behavioral benefit for initiating a response when anticipating a reward over the response initiation when anticipating to avoid a punishment. PD patients with DBS OFF were overall slower and less accurate independent of valence. Also the Pavlovian congruency effect observed in HC did not reach significance in PD DBS OFF, presumably because there was high performance variability (*Figure 6*). Importantly, DBS modulation of the STN enhanced the interaction of action and valence anticipation such that it was considerably stronger than under DBS OFF and in HC. PD patients under DBS ON showed the largest reward related gain in go trials when compared to DBS OFF and to HC.

Thus my present data show that STN-DBS does not lead to a valence-independent motor improvement. Instead, my data demonstrate the impact of STN-DBS on motivational action control in PD. I hypothesize that this DBS-related enhancement of the interaction between action and valence (Pavlovian congruency) results from a modulation of both the limbic-ventral- as well as the motor-dorsal striatum.

For the motor domain, previous studies of STN-DBS in PD reported an impairment of the ability to withhold strong predominant answers in response conflict tasks, as required in the Stroop Task (Schroeder et al., 2002), the Simon reaction task (Wylie et al., 2010), go/ nogo tasks (Ballanger et al., 2009; Hershey et al., 2004) and decision-making tasks (Frank, 2006). My task also involved a response conflict component because participants had to sometimes make actions and sometimes withhold actions to obtain a reward or to avoid punishment. Thus, a strategy to always act for a reward or to avoid punishment would have impaired performance. The selective effect of STN-DBS on the go-reward condition rules out a general increase in response impulsivity. This is remarkable because STN-DBS acts via a reduction of the inhibitory influence of the basal ganglia nuclei on thalamo-cortical projections in the indirect basal ganglia-pathway (Limousin et al., 1998) and it is feasible to assume STN-DBS could lead to a general motor improvement irrespective of an expected reward. As for limbic consequences, STN-DBS has been shown to influence mood states such as depression, mania, anxiety or apathy (Temel et al., 2006), as well as to alter emotion processing by either improving (Castner et al.,

2007) or worsening emotion recognition (Schroeder et al., 2004), and finally is also affecting aversive and appetitive motivational processing (Serranová et al., 2011). It is therefore feasible to assume that a combination of limbic and motor consequences of DBS led to the behavioral pattern that I have observed here. Indeed, there is evidence indicating a role of the STN in reward and valence coding (Lardeux et al., 2009; 2013; Baunez et al., 2005). The found effects cannot be attributed to possibly biasing variables as age, gender, disease duration, assessment time post surgery or supplementary dopamine agonist medication.

A limitation of my study is that because PD patients were ON medication the study was not designed to isolate the effect of PD per se on the interaction between action and valence. Therefore it is likely that the results underestimate the impact of the disease on this interaction. Furthermore, by the same argument, the results might overestimate the impact of STN-DBS on the reported action and valence interaction due to possible amplifying effects of the dopaminergic medication.

In conclusion, I show that STN-DBS in PD invigorates actions specifically when these actions lead to rewards. There is no enhancement of actions that are performed to avoid punishment. This tight coupling between action and valence indicates that STN-DBS influences the congruency between action and valence (Pavlovian congruency) rather than enhancing action initiation per se.

PROJECT B

3. Effects of STN-DBS on perceptual decision-making in PD patients

Specific aim:

This project investigates the impact of STN-DBS on perceptual decision-making in PD patients in difficult and high-risk status quo choices, depending on the individual baseline impulsivity.

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Abstract

When faced with difficult decisions, people prefer to stay with the default. This status quo bias often leads to suboptimal choice behavior. Neurophysiological evidence suggests a pivot role of the STN for overcoming such status quo bias in difficult decisions, but causal evidence is lacking. The present study investigated whether subthalamic DBS in patients with PD influences the status quo bias. Eighteen PD patients treated with STN-DBS performed a difficult perceptual decision task incorporating intrinsic status quo option. Patients were tested with (ON) and without (OFF) active STN stimulation. My results show that DBS of the STN affected perceptual decision-making in PD patients depending on the difficulty of decision. STN-DBS improved difficult perceptual decisions due to a selective increase in accuracy (hit rate) that was independent of response bias (no effect on false alarm rate). Furthermore, STN-DBS impacted status quo bias as a function of baseline impulsivity. In impulsive patients, STN-DBS increased the default bias, whereas in less impulsive PD patients, DBS of the STN reduced the status quo bias. In line with my hypothesis, STN-DBS selectively affected the tendency to stick with

the default option on difficult decisions, and promoted increased decision accuracy. Moreover, I demonstrate the impact of baseline cognitive abilities on DBS-related performance changes in PD patients.

3.1 Introduction

Beliefs, previous choices or set routines contribute to an individual´s status quo which people prefer to maintain. As a result, pre-set or default options are preferably chosen and people tend to stay with the current state of affairs even when better alternatives are available (Suri et al. 2013). This cognitive status quo bias is defined as the suboptimal acceptance of a default choice option (Fleming et al., 2010; Yu et al, 2010; Nicolle et al., 2011). Importantly, many decisions take place under conditions of high uncertainty. In such complex decisions, the tendency to accept a status quo increases, leading to more pronounced status quo bias on high- compared to low-difficulty decisions (Fleming et al., 2010). While a suboptimal bias toward accepting the status quo option in decision-making is behaviorally well-established, its underlying neural mechanisms are less clear. The process of rejecting a status quo during difficult perceptual decisions has been associated with a specific prefrontal-basal ganglia network incorporating the inferior frontal cortex (IFC) and the STN (Fleming et al., 2010), a component of the basal ganglia thought to play a pivotal role in action selection (Bergman et al., 1990; Frank 2006). A specific role for STN activity in overcoming a status quo bias is consistent with findings from DBS studies that report a contribution of STN to decision-making under conditions of high but not low difficulty (Hershey et al., 2004; Alberts et al., 2008). Moreover, DBS in PD indicates a causal role for the STN in the modulation of decision-making (Frank et al., 2007; Ray et al. 2009; van den Wildenberg et al. 2006), and lesions to the STN in rodents produce impaired response selection under situations of high conflict (Baunez et al. 2001; Eagle et al.2008).

Recent theoretical models illuminate the putative role of the STN in response inhibition and action selection. The model proposed by Frank (2006) suggests the normal function of the STN is to relay a “nogo” signal, raising response thresholds when making decisions in situations of conflict to prevent premature and impulsive responding, allowing more time for further information accumulation before a decision is made. According to this model, alteration of STN activity as with STN-DBS in PD should interfere with this normal function of the STN in raising the response threshold in situations of conflict and therefore should be associated with impulsive responding. Confirmatively, Cavanagh et al. (2011) found that the medial prefrontal cortex activity predicted an increase in decision threshold during high-

conflict trials and that STN-DBS reversed this relationship, resulting in impulsive choices. A related proposal is that the STN receives a switching signal from regions of the prefrontal cortex, including the pre-SMA which enables a shift from automatic habitual to controlled processing (Isoda and Hikosaka, 2008; Fleming et al., 2010). Consequently, high frequency stimulation of the STN during STN-DBS in PD may interfere with the ability to switch between automatic and controlled processing when a situation/task demands it. These computational roles for STN are consistent with a prominent role for this region in rejecting an automatic default option in favor of a more controlled, non-default response, particularly when decision difficulty is high. However, causal evidence for the contribution of STN to the status quo bias is lacking.

In the present study, I investigated the effects of STN stimulation on the performance of PD patients in a difficulty perceptual decision task. Furthermore, I specifically considered the effect of individual state impulsivity. Accordingly, I investigated the effects of STN stimulation in PD patients with high or low individual baseline impulsivity on preferences for a default option in a difficult perceptual decision task. This task required subjects to make an active "go" response to reject the default, and a "nogo" response to accept the default. Two alternative hypotheses regarding the effect of STN can be formulated, under the assumption that STN-DBS interferes with normal STN function. If the dominant function of the STN is to inhibit action, interference with STN function via DBS should result in a tendency to respond and therefore in a decreased default bias. If, however, the dominant STN function is to initiate a controlled mode of responding, DBS of the STN should lead to an increased default bias.

3.2 Materials and methods

Participants

Eighteen PD patients with STN-DBS (mean age: 61,1 years, 7 female; see *Table 3*) were recruited from the Departments of Neurology and Stereotactic Neurosurgery at the University of Magdeburg, Germany, and the diagnosis of PD was confirmed by a neurologist specialized in movement disorders. Each patient had been treated with STN-DBS for at least 6 months (mean duration since surgery: 27.6 months). All

patients were taking supplementary dopaminergic medications in conjunction with DBS and were tested during the ON state of their medication cycle. All patients had chosen DBS surgery because their medications were no longer providing optimal control over their motor symptoms.

Electrodes were placed bilaterally in the STN of all patients. The surgical procedure for STN -DBS utilized standard stereotactic techniques with microelectrode recordings for electrophysiological localization and has been described previously (Elias et al., 2007). Briefly, macroelectrodes (Medtronic Model 3389) consisting of four platinum–iridium cylindrical surfaces, each with diameter 1.27 mm, length 1.5 mm, and edge-to-edge separation of 0.5 mm, were guided into the STN using MRI-guided stereotaxy and intraoperative microelectrode recordings. The planned coordinates for macroelectrode placement was based on direct visualization of the STN on T2-weighted magnetic resonance images. Final electrode position was based on microelectrode recordings and confirmed intraoperatively with macrostimulation after implantation of the DBS electrode. Selection of final bipolar contacts and stimulation settings were determined on an individual basis to optimize control over clinically manifest motor symptoms.

Patients were excluded from the study if they had a history of neurological condition (other than PD), untreated or unstable mood disorder, bipolar affective disorder, schizophrenia or other psychiatric condition known to compromise executive cognitive functioning, or an untreated or unstable medical condition known to interfere with cognitive functioning (e.g. diabetes, pulmonary disease etc.). All participants had normal or corrected-to-normal vision. Prior to participating in the study they all provided informed consent. The study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki.

Table 3. Demographic and disease characteristics in PD patients

Patient #	Age [yrs]	Gender	Active DBS contacts left-right		Frequency [Hz]	LED [mg/d]
1	69	M	1− G+/5.5 V	5− G+/5.5 V	130	650
3	56	F	3− G+/4.5 V	7− G+/3.5 V	180	100
4	74	F	1− G+/4.7 V	6− G+/3.5 V	130	400
6	49	M	1− G+/3.6 V	6− G+/3.1 V	130	600
8	63	F	2− G+/2.8 V	7− G+/2.3 V	180	475
9	63	M	2− G+/3.7 V	4− 5+/4.6 V	130	550
13	57	M	2− G+/4.5 V	6− G+/3.9 V	125	100
16	59	M	3− G+/3.6 V	7− G+/4.0 V	130	125
18	54	M	1− G+/3.0 V	5− G+/2.0 V	160	394
2	56	F	1− G+/2 V	5− G/2.5 V	130	100
5	65	M	3− G+/5 V	6− 7+/3 V	130	0
7	67	M	3− G+/4.5 V	7− G+/4.5 V	130	827
10	65	F	3− G+/4 V	6− G+/3.5 V	130	358
11	57	M	0− 1+/4 V	5− 10+/4 V	130	1385
12	61	F	1− G+/1.5 V	6− G+/2 V	130	35
14	50	M	0+ 1− /3.2 V	6− 11+/4.7 V	180	520
15	66	F	3− G+/5.5 V	7− G+/5.5 V	130	650
17	69	M	1− G+/1.5 V	5− G+/1.0 V	130	0

Upper side of the table lists patients with high impulsivity performance in the flanker task, lower side lists patients with low impulsivity performance in the flanker task.

Experimental procedure

All participants completed the tasks during one single session. PD patients completed two counterbalanced sessions of the task on the same day, one with DBS being ON and one with DBS switched OFF. After turning stimulation ON or OFF, respectively, a break of 30 minutes was instigated before resuming the task. This ensured that motor symptoms had largely subsided after inducing stimulation and that the increase in motor symptoms had reasonably stabilized after terminating stimulation (Hristova et al., 2000; Lopiano et al., 2003). Additionally, to determine baseline impulsivity, patients performed the Eriksen Flanker go- nogo paradigm during the DBS OFF state.

Tasks

Status quo task. I applied the "tennis line judgment" paradigm by Fleming et al. (2010) (see *Figure 7*). This paradigm assesses preference for a default option in a task that involves graded perceptual difficulty, thus generating both easy and difficult decisions. It was shown previously that healthy human participants were more likely to accept the default on high-difficulty decisions leading to suboptimal choices (Fleming et al., 2010). Each trial started with a central fixation cross flanked by two longitudinal white tram lines presented in peripheral vision. Participants were instructed to maintain fixation and that not doing so would compromise their performance in the task. A target ball was presented at one of the tramlines either overlapping the line ("in") or completely outside the line ("out"). These two possibilities were then presented as response choices on the screen with one answer being indicated as the default. Participants were asked to judge whether the ball was in or out. Responses consisted of a go-nogo decision to reject or accept the default, respectively. Patients were asked to press a button to change the default or to give no response to accept the default. Low and high difficulty trials were randomly interleaved and counterbalanced across whether the correct response was to accept or reject the default. The difficulty of the decision was manipulated by altering the distance of the stimulus from the outside edge of the tramline, using a 2-up-1-down staircase procedure (Levitt, 1971) in steps of 0.1 degrees of visual angle. To individually adjust the difficulty level, prior to the experimental session PD patients

under DBS ON performed a short training session with an increasing difficulty level. After training, half of the patient group started the task with DBS being ON, the other half with DBS being OFF.

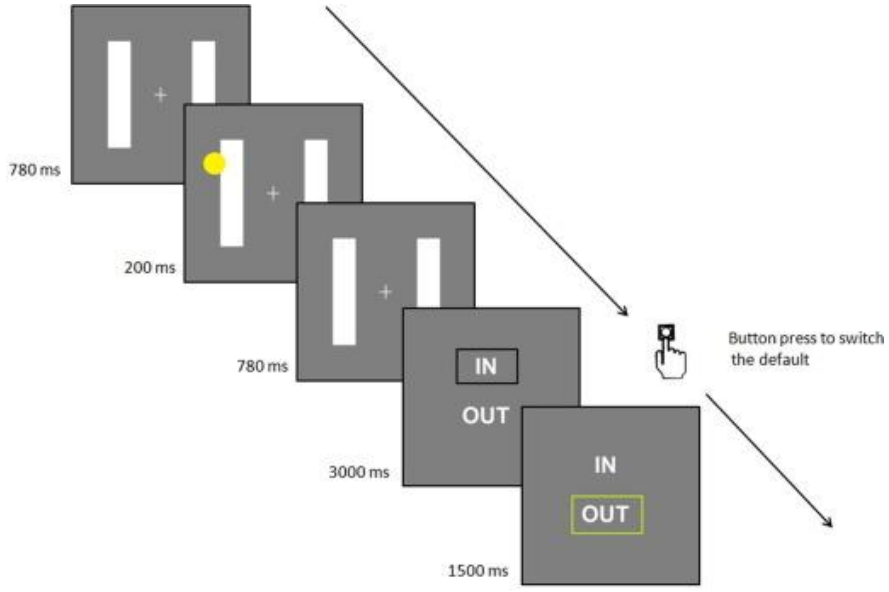

Figure 7. Experimental design of the „tennis line“ judgment paradigm, adapted from Fleming et al. (2010). First, patients were requested to look at a fixation cross in the middle of a computer screen. In each trial, they then saw a yellow ball land on the “tennis court” with the target ball either overlapping the tramline (“in”) or being completely outside the line (“out”). These two possibilities were presented as response choices on the screen with one answer being indicated as the default. Participants were asked to judge whether the ball was in or out and to press a button to change the default or to give no response to accept the default.

Eriksen-flanker task. The Eriksen flanker task allows for quantification of impulsivity and interference control (Eriksen & Eriksen 1974). Here, a centrally presented target (“X”) is flanked by distractors (flankers “+”) that are positioned to the left and right of the target. The flankers can be congruent, i.e. either signal has the same response characters as the target, or incongruent (response information that conflicts with the response tendency of the target). The participant is asked to press a key to the target stimulus and to omit a response to non-target stimuli. Patients performed the flanker test while STN stimulation was OFF. Impulsivity is associated with the frequent appearance of commission errors in the absence of omission errors. Accordingly, individual impulsivity was measured by subtracting the number of

omission errors from the number of commission errors; resulting in negative scores for impulsive and positive scores for non-impulsive behavior.

Statistical analysis

Behavioral measures were entered into 2x2 repeated-measures ANOVAs with the factors *difficulty* (high/ low) and *DBS* (ON/ OFF). Furthermore, each individual's status quo bias was calculated as the percentage of default acceptance greater than 50% separately for high- and low-difficulty trials. Finally, I tested the impact of individual baseline impulsivity on the status quo bias under uncertainty using 2x2 repeated-measures ANOVAs with the factors *DBS* (ON/ OFF) and *impulsivity* (high/ low). For that purpose, patients were median split into two groups based on their STN-DBS OFF performance in the flanker task (high/low impulsivity).

3.3 Results

A 2 x 2 repeated measures ANOVA with the factors *difficulty* (high/low) and *DBS* (ON/OFF) on performance (percent correct responses) revealed a significant ME of the factor *difficulty* [$F(1,17)=58.5$; $p<0.001$] and a significant *difficulty* x *DBS* interaction [$F(1,17)=4.6$; $p<0.05$]. Thus, whereas performance was generally worse in difficult trails (ME difficulty), performance was also modulated by the DBS-mode (difficulty x DBS). Whereas DBS ON as compared to DBS OFF increased correct decision for difficult trials [$T(17)=1.76$; $p<0.05$ one-tailed], performance level was decreased for easy trials [$T(17)=-1.9$; $p<0.05$ one-tailed], see *Figure 8*.

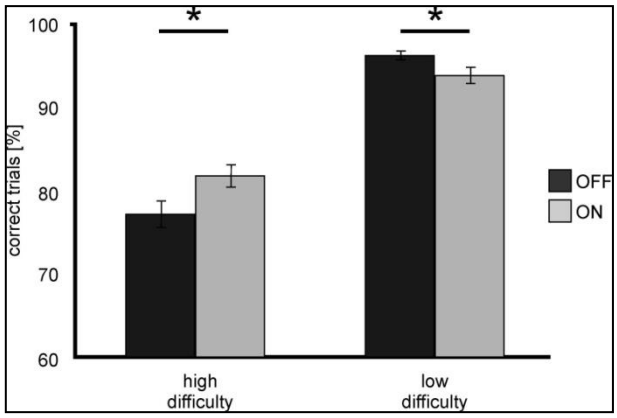

Figure 8. The performance for DBS ON and DBS OFF conditions for easy and difficult trials (in %). Light grey bars indicate DBS ON, black bars indicate DBS OFF conditions. All bars show M ± SE.

In order to establish whether DBS affected sensitivity (d') rather than an overall tendency to respond, I carried out a similar analysis of hit and FA rates. An ANOVA on hit rate revealed significant main effects of the factors *difficulty* [$F(1,17)=53.3$; $p< 0.001$], *DBS* [$F(1,17)=7.03$; $p<0.05$] as well as a significant *difficulty* x *DBS* interaction [$F(1,17)=7.1$; $p<0.05$]. Thus hit rate was selectively reduced under DBS OFF (ME DBS) on uncertain trials [$T(17)=1.76$; $p<0.05$, one-tailed] only. A similar ANOVA for FA revealed an effect of *difficulty* [$F(1,17)=32.3$; $p<0.001$] demonstrating a more conservative responding on difficult compared to easy trials, but no interaction with DBS [$F(1,17)=1.28$; $p=0.28$]. An ANOVA of RT revealed a significant main effect of *difficulty* [$F(1,17)=10.29$; $p<0.01$] due to longer RTs on difficult trials.

In sum, these results demonstrate that DBS of the STN impacts perceptual decision-making of PD patients depending on decision difficulty. STN-DBS improved difficult perceptual decisions due to a selective increase in decision sensitivity (hit rate) rather than a change in response bias.

After controlling for the initial baseline impulsivity of the patients, and focusing on the high difficulty condition, a repeated measures ANOVA of the default bias with within-subjects factor *DBS* (ON/OFF) and between-subjects factor *impulsivity* (impulsive/non-impulsive) revealed a significant *DBS* x *impulsivity* interaction [$F(1,16)=6.03$; $p<0.05$], due to DBS ON increasing the default bias in impulsive

patients [T(8)=2.33; p<0.05] and decreasing the bias in non-impulsive patients [T(8)=-2.12; p<0.05, one-tailed], see *Figure 9*.

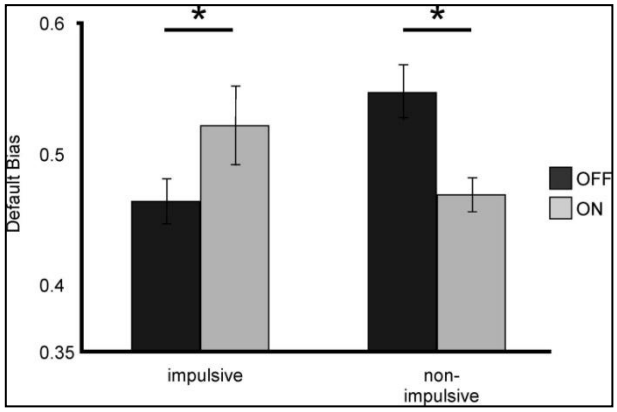

Figure 9. Default bias for difficult trials. Light grey bars indicate DBS ON, black bars indicate DBS OFF conditions. All bars show M ± SE.

3.4 Discussion

Previous research has demonstrated that rejecting a default on difficult, but not on easy trials activated the STN (Fleming et al., 2010), a region implicated in overcoming response suppression and initiating an overt action (Isoda and Hikosaka, 2008). In accordance with this, in the present study I demonstrate that DBS of the STN impacts perceptual decision-making in PD patients depending on the certainty of decisions. STN-DBS improved uncertain perceptual decisions due to a selective increase in accuracy (hit rate) and not due to a generally increased response tendency (no effect on FA). Accordingly, I further highlight the key role of the STN in overcoming a default during ambiguous perceptual decision-making.

These present results are in line with research showing that STN-DBS generally improves cognitive outcomes in PD despite enhancements of motor constraints (Cools, 2006; Parsons et al., 2006). Notwithstanding, my results also seem to contradict to studies showing that STN-DBS causes general impulsive premature behavior by impairing the ability to withhold strong predominant answers in response conflict decisions (Green et al., 2013; Zaghloul et al., 2012; Cavanagh et al., 2011; Schroeder et al., 2002; Frank et al., 2007). In contrast to the present task requiring decision-making under high ambiguity, these former studies investigated

behavior in probabilistic selection tasks (Zaghloul et al., 2012; Frank et al., 2007) or choice conflict tasks (Cavanagh et al., 2011). Since there is good evidence for differential impact of ambiguity on decision-making in PD (Euteneuer et al., 2009), the differences observed might be related to different classes of decision-making with respect to the degree of knowledge about the possible future consequences. Decision-making under ambiguity relies on the integrity of the limbic loop and the amygdala, connected by the ventral striatum. Specific activation of the ventral striatum during default selection and reward receiving imply that selecting the default might be rewarding in itself, highlighting the key role of emotions in mediating default inertia (Yu et al. 2010). Although contradictory reports exists (Kobayakawa et al., 2008; Pagonabarraga et al., 2007; Perretta et al., 2005), PD patients seem to be less impaired in ambiguous when compared to risky decisions (Czernecki et al., 2002; Mimura, Oeda, & Kawamura, 2006; Thiel et al., 2003, Euteneuer et al., 2009). This might be related to the fact that tasks with open answer modes increase participants´ response caution whereas tasks that provide a default response might imply per se more safety in making a decision. Due to the default, patients might get the impression that decisions are not at high-risk. DBS patients tend to prefer high-risk options and are overconfident due to impairment in relating their own performance to a correct reference frame (Florin et al. 2013). Thus, this combination of self-overestimation and high risk-taking in STN-DBS might accelerate impulsive behavior for risky decisions whereas it is less influential for ambiguous decisions with default answers.

Importantly, in the present study I revealed that STN-DBS impacted status quo bias as a function of baseline impulsivity; for high difficulty decisions DBS of the STN differentially interacts with the default bias depending on the initial baseline impulsivity of these patients. In impulsive patients, STN-DBS increased the default bias. Under DBS of the STN these patients increased their preference to stay with the default. In less impulsive PD patients, DBS of the STN reduced the status quo bias and those patients more often overcame suboptimal acceptance of the default choice option. Thus, the individual ability of the patients to withhold strong predominant answers without stimulation systematically affects the impact of subthalamic DBS on suboptimal acceptance of a default choice option. First evidence supporting the dependence of DBS outcomes on pre-surgery or baseline status is provided by

Gombert et al. (2014), who found that PD patients´ baseline performance in the Stroop test was significantly related to the motor outcome after STN-DBS. Alike, Chen et al. (2006) demonstrated that DBS outcomes are different according to the patients´ baseline motor task performance. While subjects with motor difficulties prior to DBS surgery improve performance due to DBS, patients with relatively normal motor performance are likely to have less benefitting from DBS. Thus, there seems to be compelling evidence corroborating the notion that prior motor as well as cognitive functions are predictive for the DBS-related performance changes in PD patients. STN-DBS in patients with pathological physiological processing improves performance due to a suppression of pathological activity and accordingly, these patients have more gain from the suppression of local activity. Alike, in those patients with relatively intact task-related processing, DBS suppresses intact physiological activity and thereby impairs performance. Such mechanisms might explain the observation that STN-DBS is beneficial for reducing impulsive behavior in patients with obsessive-compulsive diseases (OCD) and – at the same time – it can increase impulsivity in patients suffering from PD. Thus, whereas STN-DBS restores behavior due to a suppression of the striatal dysfunctions in OCD (Fontenelle et al. 2011), it interacts with the intact physiological activity, inducing maladaptive impulsive behavior in PD.

DBS of the STN constitutes an effective therapeutic treatment of the major motor symptoms in PD, especially when medication is less effective. While STN-DBS has widely been shown to be effective in improving motor impairments (Selzler et al., 2013; Bronstein et al., 2011; Volkmann, 2007; Ballanger et al., 2009), also declining influences on cognitive and emotional aspects were observed (Hershey et al., 2004; 2010; Alberts et al, 2008), such as maladaptive impulsive behavior (Weintraub et al., 2010; Voon et al., 2006; 2007) and depression, mania, anxiety or apathy (Strutt et al., 2012; Temel et al., 2006). Those effects are usually seen as “side effects” in PD, but are additional evidences for a heretofore- underappreciated role that STN plays in limbic circuitry. Accordingly, I demonstrated the impact of STN-DBS on motivational action control in PD by showing that modulation of the STN by DBS improves action execution specifically when rewards are anticipated (Wagenbreth et al., 2015). Additionally, the seminal function of the STN as part of the ventral

striatum is further evidenced by the success of STN–DBS for the treatment of OCD (Mallet et al., 2008).

In this and in previous studies (Fleming et al., 2010; Nicolle et al., 2011), status quo bias and inaction bias (i.e. decision not to act) are synonymous by design. However, apart from the default bias, people are also biased not to act (Ritov & Baron, 1992). This inaction bias has to be confined from the cognitive default bias which refers to the tendency to stay with a status quo, irrespective if achieved through action or inaction. However, it is unclear whether an inaction bias and a status quo bias are independent or are driven by the same underlying cause (Ritov & Baron, 1992; Baron & Ritov 1994; Anderson 2003). A further limitation of this study is that because PD patients were ON medication during testing, the study was not designed to isolate the effect of PD per se on perceptual decision-making. Therefore, it is likely that the results underestimate the impact of the disease. Furthermore, by the same argument, the results might overestimate the impact of STN-DBS on the behavioral changes due to possible amplifying effects of the dopaminergic medication.

In conclusion and in concert with former investigations, the data yielded by this study further provides important implications. STN-DBS can influence perceptual decision-making, especially under high ambiguity. Moreover, effects of DBS are highly inter-individually variable and might depend on baseline characteristics of special features. Finally, to address therapeutic implications, the results of this study suggest that pre-surgical evaluation of individual impulsivity of PD patients under consideration for STN-DBS could reduce the risk of STN-DBS induced impulse control disorders (Hälbig et al., 2009).

PROJECT C

4. Study C1: Implicit emotional processing induced by single facial emotional information in healthy participants

Specific aim:

This study investigates if reduced facial emotional information is sufficient to induce implicit emotional processing in healthy participants.

The content of this chapter has been published as: Wagenbreth, C., Rieger, J., Heinze, H.J., and Zaehle, T. (2014). Seeing emotions in the eyes – inverse priming effects induced by eyes expressing mental states. Front Psychol, 5, 1039.

Abstract

Objective. Automatic emotional processing of faces and facial expressions gain more and more of relevance in terms of social communication. Among a variety of different primes, targets and tasks, whole face images and facial expressions have been used to affectively prime emotional responses. This study investigates whether emotional information provided solely in eye regions that display mental states can also trigger affective priming.

Methods. Sixteen subjects answered a lexical decision task (LDT) coupled with an affective priming paradigm. Emotion-associated eye regions were extracted from photographs of faces and acted as primes, whereas targets were either words or pseudo-words. Participants had to decide whether the targets were real German words or generated pseudo-words. Primes and targets belonged to the emotional categories “fear”, “disgust”, “happiness” and “neutral”.

Results. A general valence effect for positive words was observed: Responses in the LDT were faster for target words of the emotional category happiness when compared to other categories. Importantly, pictures of emotional eye regions preceding the target words affected their subsequent classification. While I show a classical priming effect for neutral target words - with shorter RT for congruent compared to incongruent prime-target pairs-, I observed an inverse priming effect for fearful and happy target words - with shorter RT for incongruent compared to congruent prime-target pairs. These inverse priming effects were driven exclusively by specific prime-target pairs.

Conclusion. Reduced facial emotional information is sufficient to induce automatic implicit emotional processing. The emotion-associated eye regions were processed with respect to their emotional valence and affected the performance in the LDT.

4.1 Introduction

Due to the important role of facial features in social communication, effects arising from automatic affective processing of faces and facial expressions gain more and more of interest (Sassi et al., 2014; Rohr et al., 2012; Andrews et al., 2011; Suslow et al., 2010; Li et al., 2008). Faces are complex, concrete and socially significant stimuli that are linked to emotional reactions (Murphy & Zajonc, 1993). In addition, a human face holds a natural salience, i.e. it is an interesting stimulus that attracts attention more than other visual stimuli (Krebs, 2011). A faster detection of fearful or angry when compared to neutral faces (Ishai et al., 2004) as well as an attentional bias to threatening facial expressions could be observed (Susa et al., 2012). Moreover, a facilitation of a visual search task to identify fear-related pictures among fear-irrelevant ones was shown (Öhman et al., 2001) as well as a slower attention disengagement from angry faces compared to neutral or happy ones (Fox et al., 2002). In agreement with the evolutionary point of view this suggests a faster processing of threatening or possibly life-endangering stimuli. Thus, decoding and interpreting emotions displayed in facial expressions, especially those with negative valence, play a fundamental role in human interactions.

Identifying emotional states of other persons also constitutes the basis of the social construct of Theory of Mind (ToM). ToM refers to the process of emotion recognition and allows individuals to imagine and attribute the mental states of others (Pinkham et al., 2003). The "Reading the Mind in The Eyes Task" (RMET) which was invented by Baron-Cohen et al. (1997) is an advanced test of ToM and consists of photographs showing the facial region around the eyes. Four different emotional states are offered and the participant is asked to decide which of these emotional states describes best what the person on the photograph is thinking or feeling. Thus, the RMET is a social cognition measure to evaluate the participant´s ability to recognize and identify mental states and their intensity. It refers to explicit emotional processing which requires conscious action under deliberate control. In contrast, implicit processing of emotions is an automatic process that does not allow for the activation of expectancies or response strategies and is thus independent of cognitive resources. Implicit – or automatic – activation of emotional evaluations is often measured in affective priming paradigms (Klauer & Musch, 2003; Fazio, 2001). Here, the automatically triggered connection between two stimuli (prime and

target) which are determined through their emotional valence is essential. Faster responses and fewer errors were observed when two consecutively presented stimuli are identical (congruent) with respect to their emotional valence (e.g. positive-positive) than when they differ from each other (Andrews et al., 2011; Fazio, 2011). This congruence effect has been shown to be a robust and replicable phenomenon in a variety of studies using different primes, targets and specific instructions and tasks (Banse, 2001; Giner-Sorolla et al., 1999; De Houwer et al., 1998; Hermans et al., 2003; 1998; 1994). The effect of congruence between prime and target allows for the systematic evaluation of the automatic emotional processing that is triggered by the prime.

In affective priming paradigms, the most commonly used task for the participants is to evaluate a target concerning its valence, as applied in a LDT. The LDT is a common instrument to measure implicit emotional processing since it focuses on a non-emotional decision which is not distorted by emotional features of the stimuli. In a LDT, participants have to judge the lexical status of a presented letter string on whether it is a correct real word or a pseudo- or nonword. To ensure an "affective" influence on the LDT, words with different emotional valences are used in this task. Hence, valence is an important manipulating variable on the performance in LDTs. Different studies showed shorter RT and fewer errors of participants for emotional when compared to neutral words (Schacht & Sommer, 2009; Nakic et al., 2006; Windmann et al., 2002; Williamson et al., 1991; Challis & Krane, 1988). Positive valence is known to facilitate lexical processing in the LDT (Schacht & Sommer, 2009; Scott et al., 2009; Kuchinke et al., 2005; 2007) while negative valence itself seems to slow RT (Briesemeister et al., 2011a). This effect on RT for negatively valenced words is observed only at high levels of emotional arousal (Hofmann et al., 2009; Larsen et al., 2008; Nakic et al., 2006), which suggests a simplified and preferred processing of for instance fearful words that are expected to have a high emotional arousal.

In recent studies that applied affective priming paradigms, whole face images and facial expressions have been used as primes since facial features are supposed to be recognized ubiquitously as indicators of different affective conditions (Sassi et al., 2014; Rohr et al., 2012; Andrews et al., 2011; Suslow et al., 2010; Li et al., 2008). However, it is not clear whether these findings are also true for reduced emotional

information that is featured not in the whole face, but solely in the eye regions of a face expressing mental states. Therefore, in the present study I systematically investigated the ability of emotional eyes expressions to induce implicit emotional processing by using an affective priming paradigm. I assume that even reduced emotional information in human eyes is sufficient to influence automatic emotional responses. Here, eyes expressing mental states acted as primes to influence the subsequent answer on a target word in a LDT.

4.2 Methods

Participants

Sixteen healthy participants (female= 8) in the age of 22-28 years (mean age = 24.12 ± 1.54 years) volunteered in this study. All participants were German native speakers, right-handed, reported normal or corrected-to-normal vision and were free of any neurological or psychiatric impairment. Participants volunteered and the experiment was approved by the local ethics committee (University of Magdeburg, Germany).

Stimuli

For the LDT a set of 192 written stimuli (96 German words and 96 pseudo-words) was used. Neutral words were extracted from the "Berlin Affective Word List Reloaded" (BAWL-R; Võ et al., 2009) when they showed a valence rating of 0. Emotional words were taken from the "Discrete Emotion Norms for Nouns: Berlin Affective Word List" (DENN-BAWL; Briesemeister et al., 2011b). Here, only those words were chosen that achieved an emotional intensity score of at least 3 on a Likert-scale according to Briesemeister et al. (2011b). All 96 words were grouped in four emotional categories: 24 fear-related (e.g. "PANIK"-"PANIC"), 24 disgust-related (e.g. "PARASIT"-"PARASITE"), 24 happiness-related (e.g. "LIEBE"-"LOVE") and 24 neutral words (e.g. "WOCHE"-"WEEK"). Pseudo-words were also generated out of the words listed in the BAWL-R. Here, neutral words with a length of four to eight letters were manipulated by interchanging single vowels or

consonants within this word. By doing so, new pronounceable but meaningless letter strings were created (e.g. “POLITIK” – “PILITOK”).

The facial region around the eyes extracted from the stimulus set “60 Faces Test” developed by Ekman & Friesen (1967) were used as emotional primes. This set consists of the six basic human emotional facial expressions (happiness, sadness, disgust, fear, surprise and anger as well as a neutral condition). For the present study, I chose four different persons out of this set (two female, two male) and selected their relevant facial expressions on a picture (happiness, fear, disgust, neutral). The whole-face images were then adjusted and cut so that only the eye regions were visible. After this editing, the resulting 16 prime pictures were presented in a size of 8.6 x 3 cm (3.4° visual angle).

Primes (eye region pictures) and target stimuli (words or pseudo-words) were combined in a pseudo-randomized manner: half of the prime-target pairs of the real German words were constructed to be congruent. The sequence of combination is displayed in *Table 4*.

Table 4. Division of the prime-target word pairings in the lexical decision task (LDT) according to congruence

Congruence	**Combinations**		**Number per pair**	**Total number**
	Prime	**Target word**		
congruent	Fear	Fear	12	48
	Disgust	Disgust	12	
	Happiness	Happiness	12	
	Neutral	Neutral	12	
incongruent	Fear	Disgust	4	48
	Fear	Happiness	4	
	Fear	Neutral	4	
	Disgust	Fear	4	
	Disgust	Happiness	4	
	Disgust	Neutral	4	
	Happiness	Fear	4	
	Happiness	Disgust	4	
	Happiness	Neutral	4	
	Neutral	Fear	4	
	Neutral	Disgust	4	
	Neutral	Happiness	4	

Task

The experiment was generated and carried out with Presentation (Neurobehavioral Systems, Inc.). Patients were seated in front of a computer and were requested to look at a fixation cross in the middle of the screen. The task consisted of 192 trials and included a break after the half of the trials (96); the participants could decide how long this break would last. Depending on the understanding of instruction and the length of the break, the duration of the whole task was about 15 minutes.

Each trial started with a fixation cross that was shown for 500ms before an emotional prime was displayed for 150ms. After a short pause (inter-stimulus interval of 50ms) the target stimulus was presented for a maximum of 3000ms or until a response was made. During this time interval, the participants had to decide whether this target was a real word or a pseudo-word by pressing the corresponding button on the mouse. Afterwards, the next trial started (see *Figure 10*). The presentation order of items (primes and targets) as well as the assignment of mouse buttons to respond was counterbalanced across subjects.

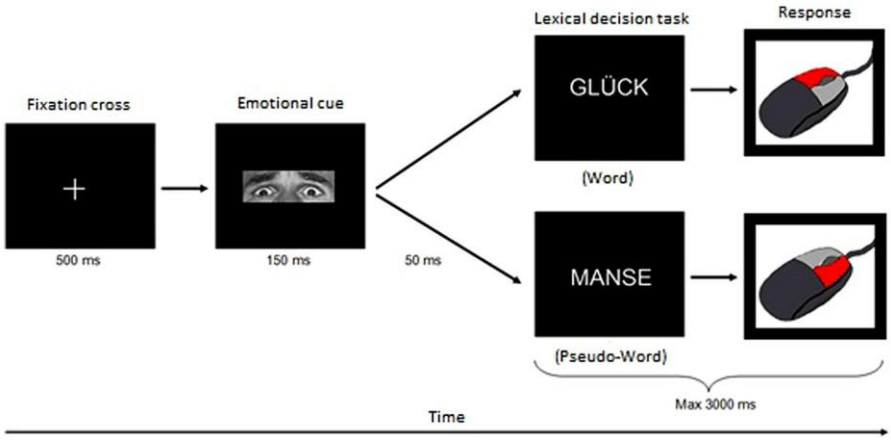

Figure 10. Experimental design of the implicit emotional processing with LDT. Each trial started with a fixation cross that was presented for 50ms. Afterwards, an emotional prime (the adjusted eye region of the Ekman-faces) was displayed for 150ms before a short break of 50ms was integrated. Finally, the target stimulus was presented. The participants were supposed to decide as fast as possible whether this target was a real German word or a pseudo-word and to press the corresponding button on the mouse within 3000ms. After this time interval the next trial started irrespective if the participant gave a response or not.

Statistical analysis

Mean RT and error rates (ER) for each participant were assessed and entered into a 4 x 2 repeated-measures ANOVA with the factors *valence* of the target word (fear/ disgust/ happiness/ neutral) and emotional *congruence* of the prime-word pairing (congruent/ incongruent). Subsequently individual prime-target pairings were evaluated separately. Prior to analysis RT normal distribution was confirmed using the Kolmogorov-Smirnov Test of Normality ($p=0.89$). All results are displayed in M ± SD.

4.3 Results

A repeated-measures ANOVA on RT showed a significant ME of the factor *valence* [$F(3,45)=14.84$; $p<0.001$], no ME of the factor *congruence* [$F(1,15)=0.27$; $p=0.61$], and a significant *valence* x *congruence* interaction [$F(3,45)=9.04$; $p<0.001$]. The ME of *valence* was driven by significantly shorter RT for happiness-related target words compared to all other emotional categories (all $p<0.001$; see *Figure 11A*).

The *valence* x *congruence* interaction was further investigated by comparing incongruent and congruent trials separately for each emotional target word category. Pairwise T- Tests revealed shorter RT for incongruent prime-target pairs compared to congruent pairs for the word categories fear [$T(15)=2.35$; $p<0.05$] and happiness [$T(15)=2.67$; $p<0.05$], and shorter RT for congruent pairs compared to incongruent pairs [$T(15)=-2.66$; $p<0.05$] for neutral targets (see *Figure 11B*). No effects were visible for the emotion category disgust [$T(15)=-1.08$; $p=0.3$]. Thus, whereas there was a classical priming effect for neutral target words with a processing advantage for congruent pairs, I revealed an inverse priming effect for fearful and happy target words with an advantage for the processing of incongruent primed targets.

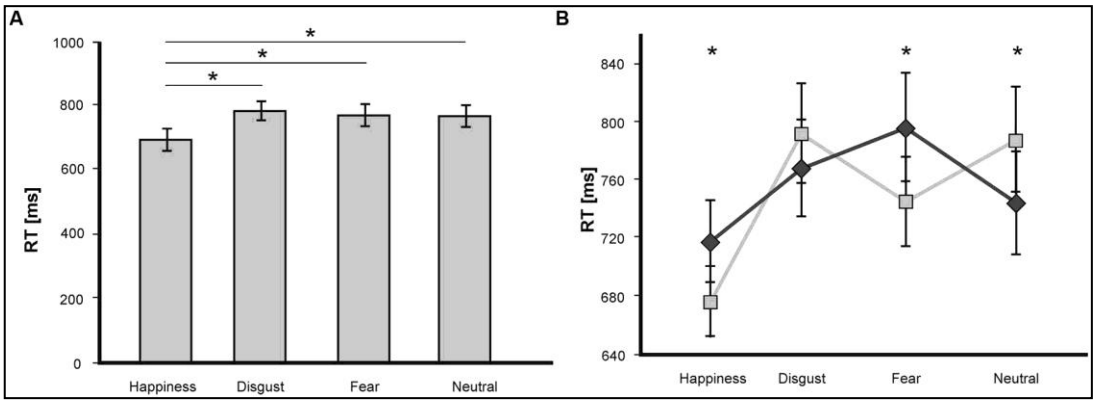

Figure 11 A. Mean RT (in ms) in the LDT for target words of the emotional categories fear, disgust, happiness and neutral. Statistically significant differences are labeled with (*). Error bars display SE.

Figure 11 B. Mean RT (in ms) in the LDT as a function of valence and congruence. Dark grey line depicts congruent trials, light grey line depicts incongruent trials. Statistically significant differences are labeled with (*). Error bars display SE.

A repeated-measures ANOVA on ER showed a non-significant statistical trend for the factor *valence* [F(3,45)=2.44; p=0.07], no effect of the factor congruence [F(1,15)=1.36; p=0.26], and no significant *valence* x *congruence* interaction [F(3,45)=0.67; p=0.57]. The trend for the ME of *valence* was driven by significantly more errors for disgust-related words compared to happiness-related words (p=0.05; see *Figure 12A*).

Further analysis showed no differences in ER for incongruent versus congruent conditions for the emotional word categories (happiness: [T(15)=0.44; p=0.67]; fear: [T(15)=0.0; p=1.0]; disgust: [T(15)=0.22; p=0.83]; neutral [T(15)=1.86; p=0.08] (see *Figure 12B*).

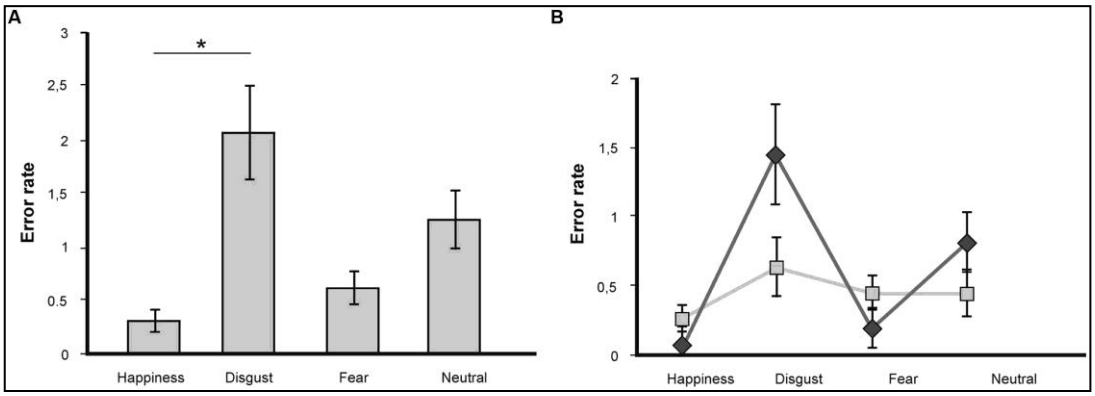

Figure 12 A. Mean number of errors in the LDT for target words of the emotional categories fear, disgust, happiness and neutral. Statistically significant differences are labeled with (*). Error bars display SE.

Figure 12B. Mean number of errors in the LDT as a function of valence and congruence. Dark grey line depicts congruent trials, light grey line depicts incongruent trials. Statistically significant differences are labeled with (*). Error bars display SE.

To further assess the observed priming effects, I analyzed responses to individual primes-targets pairs separately (see *Figure 13*).

For happy target words, analysis revealed that compared to the congruent (happy-happy) pairs only the incongruent fear-happy pairs were answered significantly faster ($T(15)=-5.73$; $p<0.001$). For fearful target words, analysis showed that the neutral-fear pairs were answered significantly faster that the congruent (fear-fear) pairs ($T(15)=-4.62$; $p<0.001$) (see *Figure 13).* No further congruent-incongruent comparison revealed statistical significance.

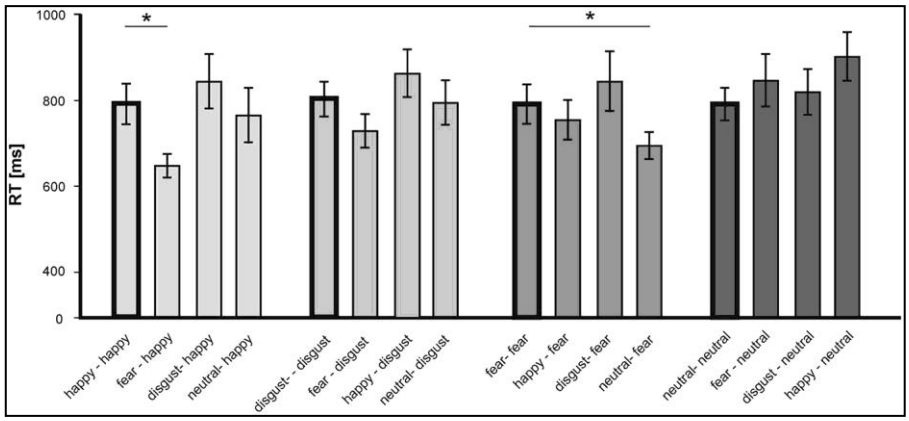

Figure 13. Mean RT (in ms) in the LDT for single emotional prime-target pairings according to the valence of the target. Statistically significant differences are labeled with (*). Error bars display SE.

In sum, the valence of the target words had a significant effect on the RT in the LDT. Happiness-related target words were answered faster than words of all other emotional categories. Importantly, the emotional content of the facial expressions (primes) modulated the LDT responses. While I was able to show a classical priming effect for neutral target words - with shorter RT for congruent compared to incongruent prime-target pairs, I observed an inverse priming effect for fearful and happy target words - with shorter RT for incongruent compared to congruent prime-target pairs. Furthermore, this inverse priming effect for happy targets was driven exclusively by the incongruent combination with fearful primes, whereas for fearful targets it was driven by neutral primes only.

4.4 Discussion

Effect of valence

Independent from the prime-target pairing, I found a general effect of valence in the LDT with shorter RT for emotional target words when compared to neutral words. Thus, an advantage in the processing of positive words (category happiness) in form of shorter RT when compared to fearful, disgust-related or neutral words was observed. However, the other categories (fear, disgust) did not differ significantly from neutral words. These findings are in good agreement with previous studies that postulate an advantageous processing of positive words (Briesemeister et al., 2011a;

Kissler & Koessler, 2011; Hofmann et al., 2009; Kuchinke et al., 2005). Slowing in RT for the processing of negative words has been described recently (Castner et al., 2007; Wentura et al., 2000). In my study this increase of RT for negative words was significant when compared to positive, but not when compared to neutral words. These findings can be attributed to the "automatic vigilance" hypothesis implying that people tend to focus their attention preferentially on negative stimuli and can also rather difficult dissolve it from them (Öhman & Mineka, 2001; Wentura et al., 2000). This is in line with findings by Estes & Verges (2008) who postulated a slower disentanglement of attention from negative stimuli and with an approach by Larsen and colleagues (2008) who suggest a RT slowing for low arousing negative words.

Effect of congruence

I observed an interaction effect between valence and congruence which demonstrates that the influence of emotional congruency depends on the valence of the target word. A general effect of congruence between prime and target, displayed in shorter RT and fewer errors in congruent when compared to incongruent trials, is often reported in affective priming paradigms (Banse, 2001; De Houwer et al., 2009). Interestingly, the present results confirm this effect only in part. The advantage of affectively congruent primed trials was found for neutral words only and selectively for RT and not for the ER. Contrary to the expectations, I found an *inverse priming effect i*n terms of an advantageous processing of incongruent trials: For the emotional categories fear and happiness, RT were shorter for incongruent than for congruent trials.

Different explanations have been suggested for the inverse priming effect (Glaser & Banaji, 1999; Mattler, 2007; Verleger et al., 2004; Banse, 2001). Glaser & Banaji (1999) underline the modulating character of the extremeness of primes that would provoke an automatic and unconscious correction of information processing. Following their argumentation, primes of extreme valence have the potential to distort the answer on a target. Thus, the emotional processing of "extremely valenced" primes (e.g. fearful or happy) would be increased and a proper lexical decision would require more time. In contrast, neutral primes have lower salience

and no correction of distorting influences is necessary, which is reflected in shorter RT. Critically, this approach highlights the importance of the emotional information content of the primes. However, the role of the valence of targets for emotional processing is not affected and thus this explanation does not sufficiently account for the present findings.

Another approach is given by Maier, Berner and Pekrun (2003). They suggested the existence of activation dependent inhibitory processes in memory. According to the authors, a strengthening of some examples of a category (i.e. either positive or negative) is connected with an automatic inhibition of related, but interfering examples of the same category. For instance, as soon as the representation of a positive stimulus as "positive" is enhanced, automatic activation processes start inhibiting stimuli of the same category ("positive"). Effects of congruency would lose ground in favor of automatic inhibitory processes and the accessibility for an incongruent target word would thus increase. This could explain RT advantages of incongruent pairs of the category happiness and fear, but not why RT are faster for incongruent neutral word trials.

Based on different explanatory attempts one might suggest a concluding approach that integrates different theories. The basic assumption here is that the valence of the primes and targets is processed unconsciously and that correction and inhibition processes are involved in affective priming. In this hypothesis, the presentation of an emotional prime activates the appropriate concept node in the semantic network (De Houwer & Hermans, 1994). According to Maier and colleagues (2003) the corresponding representation in the greater valence system (e.g. the concept "negative") is enhanced through automatic activation dispersion. If a congruent target stimulus follows, a stronger activation of the belonging memory network is run due to the additive effect of the valence information of both prime and target (Dagenbach & Carr, 1994) which results in longer RT for congruent trials. For incongruent trials, both valence representations are activated in memory, but each system apart has only a low activation level. Thus, the automatic correction system for the distortive influence of emotional information (Klapp, 2005; Glaser & Banaji, 1999) can be inhibited in favor of an adequate response. Since the activation levels of both representations are low, the activation of both valence systems is faster which results in shorter RT for incongruent trials. Thus, the strength of the activation levels

determines the strength of the activation of the automatic correction system which in turn is expressed in RT. For neutral words that do not carry emotional information, no activation of greater valence systems is necessary as well as no corrective efforts. Thus, RT for neutral congruent prime-target pairs (which have no influence of relevant emotional information) are shorter than RT of neutral incongruent pairs.

Beyond the general inverse priming effects for happiness and fear, the present data show that the processing advantage for incongruently primed happy targets was mainly driven by the fearful primes. The combination of fear (prime) and happiness (target) was answered faster than all other conditions. This implies a special role of fear as characteristic for a prime. In general, fear expressions have been shown to reveal stronger subliminal priming effects than other negative emotional expressions as for instance disgust (Lee et al., 2011; Murphy & Zajonc, 1993). Fear is thus suggested to activate subliminal processing as an alarm for possible threat. In my study, the pairing "fear – happy" was answered fastest. It might be suggested that the fear primes acted as threat signals and increased attentional vigilance. Thus, fearful faces are processed more quickly during encoding and are more available for subsequent processing (Suslow et al., 2006). However, since happy stimuli convey quite clear and undoubted safety signals, the emersion of a happy word might resolve the alertness and elicit faster RT.

But advantage in fear processing does not only apply to primes, but also to targets. Interestingly, negative stimuli (such as fear-associated) are reported to elicit longer RT than positive ones (Castner et al., 2007). And in general, fearful expressions are detected more quickly than neutral or happy expressions (Wang et al., 2014; Yang et al., 2007). In my study, I detected a fast processing of fear target words that were preceded by neutral primes, which determined the general inverse priming effect for fearful targets. The neutral facial expression corresponds to the normal, everyday facial expression that one is most accustomed to when looking in faces of other persons. No emotional processing is necessary when assessing neutral expressions. I assume that the discrepancy between this neutral expression and a sudden appearance of a threatening fear target word leads to fast responses, especially when compared to other emotional facial expressions that always imply emotional anticipation.

Affective information is not distributed constantly in the face. There is agreement that the recognition of fearful and angry faces depend more on information in the eye region, while disgust is conveyed mainly by the mouth (Calder et al., 2000; Calvo & Marrero, 2009, Leppänen & Hietanen, 2007). In contrast to the emotions fear or happiness, the emotional category disgust captures an exceptional position. When analyzing the influence of the targets´ valence on performance, most errors were detected for disgust-related target words. At the same time, no differences between congruent and incongruent conditions for disgust target words could be detected. Thus, for target words of this category no priming effect was present. Recent findings support the special role of disgust in comparison to other emotions (Lee et al., 2011; Phillips et al., 1997; Hayes et al., 2007; Montagne et al., 2006; Wang et al., 2003; Sprengelmeyer et al., 1996; Buxton et al., 2013; Baggio et al., 2012; Borg et al, 2012) indicating disgust as a negative but nonetheless non-threatening emotion in social contexts. Moreover, disgust is a highly-evaluative emotion that is predominantly affected through the culture a society lives with. Thus, there are considerable differences in what people sense or perceive as "disgusting". The choice of disgust-associated stimuli therefore constitutes a challenging task for affective priming paradigms to prevent ambiguity and future studies should consider this point carefully.

Limitations

Despite the strength of this study to demonstrate that eye regions of a face displaying mental states elicit affective priming, some confining points have to be taken into account. I present data from a rather small and very homogeneous sample concerning age and educational background. Future studies should consider more variability to report different characteristics of affective priming during implicit emotional processing. Moreover, the words used in this investigation were not selected with respect to an equally distributed word frequency. I cannot exclude possible influences of this variable on the results. However, recent studies could demonstrate RT advantage of positive words independent from the word frequency (Kuchinke et al., 2007), which underlines my findings.

Conclusion

To my knowledge, this is the first study demonstrating that even incomplete facial information induce implicit emotional responses and - in consequence - influence subsequent explicit decisions. These emotion-associated eye regions were processed with regard to their emotional valence and affected the performance on the following LDT. The primes used here clearly demonstrated their effectiveness in affective priming.

5. Study C2: Implicit and explicit processing of emotional facial expressions in PD patients

Specific aim:

This study investigates implicit and explicit emotional processing in PD patients in a lexical decision task coupled with an affective priming paradigm, using semantic and reduced facial emotional stimuli.

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Abstract

Objective. Besides motor problems, PD is associated with detrimental emotional and cognitive functioning. Deficient explicit emotional processing has been observed, whilst patients also show impaired ToM abilities. However, it is unclear whether this PD patients´ ToM deficit is based on an inability to infer others´ emotional states or whether it is due to explicit emotional processing deficits. I investigated implicit and explicit emotional processing in PD with an affective priming paradigm in which I used pictures of human eyes for emotional primes and a LDT with emotional connoted words for target stimuli.

Method. Sixteen PD patients and sixteen matched HC performed a LTD combined with an emotional priming paradigm providing emotional information through the facial eye region to assess implicit emotional processing. Second, participants explicitly evaluated the emotional status of eyes and words used in the implicit task.

Results. Compared to controls, implicit emotional processing abilities were generally preserved in PD with, however, considerable alterations for happiness and disgust processing. Furthermore, I observed a general impairment of patients for explicit

evaluation of emotional stimuli, which was augmented for the rating of facial expressions.

Conclusions. This is the first study reporting results for affective priming with facial eye expressions in PD patients. My findings indicate largely preserved implicit emotional processing, with a specific altered processing of disgust and happiness. Explicit emotional processing was considerably impaired for semantic and especially for facial stimulus material. Poor ToM abilities in PD patients might be based on deficient explicit emotional processing, with preserved ability to implicitly infer other people´s feelings.

5.1 Introduction

PD is characterized by increasing motor impairments such as tremor, rigidity, bradykinesia and postural instability due to a depletion of dopaminergic neurons in the striatum. However, PD also involves a spectrum of non-motor symptoms including changes in mood, as well as deficits in cognition and emotional processing (Cronin-Golomb, 2010; Gray & Tickle-Degnen, 2010; Chaudhuri et al., 2006; Sprengelmeyer et al., 2003; Pell & Leonard, 2005).

PD patients have been shown to have impairments in their ToM, the ability to infer other people´s mental states such as beliefs or intentions (Pinkham et al., 2003). ToM is an essential skill in social interaction and communication. The RMET (Baron-Cohen et al., 1997) is one of the most widely used measures to assess affective ToM and refers to inferences about other people´s emotions and feelings (Roca et al., 2010; Bodden et al., 2010; Santangelo et al., 2012; Péron et al., 2009; Monetta et al., 2009). Several studies revealed that PD patients show diminished performance in the RMET when compared to HC (Bodden et al., 2010; Xi et al., 2015; Poletti et al., 2013; Yu et al., 2012; Tsuruya et al., 2011).

However, to date it is not clear whether the observed deficit in ToM in PD patients is based on an inability to empathetically infer the emotional states of others or whether the diminished performance in affective ToM in PD is due to processing deficits of emotional facial expressions, specifically to explicitly processing and categorizing these emotions.

In the domain of facial emotions, a dual model has been proposed to distinguish implicit from explicit processing of emotional information, with a dissociation at the behavioral level (Mathersul et al., 2009), and distinct underlying neural bases (Winston et al., 2003). While there is considerable evidence for a deficient explicit emotional processing in PD, implicit emotional processing deficits in PD are less proven. Impaired explicit emotional processing, assessed through the explicit evaluation and naming of the emotional value of words and prosody – but also facial expressions - has been consistently observed in PD patients (Sprengelmeyer et al., 2003; Xi et al., 2015; Schröder et al., 2006; Péron et al., 2015; Yip et al., 2003; Suzuki et al., 2006; Kan et al., 2004), with diminished recognition of the specific emotions such as anger (Sprengelmeyer et al., 2003; Clark et al., 2008; Dujardin et

al., 2004; Lawrence et al., 2007), surprise (Clark et al., 2008), fear (Sprengelmeyer et al., 2003; Kan et al., 2002) and disgust (Suzuki et al., 2006; Dujardin et al., 2004; Kan et al., 2002). Accordingly, the observed reduced performance on the RMET in PD might be related to these explicit emotional processing deficits, while the ability to empathetically appreciate the emotional states of others might be implicitly preserved. However, implicit emotional processing abilities in PD have received limited attention so far. Borg et al. (2012) reported preserved implicit emotional processing of words in PD patients. Analogously, Castner et al. (2007) provided evidence for preserved implicit emotional processing abilities in PD. In their study, semantic and affective priming effects in a LDT with words as primes and targets indicated intact implicit emotional evaluative processes in PD patients. However, these studies investigated implicit emotional processing of pictorial and verbal affective stimuli, but did not test for emotional facial expressions.

To investigate implicit emotional processing of facial expressions I combined a LDT with an affective priming paradigm using an analogous facial stimulus material as applied in the RMET. In an affective priming paradigm, the automatically triggered connection between two stimuli (prime and target), which are determined through their emotional valence, is essential. Faster responses and fewer errors were observed when two consecutively presented stimuli were identical (congruent) with respect to their emotional valence (e.g., positive–positive) than when they differed from each other (Andrews et al., 2011). This *congruency effect* has been shown to be a robust and replicable phenomenon in a variety of studies using different primes, targets and specific instructions and tasks (Hermans et al., 2003; De Houwer et al., 1998; Banse, 2001) and indicates the implicit emotional processing of prime and target valence. Furthermore, in a LDT, participants focus on a non-emotional decision (word vs. non-word). They have to judge the lexical status of a presented letter string on whether it is a correct real word or a pseudo- or nonword. To assess implicit emotional processing, words with different emotional valences are used in this task. This *valence effect* manifests in faster reactions and fewer errors for emotional when compared to neutral target words (Challis & Krane, 1988; Williamson et al., 1991; Windmann et al., 2002; Nakic et al., 2006; Schacht & Sommer, 2009).

In a previous study, I successfully combined affective priming of emotional facial stimuli with an emotional target word in a LDT. Participants had to judge the lexical

status of letter strings (real or pseudo-words) that were preceded by emotional eye expressions (Experiment C, Study C1). In healthy young participants, I demonstrated that the reduced information in the facial eye regions affected the LDT performance by inducing implicit emotional processing.

In the present study, I applied this paradigm in a group of PD patients and an age-matched control group to systematically investigate explicit and implicit emotional processing in PD. In light of difficulties for developing remediation strategies for further cognitive deficits observed in these patients, it would be of great interest to probe whether PD patients are – besides their known explicit emotional processing deficits - still responsive to implicit emotion. By using emotional primes consisting of facial eye regions, I tested whether ToM disabilities in PD can be attributed to an explicit emotional processing deficit or to a general, - explicit as well as implicit - malfunction to process emotional states of others to provide further insights to diminished ToM impairments observed in PD patients.

5.2 Methods

Participants

Sixteen PD patients (mean age: 62.7 ± 11.2 years, 10 female; all right-handed; see *Table 5*) were recruited from the Departments of Neurology and Stereotactic Neurosurgery at the University of Magdeburg, Germany. The diagnosis of PD was confirmed by a neurologist specialized in movement disorders. Mean time since diagnosis was 6.0 ± 3.71 years (range 1-14) and patients had a mean UPDRS-III value of 19.94 ± 8.69 (range 7-37). All patients were tested during the ON state of their dopaminergic medication cycle, and no patient had undergone a DBS surgery. The HC group consisted of 16 matched participants (mean age: 62.3 ± 7.4 years, 10 female, all right-handed).

Patients and HC were excluded from the study if they had a history of neurological condition (for patients others than PD), untreated or unstable mood disorder, bipolar affective disorder, schizophrenia or other psychiatric condition known to compromise executive cognitive functioning, or an untreated or unstable medical condition known to interfere with cognitive functioning (e.g. diabetes, pulmonary

disease etc.). All participants had normal or corrected-to-normal vision. Prior to participation in the study they all provided informed consent. The study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki.

Table 5. Demographic and clinical characteristics of patients

Patient #	Age	Sex	Disease duration (in years)	LED (in mg)	UPDRS-III
1	59	female	4	590	9
2	35	male	3	105	21
3	74	male	4	800	20
4	68	female	2	0	18
5	62	female	3	800	37
6	65	female	2	300	29
7	58	male	6	740	19
8	67	female	14	1400	18
9	78	male	5	300	23
10	74	female	10	900	15
11	75	female	10	1000	7
12	45	male	1	300	25
13	54	female	6	0	10
14	64	female	7	0	19
15	63	male	10	1375	13
16	62	female	9	900	36

UPDRS-III= Unified Parkinson Disease Rating Scale – III (motor evaluation).

Stimuli

Implicit emotional processing is measured with a LDT in which participants have to judge the lexical status of a presented letter string on whether it is a correct word or a pseudo-word. This letter string (target) is preceded by emotionally valenced facial eye regions (primes). For the LDT, I used a set of 192 written stimuli (96 German

words and 96 pseudo-words) (Briesemeister et al., 2011b; Võ et al., 2009) as targets. The selection of the stimuli (faces and words) as well as the construction of the pseudo-words is described in detail in Section 4.2., page 57. In short, all 96 real German words were taken from a standardized word list (Briesemeister et al., 2011b) and were then grouped in four emotional categories (happiness, fear, disgust and neutral). Pseudo-words were also generated out of a word list (Võ et al., 2009). Real words were existing German words; pseudo-words were readable, but senseless letter strings. Facial regions around the eyes were extracted from the stimulus set "60 Faces Test" developed by Ekman and Friesen (1976) and were used as emotional primes (happy, fearful, disgust-related and neutral faces of two men and two women). The whole-face images were adjusted and cut so that only the eye regions were visible which were presented in a size of 8.6 cm x 3 cm (3.4 visual angle). For the implicit task, primes and target stimuli were combined in a pseudo-randomized manner: half of the prime-target pairs with the real German words were constructed to be emotionally congruent which resulted in 12 congruent and 12 incongruent trials for each emotion.

Task

The experiment was generated and carried out with Presentation (Neurobehavioral Systems, Inc.). Participants were seated in front of a computer and looked at a fixation cross in the middle of the screen.

Implicit. The detailed description of the implicit task can be found in Section 4.2., (Project C, Study 1), at pages 57/58. *Figure 14A* gives an overview of the implicit task.

Explicit. This task included 112 trials and consisted of the same stimulus material that was used in the implicit task (16 faces, 96 real German words). Depending on the understanding of the instruction and the participants´ time to decide, this task lasted about 10 min.

The trial started with a fixation cross (500 ms) before the target (face or word) was presented. Participants had to explicitly decide which emotional category (fear, disgust, happiness or neutral) the presented target stimulus belonged to. They had to

press a corresponding button on a keyboard as fast as possible; but no time limit was given for the decision. Afterwards, the next trial started (see *Figure 14B*).

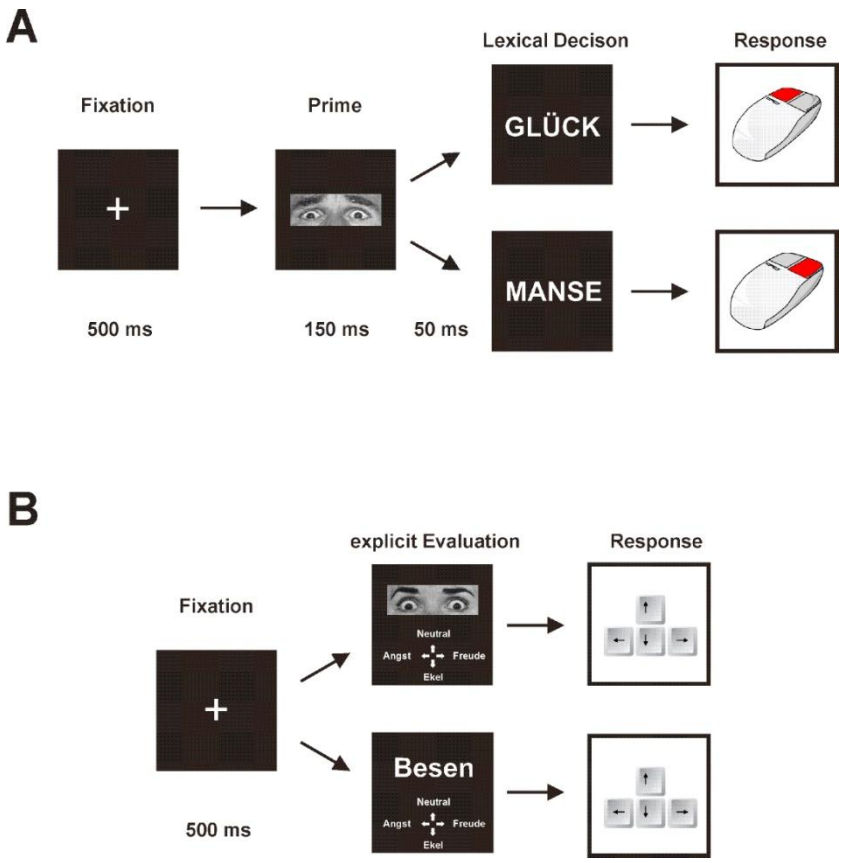

Figure 14. Affective priming paradigm including (A) the LDT of the implicit task and (B) the explicit task with the evaluation of emotional stimuli. (A): Each trial in the LDT started with a fixation cross that was presented for 500ms. An emotional prime (the adjusted eye region of Ekman-faces-photographs) followed and was displayed for 150ms followed by a break of 50ms. Subsequently, the target stimulus was presented without time limit. The participants were supposed to decide as fast as possible whether this target was a real German word or a pseudo-word and to press a corresponding button on a computer mouse. After the button press, the next trial started. (B): In the second task, participants were requested to explicitly decide which emotional category the presented stimulus material belonged to. Each trial started with a fixation cross that was presented for 500ms. After further 50ms break, the stimulus was presented. Participants were instructed to press one of the four buttons on a keyboard which corresponded to the emotional category of the stimulus as fast as possible. No time limit was given. First, the eye regions were presented, afterwards the real German words followed.

Statistical analysis

Implicit emotional processing: For RT and ER, separate repeated-measures ANOVAs with the within-subject factors *valence* of the target word (happiness/ fear/ disgust/ neutral), *congruence* between prime and target (congruent/ incongruent) and a between-subject factor *group* (PD/ HC) were performed. Subsequently, ANOVAs with the factors *valence* of the target word and *congruence* between prime and target were conducted and post-hoc T-tests were executed. Subsequently, ANOVAs with the factors *congruence* and *group* separately for each valence category were performed. Finally, response accuracy (RA) rates (%) for congruent and incongruent trials were assessed and compared for both samples.

Explicit emotional processing: Separate repeated-measures ANOVAs for RT and ER with the within-subject factors *valence* of the emotional stimuli (happiness/ fear/ disgust/ neutral), *condition* (words/ eyes) and *group* (PD/ HC) were performed. Subsequently, post-hoc T-tests were performed.

RT refer to correct response trials only, i.e. trials in which correct button press responses were given.

5.3 Results

Implicit emotional processing

The repeated-measures ANOVA on RT with the factors *valence*, *congruence* and *group* revealed a general *valence effect*, i.e. a significant ME of the factor *valence* [$F(3,45)=9.64$; $p<0.001$]. As shown in *Figure 15*, all participants responded consistently faster to happy target words than to all other valence categories, with PD and HC being not generally different in their RT (no significant main effect of the factor *group* ($p=0.72$)).

The global ANOVA furthermore revealed a significant *valence x congruence x group* interaction [$F(3,45)=7.76$; $p<0.001$]. To assess the effect of congruency, i.e. the influence of the emotional content of the prime on LDT performance, I subsequently conducted 4x2 repeated-measures ANOVAs with the factors *valence* and *congruence* for each group separately. For PD patients as well as the HC group, analyses

revealed a significant ME of the factor *valence* (PD: [F(3,45)=6.01; p=0.002]; HC: [F(3,45)=5.22; p=0.004]) confirming general faster RT in response to happy targets. Furthermore, for both groups ANOVAs revealed significant *valence x congruence* interactions (PD: [F(3,45)=5.75; p=0.002], HC: [F(3,45)=3.53; p=0.022]), demonstrating that the primes influenced LDT performance.

Additional post-hoc T-tests revealed that this interaction was driven by faster RTs for congruently primed disgust targets [T(15)=-2.6; p=0.02] and slower RTs for congruent happy trials [T(15)=2.38; p=0.03] in PD (fear: [T(15)=-0.36; p=0.72]; neutral: [T(15)=-1.94; p=0.07]). However, HC showed the opposite pattern with slower reactions in congruently primed disgust targets [T(15)=2.09; p=0.05] and faster responses in congruent happy trials [T(15)=-2.73; p=0.02] (fear: [T(15)=-1.27; p=0.22]; neutral: [T(15)=-0.42; p=0.68], (see *Figure 15A*). This opposite directed congruency effect was further evidenced by additional 2x2 ANOVAs with factors *congruence* and *group* separately for each valence category. Whereas no effects were detected for fear [F(1,15)=0.45; p=0.52] and neutral stimuli [F(1,15)=1.56; p=0.23], happy [F(1,15)=10.84; p=0.005] and disgust targets [F(1,15)=4.92; p=0.04] revealed significant *congruence x group* interactions. To illustrate this effect, I calculated congruency parameters by subtracting the RTs of congruent from incongruent trials (see *Figure 15B*) and compared them between PD and HC. In result, for happy [T(30)=-3.52; p<0.001] and disgust target words [T(30)=2.56; p=0.016], congruency affected LDT performance differentially in PD and HC. For happy target words, HC profited from congruent cues, whereas in PD congruent cueing diminished performance. In contrast, for disgust-related target words, congruent cueing slowed RT in HC, but fastened responses in PD.

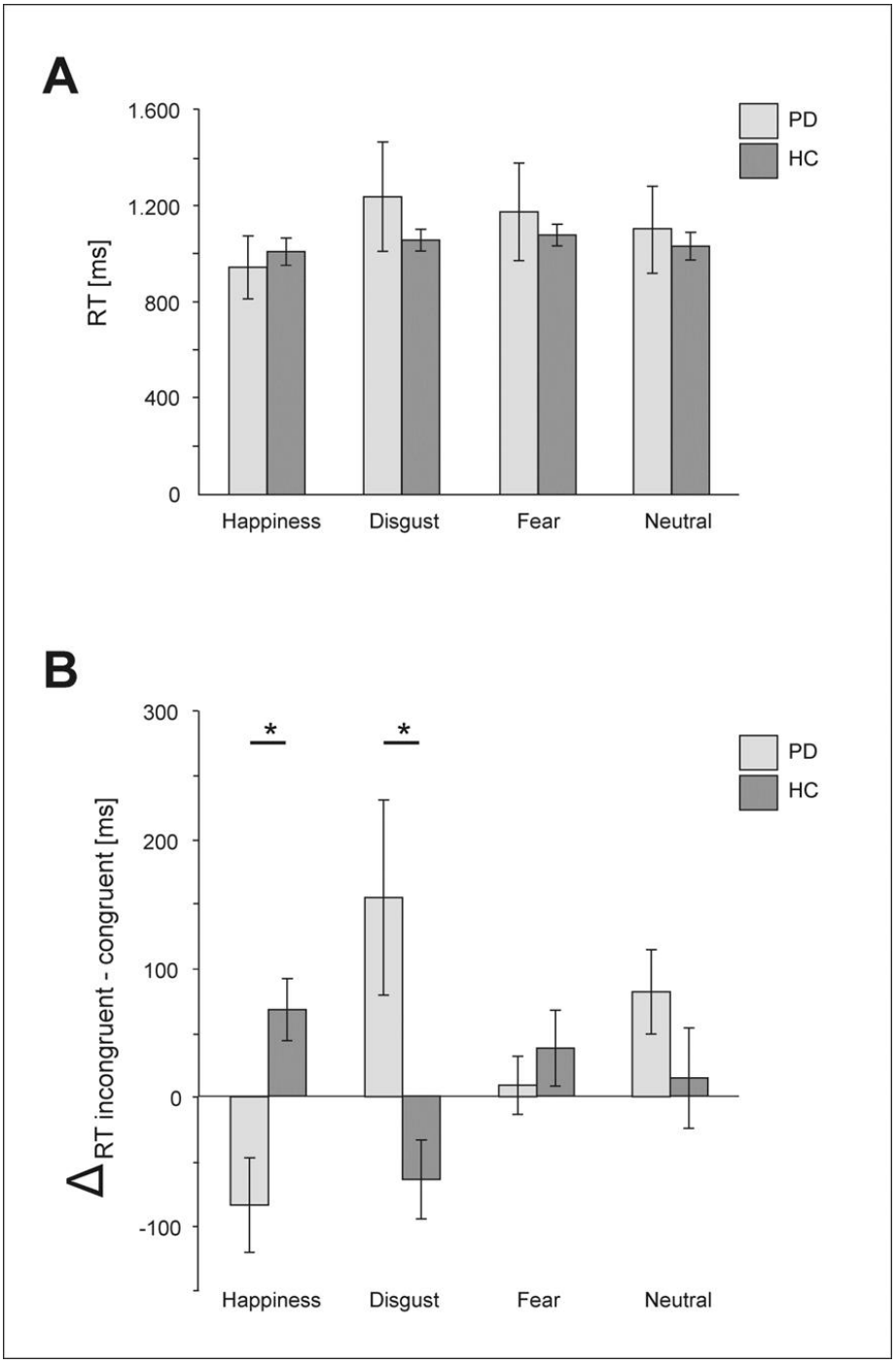

Figure 15. (A) Mean RT (in ms) for target words in the implicit LDT task for the emotional categories happiness, disgust, fear and neutral for PD patients and HC. Error bars display SE. (B) RT difference values as a mean of subtracting congruent from incongruent trials (in ms) in the LDT for both groups. Statistically significant differences are labeled with (*). Error bars depict SE.

Generally, there were no differences in RT for pseudo-words between PD and HC (PD: 1622.7±1439.95 ms; HC: 1232.16±256.91 ms; T(30)=1.07; p=0.29). RA rates are displayed in *Table 6*. PD patients showed generally lower performance rates in congruent fear and disgust trials and in incongruent fear – neutral, happy – disgust and neutral – disgust trials when compared to HC (all p<0.034).

Table 6. RA rates (in %) for congruent and incongruent trials during the implicit emotional task for PD patients and HC

	PD patients	**HC**	**Significance**
congruent			
Fear-Fear	95.31 ± 5.24	99.48 ± 2.08	T=-2.95; p=0.006
Happy-Happy	98.96 ± 1.04	100.00 ± 0.00	n.s.
Disgust-Disgust	86.46 ± 3.22	98.44 ± 3.36	T=-3.6; p<0.001
Neutral-Neutral	95.83 ± 1.32	97.92 ± 4.81	n.s.
incongruent			
Fear-Disgust	96.88 ± 8.54	100.00 ± 0.00	n.s.
Fear-Happy	100.00 ± 0.00	100.00 ± 0.00	n.s.
Fear-Neutral	87.5 ± 18.26	100.00 ± 0.00	T=-2.74; p=0.01
Disgust-Fear	100.00 ± 0.00	100.00 ± 0.00	n.s.
Disgust-Happy	95.31 ± 13.59	100.00 ± 0.00	n.s.
Disgust-Neutral	96.88 ± 8.54	100.00 ± 0.00	n.s.
Happy-Fear	98.44 ± 6.25	100.00 ± 0.00	n.s.
Happy-Disgust	73.44 ± 23.22	95.31 ± 10.08	T=-3.46; p=0.002
Happy-Neutral	98.44 ± 6.25	100.00 ± 0.00	n.s.
Neutral-Fear	92.19 ± 15.05	98.44 ± 6.25	n.s.
Neutral-Happy	98.44 ± 6.25	98.44 ± 6.25	n.s.
Neutral-Disgust	89.06 ± 15.72	100.00 ± 0.00	T=-2.22; p=0.034

All values are M ± SD (in %). n.s.= not significant

The repeated-measures ANOVA on ER with the within-subject factors *valence* and *congruence* and the between-subject factor *group* revealed a general effect of *valence*

[F(3,45)=13.51; p<0.001], due to consistently more errors for disgust-related target words and a significant main effect of the factor *group* [F(1,15)=23.59; p<0.001], due to more errors committed by PD patients than HC. Moreover, the ANOVA revealed a significant *valence x group* interaction [F(3,45)=14.18; p<0.001]. Whereas PD and HC performed equally for happy target words [T(15)=2.08; p=0.06], PD made significantly more errors than HC for disgust words [T(15)=4.63; p<0.001], fear words [T(30)=3.31; p=0.05] and neutral target words [T(30)=2.46; p=0.03], with the most considerable difference between groups for disgust target words (see *Figure 16*).

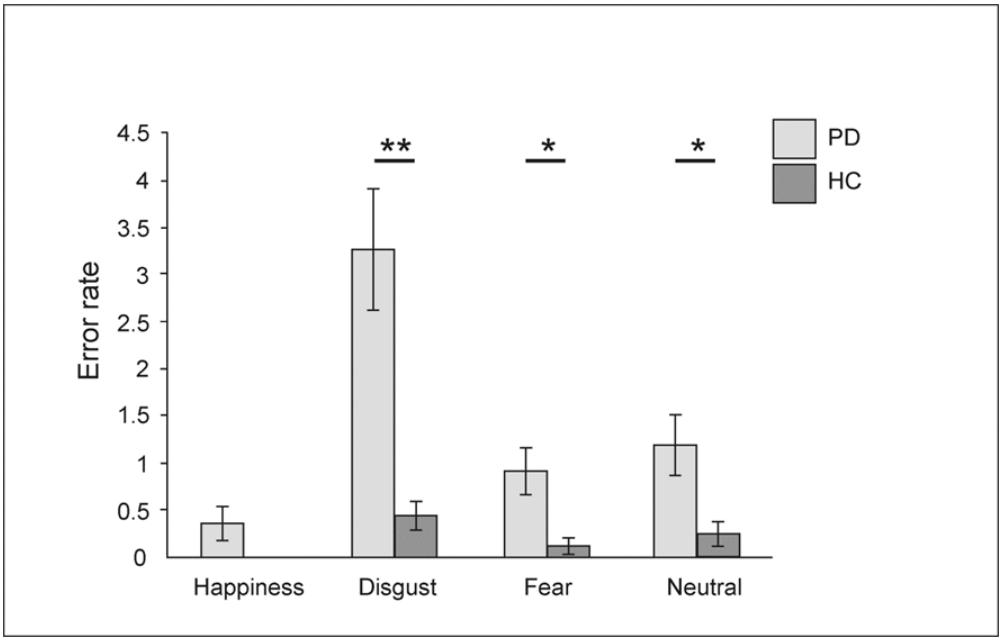

Figure 16. Mean ER (absolute) for target words in the implicit LDT task for the emotional categories happiness, disgust, fear and neutral for PD patients and HC. Statistically significant differences are labeled with (*). Error bars display SE.

Summary implicit task:

Behavior in the implicit task demonstrated a general valence effect. All participants answered happy target words faster than all other emotional categories and made most errors for disgust target words. Furthermore, RTs of both PD and HC depended on the valence of the target word and the congruency of the previously presented eye

cues. However, whereas HC profited, PD incurred losses from congruently primed happy words. In contrast, for disgust-related target words, congruent cueing slowed RT in HC but fastened responses in PD. Finally, even though PD made generally more errors than HC, the number of errors for PD and HC also depended on the valence of the target words. Specifically, whereas PD and HC performed equally for happy target words, both groups showed a considerable ER difference for disgust target words. Accordingly, both PD and HC showed a valence effect that demonstrated intact implicit processing of the emotional content of the target words. Furthermore, PD as well as HC performances on target words were influenced by the emotional content of the facial primes, demonstrating intact implicit processing of the emotional content of the circumscribed facial expression. However, the direction of this influence differed between patient and control group, particularly for the emotions happiness and disgust.

Explicit emotional processing

RTs for the explicit task are illustrated in *Figure 17A*. A repeated-measures ANOVA on RT with the within-subject factors *valence* of the emotional stimulus (happiness/ fear/ disgust/ neutral), *condition* (words/ eyes) and a between-subject factor *group* (PD/ HC) revealed a significant ME of the factor *valence* [$F(3,45)=19.99$; $p<0.001$] with shortest RT for happiness-related stimulus material. The ANOVA further revealed a ME of the factor *condition* [$F(1,15)=17.73$; $p<0.001$] due to shorter RT for words than for eyes in all emotional categories (all $p<0.027$), as well as a significant ME of the factor *group* [$F(1,15)=4.37$; $p=0.05$] due to longer RT for PD than for HC for all emotional stimuli. Finally, analysis showed a significant *condition x group* interaction [$F(3,15)=6.48$; $p=0.022$], demonstrating that RT differences between PD and HC were more pronounced for eyes than for words.

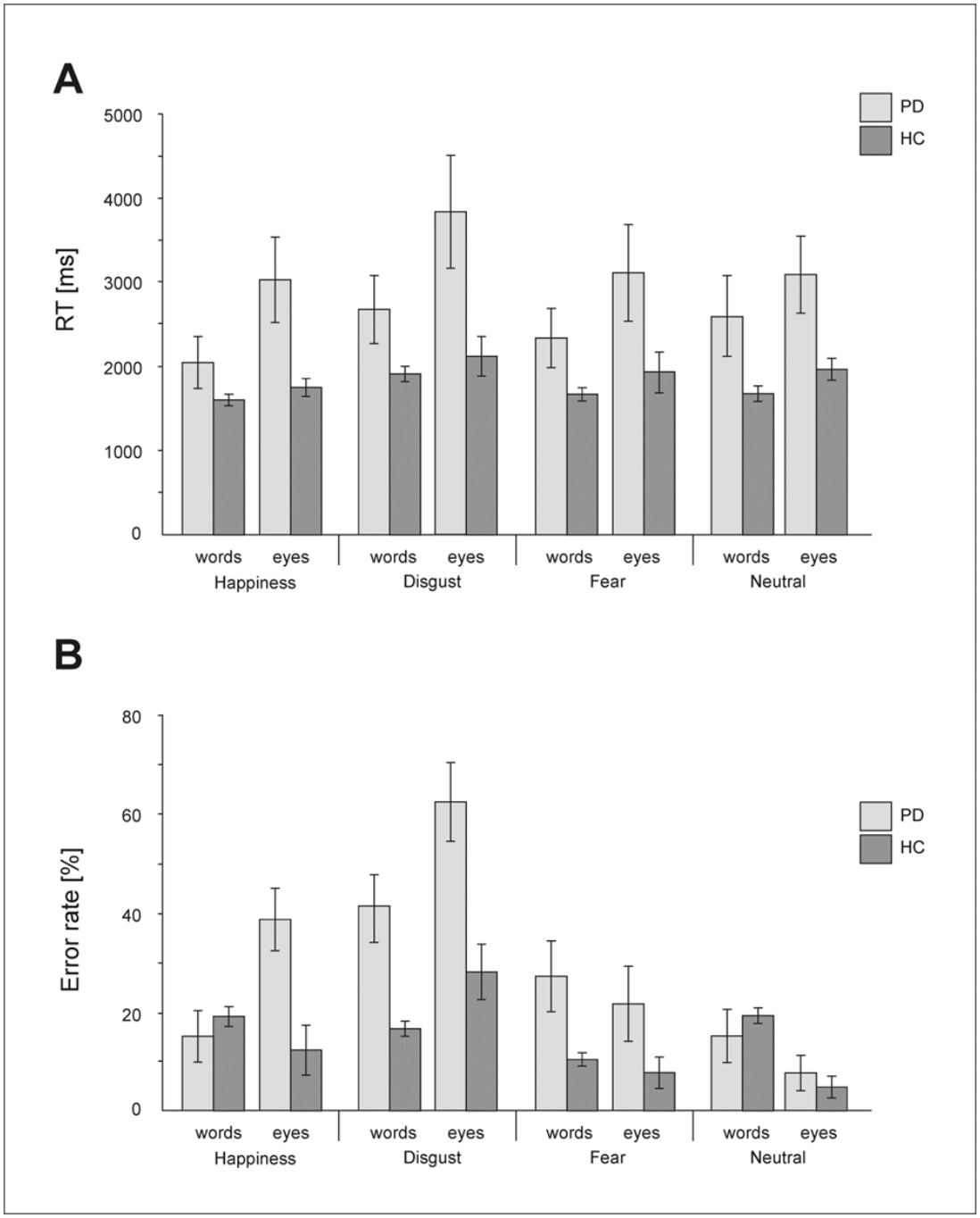

Figure 17. (A) Mean RT (in ms) for eyes and words in the explicit evaluation task for PD patients and HC. Error bars display SE. (B) Mean ER (in %) for eyes and words in the explicit evaluation task for PD patients and HC. Error bars display SE.

Figure 17B illustrates ER in the explicit task. The repeated-measures ANOVA with the factors *valence*, *condition* and *group* showed a significant ME of the factor *valence* [$F(3,45)=22.72$; $p<0.001$] with higher ERs for disgust-related stimulus

material and a significant ME of the factor *group* [F(1,15)=10.47; p=0.006] due to an overall higher ER in the PD group.

Furthermore, the ANOVA revealed a significant *valence x condition* interaction [F(3,45)=12.38; p<0.001], a *valence x group* interaction [F(3,45)=8.07; p<0.001], a *condition x group* interaction [F(1,15)=5.3; p=0.036], and a *valence x condition x group* interaction [F(3,45)=4.27; p=0.01]. To elucidate these effects, subsequent ANOVAs with the factors *valence* and *group* separately for each stimulus condition (words/eyes) were performed. For words and eyes, separate analysis revealed significant MEs of the factor *valence* (words: [F(3,45)=6.08; p=0.001], eyes: [F(3,45)=25.34; p<0.001]), as well as significant *valence x group* interaction (words: [F(3,45)=10.42; p<0.001], eyes: [F(3,45)=4.7; p=0.006]). While PD patients made more errors for disgust and fear words compared to HC, for eyes they showed a general impairment in the rating of all emotional categories except happiness. Additionally, only analysis on the explicit rating of eyes revealed a significant ME of the factor *group* [F(1,15)=15.45; p=0.001].

Summary explicit task:

Behavioral analysis of the explicit emotional rating revealed a general valence effect; all participants were fastest to rate happy stimuli and slow for disgust material, and also produced most errors for disgust-related stimuli. Furthermore, PD responded generally slower and produced more errors than HC. Importantly, the slowing and the high ERs in PD compared to HC were more pronounced for eyes than for words and highest for disgust-related material. Concluding, PD patients show a considerable impairment in explicit emotional processing of stimulus material, especially of facial eye regions, when compared to HC.

5.4 Discussion

The present study investigated implicit and explicit emotional processing in PD patients. I applied an affective priming paradigm in which emotional primed information was portrayed in the eye region of a face only. To the best of my

knowledge, this is the first study investigating implicit and explicit emotional processing of reduced facial expressions in PD patients.

The results reveal that, generally, implicit emotional processing abilities are preserved in PD. In both, patients as well as HC participants, the valence of the target word influenced the speed of lexical decisions and the amount of errors, demonstrating comparable implicit processing abilities for the emotional content of a target word. Furthermore, also the congruency between prime and target affected performance in all participants, demonstrating implicit processing of the emotional content of the circumscribed facial expressions. However, the direction of the congruency effect differed between patient and control group. HC profited whereas PD incurred a loss from congruent primed happy words. In contrast, for disgust-related target words, congruent priming slowed RT in HC, but fastened responses in PD. Moreover, even though PD generally made more errors than HC, these error differences were mainly committed for the emotional category disgust. Accordingly, the findings indicate that - while the implicit emotional processing of both words and facial expressions was generally preserved - PD also exhibited altered implicit emotional processing specifically for the emotions disgust and happiness. Finally, I observed a general impairment of PD patients for the explicit evaluation of emotional stimulus material, which was significantly augmented for the rating of facial eye expressions. Particularly, in PD patients the slowing of RT and elevated ERs were more pronounced for eyes than for words and most striking for disgust material, pointing to a specific deficit in the explicit processing of emotional information that is portrayed in the eye region of a face.

According to the dual model theory of emotion (Mathersul et al., 2009; Winston et al., 2003), implicit recognition and explicit identification of facial emotions are independent. While both forms of emotional processing underlie a continuum of feedback and conscious awareness, implicit processing of emotions occurs via direct neural pathways that do not require conscious awareness. In contrast, explicit emotional evaluation is processed by slower, indirect pathways that rely on feedback and conscious attention (Williams & Gordon, 2007; Morris et al., 1998). Hence, while explicit emotional performance might be affected in PD, the automatic implicit recognition can still be intact. This disconnection may account for the observed impaired ability to explicitly access the meaning of an emotional stimulus in

combination with a relative preserved implicit processing ability in the PD patients. So far, only few studies investigated the interplay of implicit and explicit emotional processing in PD patients. These studies consistently reported evidence for preserved implicit, but deficient explicit emotional processing in PD patients. Wieser et al. (2006) tested implicit and explicit emotion processing by means of event-related potentials in response to affective pictures. The authors reported preserved early implicit processing but blunted explicit emotional responses in PD patients, supporting the view that the elementary – implicit – reaction to an emotion is independent from the conscious response to it. Also Borg et al. (2012) reported a disconnection between implicit and explicit emotional processing in PD. In this study, patients were less accurate in the explicit lexical decisions on disgust stimuli than on any other stimuli, even though they were still implicitly sensitive to the emotional content of the presented words. Accordingly, Castner et al. (2007) gave proof for an unimpaired implicit activation of emotional evaluations in PD patients by means of a combined affective and semantic priming paradigm. Results of the present study are in good agreement with these findings. I show preserved implicit combined with deficient explicit emotional processing abilities in PD. Importantly, I demonstrated for the first time that for circumscribed facial expressions the deficient explicit processing abilities are considerably augmented, while the implicit processing abilities for these facial expressions are still largely preserved in PD.

It has been assumed that the general emotional facial recognition deficit in PD is based on the patients´ reduced intensity of their own emotional facial expressions, due to a loss of facial mobility and "mask-like" appearance of the face (Marneweck et al., 2014; Jacobs et al., 1995; Katsikitis & Pilowsky, 1988). PD patients exhibit reduced facial muscle activity and also have problems to control facial muscles combinations to build facial emotion pattern (Wu et al., 2014). As assumed by the theory of embodied simulation, the disrupted production of emotional expressions will also impair the perception of emotional expressions (Goldman & Sripada, 2005). Accordingly, the inability of PD patients to produce emotional facial expressions might cause the reduced ability to discriminate emotions in faces. The lack of whole facial information might additionally contribute to my observation of an augmented deficit in the explicit processing of emotional information that is portrayed only in the eye region of a face. Since PD patients have been shown to be already impaired

in the recognition of emotions that are displayed in whole faces (Sprengelmeyer et al., 2003; Xi et al., 2015; Yip et al., 2003; Suzuki et al. 2006; Kan et al., 2004), it can be assumed that these deficits are even enhanced if emotions are to be recognized in single facial parts only. Especially the mouth of a face – which was eliminated in my emotional stimuli – is important for the correct recognition of facial emotional expressions, specifically for the emotion disgust (Eisenbarth & Alpers, 2011; Beaudry et al., 2014; Calder et al., 2000; Leppänen & Hietanen, 2007).

The present study also revealed a specific alteration of the implicit as well as explicit processing of the emotions disgust and happiness. A disgust-specific impairment in PD patients is in line with recent findings showing deficient disgust recognition for words, prosody, but also facial expressions (Sprengelmeyer et al., 2003; Suzuki et al., 2006; Dujardin et al., 2004; Kan et al., 2002; Borg et al., 2012; Lachenal-Chevallet et al., 2006). In fact, disgust has often been described to capture a special role in contrast to other emotions (Borg et al., 2012; Sprengelmeyer et al., 1996; Hayes et al., 2007; Baggio et al., 2012; Buxton et al., 2013). Disgust is a highly-evaluative emotion affected through the culture a society lives with and is thus considerably determined by what people perceive as "disgusting". This enhanced ambiguity was also present in my results in the explicit categorization task. Here, PD patients but also HC tended to make most errors when rating disgust-related words. Interestingly, problems in recognition of disgust in PD patients are also reported for other communication channels. Pell & Leonard (2003; 2005) investigated PD patient´s ability to comprehend basic emotions from prosody. PD patients were impaired in recognizing emotions and especially disgust from prosodic cues in the vocal channel. It has been noted that PD patients often display selective difficulties to express disgust through prosody when compared to other emotions (Pell et al., 2006; Caekebeke et al., 1991).

Functional neuroimaging studies investigating the neural basis of emotion recognition have shown the involvement of the striatum and specifically the insula in the processing of disgust (Calder et al., 2000; Sprengelmeyer et al., 1996; Phillips et al., 1997). The insula is highly interconnected with the basal ganglia and cortical regions and interacts with multiple brain networks (Chikama et al., 1997; Fudge et al., 2005). Importantly, the insula is one of the first cortical regions to be pathologically affected in PD (Braak et al., 2006). Hence, the insula has been found

to have abnormal activation patterns in PD patients during cognitive tasks (Shine et al., 2013), but also to exert influence on social behavior. Lesioning of the insular impairs the recognition of facial emotions (Calder et al., 2000) and the loss of normal metabolic activity in insular neurons in PD has been associated with the blunted emotions in patients with PD (Wieser et al., 2006; Robert et al., 2012). This is in line with my present findings of slow RT and enhanced ER for disgust in patients, for both implicit and explicit emotional tasks. Interestingly, congruent priming with disgust-related facial expressions (primes) and words (targets) fastened responses in PD. This reproduces the typical congruency effect often described in priming studies, which refers to improved RT and ER performance when two successive stimuli are identical in their emotional valence (Andrews et al., 2011). Hence, the concurrence of concomitantly presented disgust primes and targets might enhance their processing as "disgust-related" and might thus overcome the impairment of sole facial expression recognition due to insula damage in consequence to PD. This may tackle the impaired performance normally observed in PD patients. I accordingly demonstrated impaired RA rates for disgust in PD patients, but also for the emotion fear, which is in line with other studies showing diminished abilities in perception of negative emotions in PD (Sprengelmeyer et al., 2003; Clark et al., 2008; Dujardin et al., 2004; Lawrence et al., 2007; Kan et al., 2002). This is even the case for congruent trials, hence, for concomitant presentation of fear primes and fear targets in one trial.

In the present study, I also observed a processing advantage for happy stimulus material in my implicit as well as explicit task. Happy stimuli were answered fastest by both, HC and PD patients, despite limited facial information. This finding is in accordance with other studies reporting unimpaired and fast processing of happiness stimuli in PD patients (Kan et al., 2002; Cohen et al., 2010). Thus, the eye region of a human face obviously comprises sufficient distinctive markers to enable discrimination of happiness despite general deficits in the processing of facial emotion. An involvement of the amygdala has been proposed for the processing of happiness (Kipps et al., 2007). In a functional imaging study, Kipps et al. (2007) reported that the amygdala volume correlated with the ability to recognize happy facial expressions. In fact, projections from the amygdala reach to the striatum and the amygdala itself undergoes severe pathological changes during the course of PD

as well (Braak et al., 1994). However, PD-related amygdala involvement seems to be unrelated to cognitive impairments (Braak et al., 1994), indicating that emotion processing associated with the amygdala might be spared even with ongoing PD pathology. This might be one reason why in the present study, PD patients showed a benefit from congruent happy stimuli.

However, HC did not show this improvement in the processing of congruent happiness-related stimulus material. I can speculate that this relates to the perceived emotion intensity of the used stimulus primes and targets (Hess et al., 1997). Decoding of emotions is more accurate when the emotions are high-intensity facial expressions. Thus, in the present study, the emotional facial expressions might have been perceived as less intense by the HC, particularly as I used only limited emotional information displayed in the eyes.

In sum, the present study demonstrated a general deficit for the explicit emotional processing with a relatively preserved implicit emotional processing of emotional faces in PD. This result might have implications for the interpretation of recent findings on PD disabilities to infer the mental states of other persons (ToM). These diminished ToM abilities in PD patients have been evaluated using the RMET, a test that displays mental states in a photograph of the subject´s eye region and requires the explicit rating of these emotions (Bodden et al., 2010; Xi et al., 2015; Poletti et al., 2013; Tsuruya et al., 2011). Accordingly, it is reasonable to assume that the poor performance in the RMET in PD patients might result from deficits in explicit emotional processing rather than from a deficient ability to infer to other people´s thoughts and feelings.

Limitations and Conclusions

The presented results have to be regarded under the following possibly constraining aspects. First, I assessed emotional processing in PD patients while they were in the ON state of their dopaminergic medication. Dopaminergic treatment might have an influence on cognitive outcomes (Cools, 2006). However, different authors stated that the emotional processing in patients may be independent of medication effects since the dopaminergic status had no effect on the ability of PD patients to recognize

particular emotions (Gray & Tickle-Degnen, 2010; Péron et al., 2009; Hanby et al., 2014). Moreover, my study handles static pictures of faces which are only partly comparable with real, moving facial expressions and which might thus be insufficient for the doubtless identification of emotional impulses. According to Kan et al. (2002), photographs contain no dynamic information that helps identifying facial expressions. They also tested moving facial expressions on videotapes and found better correct responses for emotions. Future studies might concentrate on the question how moving facial expressions are evaluated by PD patients concerning their emotional connotations and how even reduced moving facial information (e.g. only eye regions) might have effects on emotion recognition in PD.

This is the first study that provides insights into affective priming with facial expressions in PD patients. My findings indicate a general deficit for the explicit emotional processing with a relatively preserved implicit emotional processing in PD, however, with a specific altered processing for the emotions disgust and happiness. Due to these results, it might be speculated that the poor performance in the RMET often observed in PD patients might result from deficits in explicit emotional processing rather than from a deficient ability to infer to other people´s thoughts and feelings.

6. Study C3: Effects of STN-DBS on implicit and explicit emotional processing in PD patients

Specific aim:

This study investigates DBS-dependent influences on implicit and explicit emotional processing in an affective priming paradigm with reduced facial emotional stimuli.

The content of this chapter has been submitted as: Wagenbreth, C., Kühne, M., Voges, J., Heinze, H.J., Galazky, I., and Zaehle, T. (submitted). Deep brain stimulation of the subthalamic nucleus selectively modulates emotion recognition of facial stimuli in Parkinson´s patients. BMC Neurology.

Abstract

Objective. Diminished emotion recognition is a known symptom in Parkinson (PD) patients and subthalamic nucleus deep brain stimulation (STN-DBS) has been shown to further deteriorate the processing of especially negative emotions. While emotion recognition generally refers to both, implicit and explicit processing, demonstrations of DBS-influences on implicit processing are sparse. In the present study I assessed the impact of STN-DBS on explicit and implicit processing for emotional stimuli.

Method. Under STN-DBS ON and OFF, fourteen PD patients performed a lexical decision task combined with an affective priming paradigm which provides emotional information through the facial eye region to assess implicit emotional processing. Subsequently, patients explicitly evaluated the emotional status of eyes and words used in the implicit task.

Results. DBS affected explicit emotional processing more than implicit processing with a more pronounced effect on error rates than on reaction speed. STN-DBS

generally worsened implicit and explicit processing for disgust stimulus material, but improved explicit processing of fear stimuli.

Conclusions. This is the first study demonstrating influences of STN-DBS on explicit and implicit emotion processing in PD patients. While STN stimulation impeded the processing of disgust stimuli, it improved explicit discrimination of fear stimuli.

6.1 Introduction

Deviant emotion production and recognition have been shown in patients with PD when compared to healthy controls, and especially impaired recognition of emotional facial expressions has been demonstrated (Enrici et al., 2015; Yip et al., 2003; Suzuki et al., 2006; Sprengelmeyer et al., 2003). In particular, diminished recognition of negative facial emotions has been consistently observed in PD patients (Suzuki et al., 2006; Sprengelmeyer et al., 2003; Clark et al., 2008; Dujardin et al., 2004; Lawrence et al., 2007; Kan et al., 2002). Furthermore, also emotion recognition of circumscribed facial information, e.g. emotional states portrayed only in the eye region is impaired in PD patients (Wagenbreth et al., 2016). While implicit emotional processing, i.e. the automatic unconscious emotional processing, is largely preserved in PD, as shown by a persistent sensitivity to emotional stimuli (Wagenbreth et al., 2016; Borg et al., 2012), explicit (conscious) recognition and discrimination of emotional facial cues seems to be generally damaged (Enrici et al., 2015; Yip et al., 2003; Suzuki et al., 2006; Sprengelmeyer et al., 2003; Clark et al., 2008; Dujardin et al., 2004; Lawrence et al., 2007; Kan et al., 2002).

STN-DBS has been proven to be a helpful therapeutic approach to improve motor disturbances in PD (Hershey et al., 2004; 2010; Frank et al., 2004), but also to have influences on cognitive and executive domains (Zaehle et al., 2017; Irmen et al., 2017; Wagenbreth et al., 2015; Fasano et al., 2010; Schneider et al., 2003). However, studies investigating the effects of STN-DBS on emotion perception in PD demonstrated rather heterogeneous results, with reports of unchanged explicit emotion recognition of facial expressions (and emotional prosody) under DBS (Schneider et al., 2003; McIntosh et al., 2015; Albuquerque et al., 2014; Berney et al., 2007) or worsening of explicit discriminating emotional faces under stimulation (Péron et al., 2010; Geday et al., 2006; Serranová et al., 2011). Precisely, a tendency for DBS to cause deficits in facial discrimination of especially negative emotions as disgust (Aiello et al., 2014; Mondillon et al., 2012), anger (Schroeder et al., 2004), sadness (Drapier et al., 2008), and fear (Mondillon et al., 2012; Drapier et al., 2008; Biseul et al., 2005) was observed. An approach to explain this effect of STN-DBS was given by Geday et al. (2006). The authors stated that stimulation of the STN inhibits the activity in the lateral fusiform gyrus, an area which is generally activated by emotional facial expressions. This would lead to significantly altered emotion

perception of facial expressions while emotional assessment per se would not be affected by DBS. Hence, explicit emotional processing would be largely diminished in PD patients under DBS, but implicit emotional processing might not be affected by stimulation.

The studies mentioned above exclusively investigated the influence of STN-DBS on explicit discrimination and rating abilities and left out automatic implicit processing of emotional states. Only Castner et al. (2007) measured the outcome of DBS on implicit emotional processing in terms of semantic and affective priming in PD patients. Using verbal material, they found unimpaired automatic (implicit) lexical-semantic and affective processing independent from DBS, while STN-DBS improved controlled, attentional priming in PD patients. The authors suggested that STN-DBS modulates basal ganglia-thalamocortical circuits involved in controlled attentional processes, but proposed automatic priming to be unaffected by stimulation. In a previous study (Wagenbreth et al., 2016), I investigated both, implicit and explicit emotional processing of words and circumscribed facial regions, in non-stimulated PD patients. Here, results showed that PD patients were impaired in the explicit discrimination of both, emotional words and of emotional facial information that was displayed solely in human eyes. Additionally, largely preserved implicit emotional processing of this stimulus material was found; with - however - specific altered processing for the emotions disgust and happiness.

In the present study I thus assessed the impact of STN-DBS on implicit and explicit processing of emotional words and facial eye cues. I tested patients with an affective priming paradigm and an explicit emotion discrimination task under STN-DBS ON and OFF for the emotions fear, disgust, happiness and a neutral condition. I expect unaffected implicit processing by DBS, but altered behavioral results in explicit emotional processing during STN- stimulation. Furthermore, based on former data (Wagenbreth et al., 2016), I expect more pronounced DBS associated alterations of the emotions disgust and happiness.

6.2 Methods

Participants

14 PD patients with DBS of the STN (mean age: 61.9 ± 11.46 years, 4 female; 12 right-handed) were recruited from the Departments of Neurology and Stereotactic Neurosurgery at the University of Magdeburg, Germany, and the diagnosis of PD was confirmed by a neurologist specialized in movement disorders. Each patient had been treated with STN-DBS for at least 3 months (mean duration since surgery: 20.86 months [range 3-77 months]). All patients were taking supplementary dopaminergic medications in conjunction with DBS and were tested during the ON state of their medication cycle. All patients had chosen DBS surgery because their medications were no longer providing optimal control over their motor symptoms (see *Table 7*).

Electrodes were placed bilaterally in the STN of all patients. The surgical procedure for STN DBS utilized standard stereotactic techniques with microelectrode recordings for electrophysiological localization and has been described previously (Elias et al., 2007). Briefly, macroelectrodes (Medtronic Model 3389) consisting of four platinum–iridium cylindrical surfaces, each with diameter 1.27 mm, length 1.5 mm, and edge-to-edge separation of 0.5 mm, were guided into the STN using MRI-guided stereotaxy and intraoperative microelectrode recordings. The planned coordinates for macroelectrode placement was based on direct visualization of the STN on T2-weighted magnetic resonance images. Final electrode position was based on microelectrode recordings and confirmed intraoperatively with macrostimulation after implantation of the DBS electrode. Selection of final bipolar contacts and stimulation settings were determined on an individual basis to optimize control over clinically manifested motor symptoms.

Patients were excluded from the study if they had a history of neurological condition (others than PD), untreated or unstable mood disorder, bipolar affective disorder, schizophrenia or other psychiatric condition known to compromise executive cognitive functioning, or an untreated or unstable medical condition known to interfere with cognitive functioning (e.g. diabetes, pulmonary disease etc.). All participants had normal or corrected-to-normal vision. Prior to participating in the study, they all provided informed consent. The study was approved by the local

University´s ethics committee and was conducted in accordance with the Declaration of Helsinki.

Experimental procedure

PD patients completed two counterbalanced sessions of the task, one with DBS being ON and one with DBS switched OFF. A break of 45 minutes was included between both sessions before resuming the task. This ensured that motor symptoms had largely subsided after inducing stimulation and that the increase in motor symptoms had reasonably stabilized after terminating stimulation (Hristova et al., 2000; Lopiano et al., 2003).

Table 7. Demographic and clinical characteristics of patients

Patient #	Gender	Age	Disease duration (years)	Time since surgery (months)	LED (mg)	UPDRS-III ON	UPDRS-III OFF	DBS contacts (l/r)	DBS voltage (V), frequency (Hz), pulse width (μs) left/right
1	female	74	16	3	225	16	38	1- G+ / 10- G+	2,5 V, 130 Hz, 60 μs / 2,0 V; 130 Hz, 60 μs
2	female	59	13	4	500		20	2- 3- G+ / 10- 9+	2,8 V, 60 Hz, 210 μs / 1,5 V, 60 Hz, 210 μs
3	male	67	18	77	630	9		3- G+ / 4- 5- 6+	4,8 V, 130 Hz, 60 μs / 3,4 V, 130 Hz, 60 μs
4	male	65	16	15	325	18	32	G+ 0- / 8- 9- G+	2,7 V, 150 Hz, 60 μs / 3,1 V; 150 Hz, 60 μs
5	female	71	20	7	350	23	38	1-2-G+ / 10-G+	1,3 V, 130 Hz, 60 μs / 1,5 V, 130 Hz, 60 μs
6	male	61	10	16	850	12	32	2- G+ / 10- G+	3,6 V, 110 Hz, 90 μs / 3,4 V, 110 Hz, 90 μs
7	female	66	11	77	200	16	27	1-G+ / 6-G+	2,0 V, 190 Hz, 60 μs / 2,5 V, 190 Hz, 60 μs
8	male	63	10	4	200	4	19	2- G+ / 10- G+	3,1 V, 130 Hz, 90 μs / 3,1 V, 130 Hz, 90 μs
9	male	36	6	14	0	13	38	2- G+ / 10- G+	2,5 V, 200 Hz, 90 μs / 2,7 V, 200 Hz, 90 μs
10	male	53	10	54	385	15	29	1- 2+ / 9- 11+	2,5 V, 180 Hz, 60 μs / 4,4 V, 180 Hz, 60 μs
11	male	74	13	8	800	22		1- G+ / 5- 6- G+	4,5 V, 130 Hz, 60 μs / 5,0 V, 130 Hz, 60 μs
12	male	41	7	6	350	19	32	2- G+ / 8- 10- G+	2,0 V, 130 Hz, 60 μs / 2,1 V, 130 Hz, 60 μs
13	male	66	8	3	600	11	26	0- G+ / 8- G+	1,5 V, 130 Hz, 60 μs / 1,5 V, 130 Hz, 60 μs
14	male	70	6	4	0	17	24	1- 2 + / 9- 10 +	3,5 V, 130 Hz, 60 μs / 3,5 V, 130 Hz, 60 μs

Material

For the implicit LDT task, words as target stimuli were extracted from the "BAWL-R" (Võ et al., 2009) and from the "DENN-BAWL" (Briesemeister et al., 2011b).

Facial regions around the eyes extracted from the stimulus set "60 Faces Test" developed by Ekman & Friesen (1976) were used as emotional primes. A detailed description of stimulus selection and preparation can be found in Section 4.2, (Project C, Study 1), at pages 57/58.

Task

The experiment was generated and carried out with Presentation (Neurobehavioral Systems, Inc.). Patients were seated in front of a computer and looked at a fixation cross in the middle of the screen.

Implicit. The detailed description of the implicit task can be found in Section 4.2., (Project C, Study 1), at page 59.

Explicit. The detailed description of the explicit task can be found in Section 5.2., (Project C, Study 2), at page 75. *Figure 14* (cf. page 76) shows the experimental setting for the implicit and explicit task.

Statistical analysis

I assessed RT and RA for all four emotions. For the implicit emotional processing, repeated-measures ANOVAs on RT and RA with the within-subjects factors *valence* of the target word (fear/ disgust/ happiness/ neutral), *congruence* between prime and target (congruent/ incongruent) and *DBS* (DBS ON/ OFF) were conducted.

For the explicit emotional processing, a repeated-measures ANOVA with the within-subjects factors *valence* of the target word (fear/ disgust/ happiness/ neutral), *condition* of the stimulus (words/ faces) and *DBS* (ON/OFF) was applied.

6.3 Results

Implicit emotional processing

A repeated-measures ANOVA on RT showed a significant ME of the factor *valence* [F(3,39)=7.61; p<0.001] which was driven by longest RT for the emotional category disgust (M=1233.98 ± 356.49ms) and shortest RT for happiness (M=1066.76 ± 283,62ms), (see *Figure 18*).

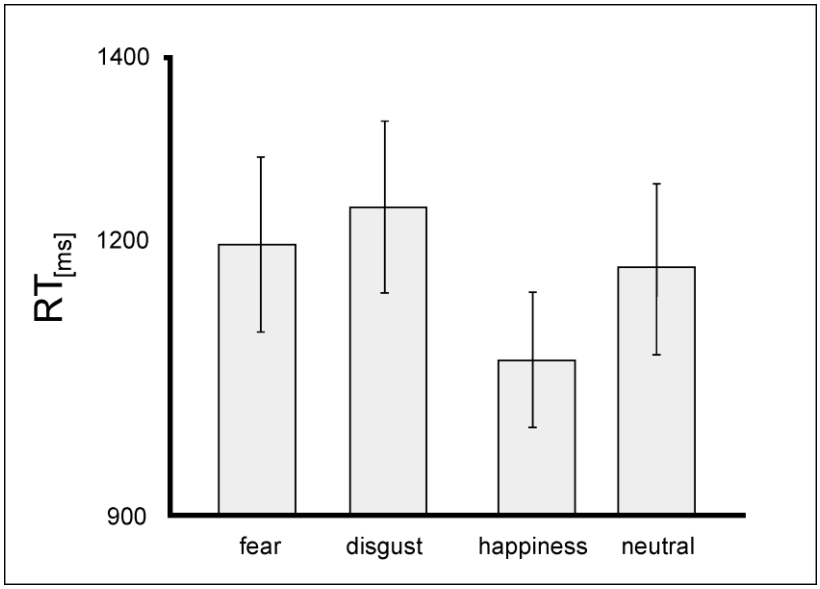

Figure 18. Mean RT values (in ms) for performance in the implicit task for patients. Error bars show SE.

Following my a priori hypothesis, subsequent ANOVAs with the factors *congruence* between prime and target (congruent/ incongruent) and *DBS* (DBS ON/ OFF) were conducted for disgust and happiness separately. Analysis revealed no interactions for happiness, but a significant trend for an interaction of the factors *congruence x DBS* for disgust [F(1,13)=4.19; p=0.06] (see *Figure 19A*). Patients answered incongruently primed disgust-connoted words significantly slower under DBS of the STN (ON vs. OFF: T(13) =2.3; p=0.039), (see *Figure 19A*). Detailed analysis which was conducted analogously to previous investigations (Wagenbreth et al., 2016) showed that DBS particularly slowed down RT for happy-disgust pairings (ON vs.

OFF: T(13)=2.06; p=0.06) and neutral-disgust pairings (T(13)=3.05; p=0.009) (see *Figure 19B*).

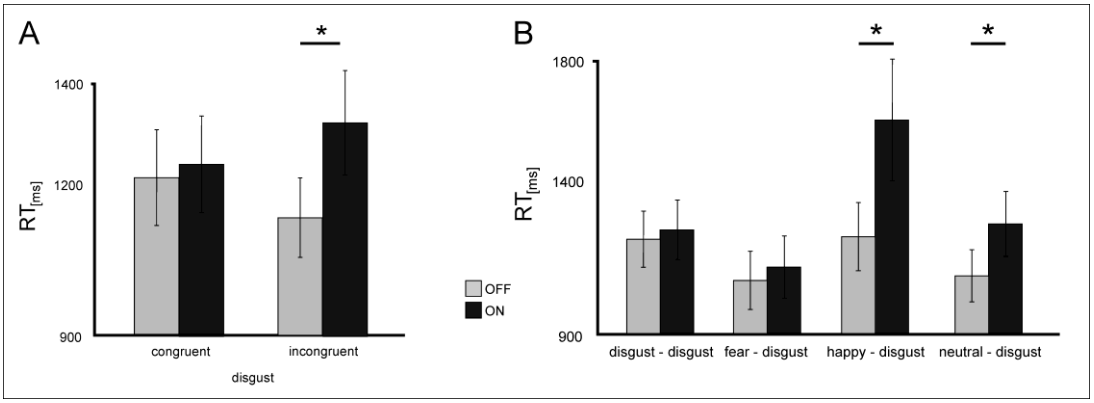

Figure 19. A) Mean RT values (in ms) for congruent and incongruent disgust-connoted stimuli in the implicit task for PD patients under DBS (light grey) and when DBS is switched OFF (dark grey). B) Mean RT values for disgust-connoted prime-target pairs in the implicit task for patients under DBS (light grey) and when DBS is switched OFF (dark grey). Error bars show SE. Significant differences are labeled with (*).

A repeated-measures ANOVA on RA revealed a significant ME of the factor *valence* [F(3,39)=6.44; p=0.001] only, which was driven by significantly more errors for disgust. RA rate for disgust was lowest compared to all other emotional categories (M=79.46 ± 20.2%). Subsequent separate ANOVAs for disgust and happiness revealed neither significant MEs nor interactions.

Summary implicit task

Performance in the implicit task revealed a general valence effect driven by longest RT and more errors for disgust targets. DBS slowed the processing of incongruently positively or neutrally primed disgust-connoted target words, specifically for positively or neutrally primes.

Explicit emotional processing

A repeated-measures ANOVA on RT revealed a significant ME of the factor *valence* [F(3,39)=6.24; p=0.001] with significantly longer RT for disgust-related stimulus material and a significant ME of the factor *condition* [F(1,13)=14.23; p=0.002] showing that answers for words were generally faster than for eyes (see *Figure 20*).

Following my a priori hypothesis, subsequent ANOVAs with the factors *congruence* between prime and target (congruent/ incongruent) and *DBS* (DBS ON/ OFF) were conducted for disgust and happiness separately. Analysis confirmed the ME for *condition* (disgust [F(1,13)=10.2; p=0.007], happiness [F(1,13)=7.25; p=0.018]), and further revealed a significant *condition x DBS* interaction for happy stimuli [F(1,13)=5.97; p=0.03]. Thus, while for all emotions words were answered faster than eyes, DBS facilitated happy words evaluation and interfered with the processing of happy eyes.

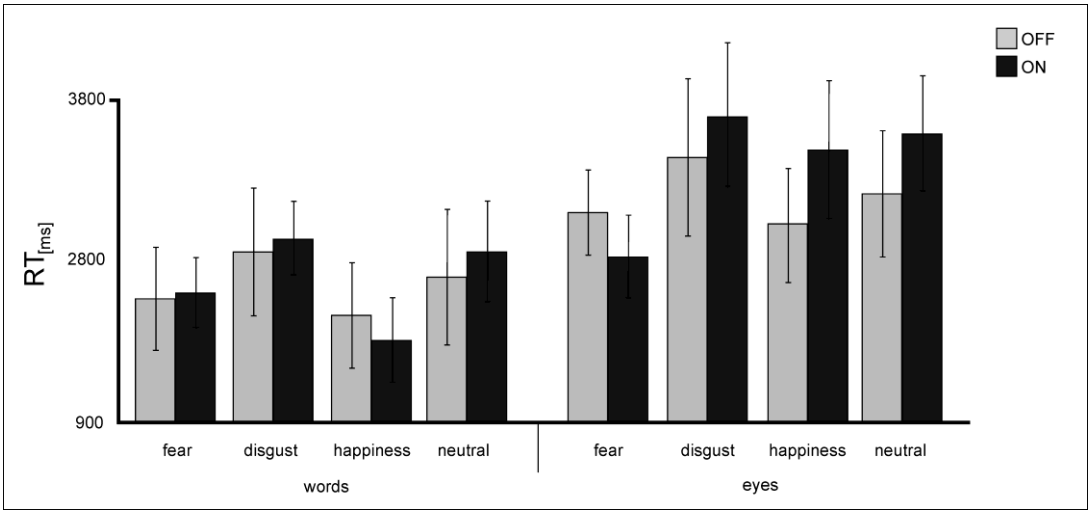

Figure 20. Mean RT values (in ms) of words and eyes for performance in the explicit task for patients under DBS (light grey) and when DBS is switched OFF (dark grey). Error bars show SE.

A repeated-measures ANOVA on RA revealed a significant ME of the factor *valence* [F(3,39)=8.48; p<0.001] due to decreased RA rates for the emotional category disgust and a significant ME of the factor *condition* [F(1,13)=25.91; p<0.001]

showing that eyes generally elicited more errors than words. Analysis also revealed a significant ME of the factor *DBS* [F(1,13)=4.84; p=0.04] demonstrating a general decrease in response accuracies under STN-DBS [ON: M=67.11 ± 17.29; OFF: M=70.05 ± 15.22]. Furthermore, results showed a significant *valence x condition* interaction [F(3,39)=4.01; p=0.014], indicating higher RA rates for words than for eyes (see *Figure 21*).

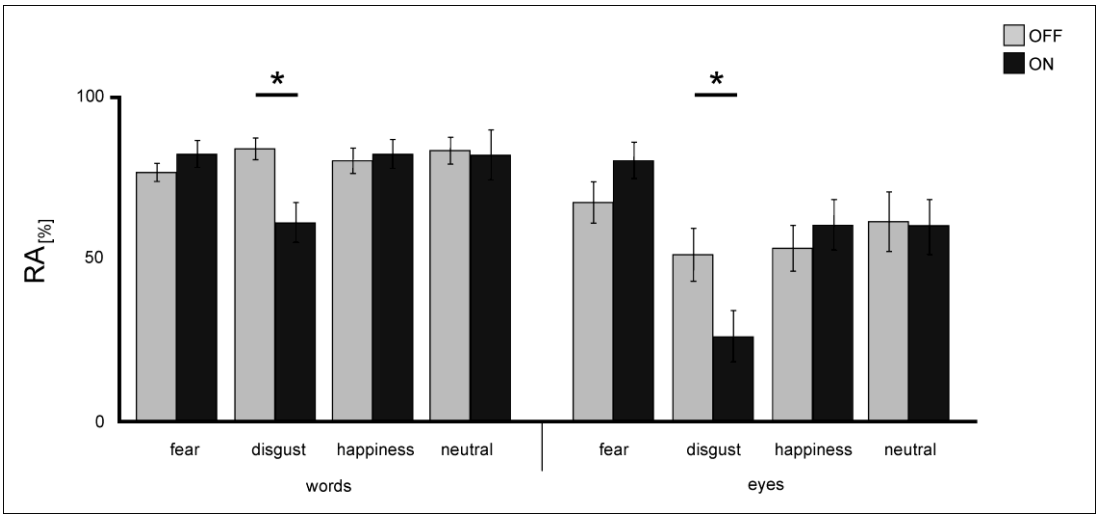

Figure 21. Mean RA values (in %) of words and eyes for performance in the explicit task for patients under DBS (light grey) and when DBS is switched OFF (dark grey). Error bars show SE. Significant differences are labeled with (*).

Importantly, analysis also revealed a significant *valence x DBS* interaction [F(3,39)=6.95; p=0.001]: independent from the stimulus condition, DBS of the STN differentially influenced RA rates for selected emotions (see *Figure 22*). STN-DBS ON compared to OFF significantly worsened RA rates for disgust-connoted stimulus material (T(13)=4.82; p<0.001) and, in contrast, improved RA rates for fear stimuli (T(13)=2.44; p=0.03).

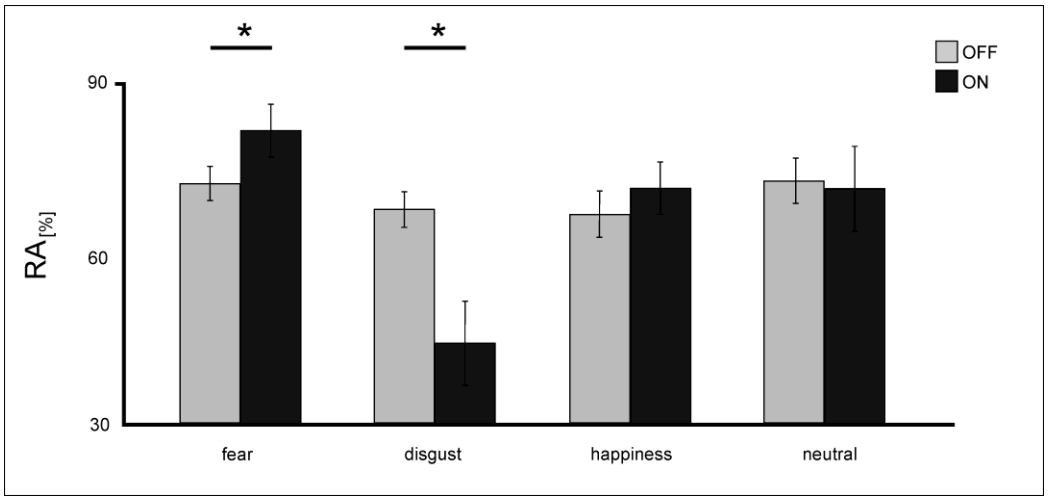

Figure 22. Mean RA values (in %) for explicit evaluation of emotional stimuli for patients under DBS (light grey) and when DBS is switched OFF (dark grey). Error bars show SE. Significant differences are labeled with (*).

Summary explicit task

Irrespective of DBS mode, patients showed prolonged RTs and highest ER for the discrimination of disgust stimulus material (ME of valence). Furthermore, words were generally answered faster than eyes, and eyes elicited more rating errors than words (ME of condition). Finally, DBS decreased RA rates for emotional ratings (ME of DBS). Importantly, DBS selectively diminished explicit processing of the emotion disgust, but had an ameliorating effect on discriminating fear stimuli (valence x DBS interaction).

6.4 Discussion

In this study, STN-DBS influenced implicit and explicit emotion processing of primed semantic and facial stimuli in PD patients. Depending on the valence of the emotional stimuli and the task condition, patients benefitted or suffered loss from STN stimulation. I observed a general deterioration for disgust-connoted material under STN-DBS, but also stimuli-dependent improvement in the explicit processing of fear stimulus material. Thus, STN-DBS did not generally manipulate emotion

processing but did selectively interpose according to the valence of the stimuli. Moreover, the observed performance differences under DBS ON when compared to OFF rather apply to RA, although considerable effects of DBS on RT were visible. STN-DBS had no global influence on the speed of responding, since patients did not generally answer faster or slower under stimulation. Instead, DBS selectively slowed processing of disgust stimuli.

In addition, I found considerable poorer performance in the perception of disgust for both, implicit and explicit emotion processing, and this effect even worsened under DBS. Generally, this finding is in good agreement with recent studies reporting diminished disgust processing under DBS using pictures of whole faces or other stimulus modalities (Aiello et al., 2014; Mondillon et al., 2012; Vicente et al., 2009). I can broaden the state of literature by investigating the influence of STN-DBS on emotion recognition out of eyes only. Aiello et al. (2014) found diminished disgust discrimination abilities under DBS for facial expressions and emotional prosodic stimuli in PD patients, but emphasized that impaired disgust recognition was prominent also before DBS implant in patients. Impaired processing of disgust thus is related to the neurodegenerative disease itself rather than just to the impact of STN-DBS. Stimulation is not capable to reduce or even eliminate this disgust-related deficit, even when these disgust-associated stimuli are primed with valence-congruent or –incongruent cues. In the present study, I found an inverse priming effect for incongruently primed disgust target words when stimulation was OFF (implicit task). This effect is displayed in terms of shorter RT for these incongruent trials. There are different explanations for the processing advantage of incongruently primed stimuli, see Wagenbreth et al. (2014) for a detailed review. DBS neutralized this inverse priming effect by slowing RT for disgust target words, which again emphasizes the deteriorating effect DBS has on disgust perception.

Disgust is an emotion clearly hard to process in PD patients, irrespective of DBS mode and even independent of the stimulus extent. Several studies support the special role of disgust (Sprengelmeyer et al., 2003; Borg et al., 2012; Phillips et al., 1997; Baggio et al., 2012), indicating it as a negative but nonetheless non-threatening emotion in social contexts. Moreover, the emotion disgust is predominantly affected by the culture a society lives with and is dependent on what people perceive as "disgusting". A possible contributing and discriminatory factor to my experimental

set-up (in which I only use eyes as facial stimuli) might be that disgust – as well as happiness – is mainly and better processed by seeing the mouth of a face, rather than the eyes (Calder et al., 2000; Leppänen & Hietanen, 2007).

This might also be a contributing factor to explain my a priori expected, but however missing significant effects of DBS on happiness processing. I did not find an influence of stimulation on implicit processing, and only marginal interfering of STN stimulation on explicit evaluation of happy words and eyes. Generally, a valence effect for happy stimuli is known, with shorter RT and better RA for positive associated (happiness-connoted) stimuli (Briesemeister et al., 2011a; Kissler & Koessler, 2011). In accordance, Ibarretxe-Bilbao et al. (2009) found a ceiling effect for the recognition of happiness stimuli both for PD patients and for healthy participants. Hence, the processing of happy stimuli is per se easier when compared to negative stimuli (e.g. disgust) and patients might have generally profited from this effect, irrespective of DBS mode.

Functional neuroimaging studies investigating the neural basis of emotion recognition showed the involvement of the amygdala in processing fear (Phillips et al., 1997; 1998; Whalen et al., 1998). For example, patients with bilateral amygdala damage are relatively inaccurate at recognizing fear from a face (Adolphs et al., 1994), and a large contributor to this deficit may be a lack of attention to the eye region of the face. A functional network linking the amygdala and both the OFC and anterior cingular cortex during the processing of fearful expressions was suggested, with activation of the inferior prefrontal cortex (Hariri et al., 2003; Marinkovic et al., 2000). Due to basal ganglia-thalamocortical circuitries, I assume STN-DBS to have influence on the modulation of the amygdala and suggest a relationship between amygdala functioning and altered fear emotion processing observed in PD patients with STN-DBS. Accordingly, I observed a significant trend for RA improvement of fear words and eyes in the explicit task under stimulation. This is contrasting to previous studies reporting reduced fear recognition in stimulated PD patients (Péron et al., 2010; Biseul et al., 2005; Le Jeune et al., 2008), and to other reports showing no effect of STN-DBS on fear processing (McIntosh et al., 2015; Albuquerque et al., 2014).

In this context and as a possible explanation, modifications to the non-motor basal ganglia-thalamocortical circuitry and to the emotional functions of the OFC and amygdala through DBS and L-Dopa medication have been proposed. The interaction between L-Dopa and STN-DBS plays a crucial role for patients, since in most cases dopaminergic medication intake is continued despite DBS implant in patients. Actually, in the presented PD patient sample, only two out of fourteen patients did not receive supplementary dopaminergic medication to STN-DBS (see *Table 7*). L-Dopa could overdose the mesolimbic projections towards the amygdala and OFC and thus lead to altered amygdala activation in response to emotion perception, for instance of fear (Aiello et al., 2014; Vicente et al., 2009; Delaveau et al., 2009). DBS would compensate for this over-activation by decreasing OFC activity and thereby restoring the necessary OFC-amygdala interaction (Mondillon et al., 2012). L-Dopa would compensate for the decreasing DBS-effect through its respective effects on the OFC and amygdala which may explain the fear recognition improvement when both therapeutic measures are "ON".

My results reveal a greater impact of DBS on explicit rather than on implicit processing. Investigations of DBS outcome on implicit emotion processing are rare. To my knowledge, only Castner et al. (2007) measured the influence of DBS on implicit emotional processing in terms of semantic and affective priming in PD patients, but used words as stimulus material, not faces. The authors reported preserved automatic lexical-semantic and emotional processing in PD patients with STN-DBS, but no direct influence of DBS on implicit processing was detected, which is mostly likewise to my results. Due to preserved priming effects for short stimulus onset asynchronies in PD patients, irrespective of STN-DBS conditions, Castner and colleagues concluded that the automatic activation of emotional evaluations is unimpaired in PD, which would be due to the functioning of basal ganglia-thalamocortical circuitry, linking structures important for facial emotion recognition. The disruption of these loops through neurodegenerative processes is thought to contribute to the accompanying cognitive decline in PD, including impaired emotional processing abilities (Owen, 2004). Since implicit verbal processing in PD is intact even under STN-DBS, it can be concluded that the basal ganglia-thalamocortical circuits are likely not to be involved in the automatic activation of emotion evaluations. I can expand these findings for nonverbal

circumscribed facial stimulus material. Moreover, I assume that implicit emotional processing is still intact in PD since it requires no cognitive demands as it is the case in conscious explicit discrimination of emotions. Basal ganglia-thalamocortical activation would be necessary if cognitive-driven decisions are requested. Since the effect of STN-DBS was more pronounced on explicit rather than on implicit emotion processing in the present study, I can confirm this assumption.

Methodological differences (e.g. medication states, early vs. late PD stages of the patient samples, different times since surgery etc.) might have contributed to the observed differences between my and recent studies. However, I would like to stress the selective influence STN-DBS can have on emotion discrimination and the importance to differentiate between implicit and explicit emotion processing. Future studies investigating the impact of DBS on emotion discrimination out of single facial regions might help to shed light on the efficacy of STN stimulation in emotion perception.

The reported findings have to be regarded under the following possibly constraining aspects. First, I tested patients under supplementary medication which might have influenced the results (Cools, 2006). However, measures with and without DBS were applied under the same medications states, so results for both conditions should be comparable. Second, pre-surgical testing of emotion recognition would have been favorable to directly draw comparisons over time and surgery. My study provides information of a rather small sample size with fewer women than men. In future studies, a gender- and age-matched patient sample would be recommended to further assess differences in emotion performance after DBS.

Conclusions

In sum, this is the first study to investigate influences of STN-DBS on implicit and explicit emotion processing in patients with PD. DBS affected explicit emotional processing more than implicit processing and had a more pronounced effect on RA than on RT. While STN stimulation generally impeded the processing of disgust-connoted stimuli, I found an ameliorating effect on RA rate in the explicit evaluation of fear stimuli.

7. General Discussion

Main findings of each study

STN-DBS is established as standard method in the treatment of motor symptoms in PD, but is always associated with concomitant influence on non-motor functioning. Possible side effects have been consistently researched in former studies. The present thesis aimed at investigating the outcome of STN-DBS in different cognitive-affective domains of PD patients.

Precisely, I assessed STN-DBS-induced changes on the cognitive and emotional level in PD patients. In a sum of five studies (three testing DBS-treated patients and two pre-studies conducted with non-stimulated PD patients and healthy participants), I collected behavioral data which can be summarized as follows.

In the first project (Chapter 2), I investigated how STN-DBS affects the motivated regulation of action control in PD patients by applying a go-nogo paradigm that decouples action and valence. STN-DBS is known to influence the flexibility of instrumental behavior in the face of a motivational outcome. Yet, flexible behavior underlies so-called “Pavlovian congruencies” that favor actions leading to rewards and inhibit actions that lead to losses or punishments. I tested whether DBS of the STN influences the ability of PD patients to act for anticipated reward or loss, or whether DBS improves action execution independent of motivational valence. Results show that modulation of the STN by stimulation improves action execution specifically when rewards are anticipated (Hypothesis A confirmed). STN-DBS hence establishes a reliable congruency between action and reward ("Pavlovian congruency") by enhancing the interaction of action and valence anticipation in a way that it was considerably stronger when compared to no stimulation (DBS OFF). Stimulation of the STN thus clearly has the potential to influence the motivational selection of actions under anticipation of valence of the possible consequences (i.e. rewards vs. punishments) in patients. Moreover, the selective effect of STN-DBS on the “go for reward” condition rules out a general increase in response impulsivity but emphasizes a valence-dependent impact of STN stimulation.

In a second project (Chapter 3), I was interested in the effects of stimulation on perceptual decision-making. The STN is said to send global "nogo" signals to evaluate different options before acting and thus to hold a central role in decision-making. Stimulation might modulate this function, leading to suboptimal impulsive behavior and to difficulties in overcoming the human behavioral tendency to stay with a default option. In this second project, it was thus investigated whether STN-DBS in patients with PD influences the behavioral status quo bias, i.e. the tendency to stay with a default option in difficult decisions. My results show that DBS of the STN improved perceptual decision-making in PD patients depending on the difficulty of decision (Hypothesis B confirmed). Results further show that for high difficulty decisions, DBS of the STN differentially interacts with the default bias depending on the initial baseline impulsivity of the patients. In impulsive patients, STN-DBS increased the default bias and patients increased their preference to stay with the default under stimulation. In less impulsive PD patients, DBS of the STN reduced the status quo bias and those patients more often overcame suboptimal acceptance of the default choice option. Hence, STN-DBS selectively affected the tendency to stick with the default option on difficult decisions, and promoted increased decision accuracy. Hence, stimulation is able to ameliorate decision-making in patients who experience uncertainty, impulsivity and maybe also paternalism in daily life due to PD-inherent impairments of executive functioning.

Finally, I aimed at investigating how STN-DBS influences emotional processing in PD patients. Emotional perception refers to automatic implicit and conscious explicit processing of emotional stimuli. While explicit emotional processing was proposed to be influenced by stimulation of the STN and its subcortical connections, emotional assessment per se (i.e. the implicit emotional processing) would not be affected by stimulation (Geday et al., 2006). STN-DBS is thus suggested to have different consequences for implicit and explicit processing, but this has not been investigated for single facial stimuli yet.

For this purpose, I conducted three different studies for gathering behavioral data, using an affective priming paradigm with a LDT for implicit and explicit evaluation of emotional semantic and facial stimuli. In the first study that was carried out with

healthy participants (Chapter 4), I could show that even reduced emotional information, which was provided solely in eye regions displaying mental states, can trigger affective priming (Hypothesis C1 confirmed). Despite a general processing advantage of happy stimuli, I found inverse priming effects in terms of an advantageous processing of incongruent prime-target trials: For the emotional categories fear and happiness, RT were shorter for incongruent than for congruent trials. I could demonstrate that even incomplete facial information induce implicit emotional responses and - in consequence - influence ensuing explicit decisions.

Subsequently, I tested non-stimulated PD patients using this paradigm (Chapter 5). I found that implicit emotional processing was largely unaffected in patients, however with specific altered processing of stimuli connoted with disgust and happiness. Explicit emotional processing was considerably impaired for semantic and especially for facial stimulus material (Hypothesis C2 confirmed). This finding has relevant implications for the frequently observed poor ToM abilities in PD patients, since these might be based on deficient explicit emotional processing, despite the preserved ability to implicitly infer other people´s mind and feelings.

Eventually, in a sample of PD patients treated with STN-DBS (Chapter 6), stimulation elicited greater influence on explicit than on implicit processing (Hypothesis C3 confirmed), and had greater effect on RA than on RT. Here, STN stimulation worsened the processing of disgust-connoted stimuli, but had an ameliorating effect on discriminating fear stimuli. Thus, STN-DBS did not generally manipulate emotion processing but did selectively interpose according to the valence of the stimuli. This study is the first to investigate STN-DBS modulations on implicit and explicit processing of semantic and facial emotional stimuli in PD patients and thus holds a relevance in emotion processing research.

Implications

The presented results considerably reveal the influence of STN stimulation on non-motor domains in PD patients and thus contribute to the growing research focusing on side effects of subthalamic stimulation, but also suggest STN-DBS to operate valence-specific. Valence can be defined as the intrinsic attractiveness or

aversiveness of a stimulus and thus holds a special importance in the processing of rewards and punishments. The selection of actions is tied to valence in a way that humans tend to act to obtain positively valenced and to avoid negatively valenced outcomes (Guitart-Masip et al., 2014). It follows that the processing of valence may sub-serve aberrations of human behavior. The construct of valence is hence a pivotal point not only in action execution (Project A), but also in decision-making (Project B) and emotional processing (Project C).

The findings presented in this thesis suggest that that STN function is complex and variable, but that cognitive and emotional constructs like action selection or decision-making, which the STN sub-serves, are as well. With the presented studies I could demonstrate empirical support indicating that the STN processes valence, which further suggests that alterations in valence processing in the STN-associated neuronal circuits may influence action selection, reward processing, decision-making and emotional processing, alike. Hence, there is clear evidence for the involvement of the subthalamic region in cognitive and emotional processing in valence-dependent ways.

Previous research has demonstrated that the STN comprises special regions with valence- and arousal-specific neurons. 17% of the STN neurons were found to be responsive to the valence of emotional stimuli, but neurons responded differently to valence or arousal (Sieger et al., 2015; Buot et al., 2013, Brücke et al., 2007). Changes in event-related electrophysiological activity in the STN in response to positive and negative emotional stimuli have been related to valence, but not arousal (Brücke et al., 2007). Péron et al. (2017) described these electrophysiological changes to be irrespective of stimulus modality (i.e. visual or vocal stimuli) or stimulus valence. Rossi and colleagues (Rossi et al., 2015; 2017) reported that STN and GPI neuronal populations in PD patients responded for different motivational context. The authors described the neuronal encoding of multiple valence conditions, including the opportunity for reward, the threat of loss, reward receipt and the successful avoidance of loss. Interestingly, STN neurons showed a clear tendency to encode positively valenced optimal outcome, and the neuronal population responding to reward opportunity was larger than that responding to threat of loss (Rossi et al., 2017). Compared with the GPI, the STN thus more strongly encodes rewarding outcomes.

The current thesis seizes these findings of valence-specific processing in the STN by assessing distinct, but yet valence-based neuronal mechanisms associated with STN functioning. I investigated valence-related consequences of actions, of made decisions and of perceived emotional states. All presented studies capture the processing of valenced stimuli and indicate that DBS of the STN operates differently and has distinct effects, depending on the valence of the processed stimulus material. I can confirm the finding of especially reward-specific encoding within the STN with regard to action control (Project A), since particularly those actions were reinforced that involved the prospect of rewards ("go for reward"). The anticipation of reward hence improved correct action selection under STN-DBS. In contrast, the behavioral data gathered from the emotional processing studies (Project C) indicated outcome of STN-DBS on especially negative emotions (fear and disgust). The influence of STN stimulation on emotional stimuli seems to be driven by negative valence in particular. Although I could also demonstrate DBS-related impact on the processing of happy-connoted stimuli, the effect of STN stimulation on negative emotional stimuli was by far more expressive. Negatively valenced stimuli hold a certain alerting and activating function in prospect of potential danger, which is mirrored in the neuronal processing. Electrophysiologial studies targeting the STN demonstrated that all valenced stimuli evoked event related potentials, but that amplitudes were generally larger for unpleasant stimuli (Buot et al., 2013). Of course, individual factors of the investigated patients regarding DBS parameters (like voltage or pulse width) or the exact positioning of DBS electrodes within the STN also contribute to DBS outcome and to the findings of the presented studies on DBS influence on non-motor functions. It was reported that valence encoding is asymmetric in the STN, with evoked changes in neuronal activity in the ventral parts of the STN after presenting emotional stimuli (Buot et al., 2013; Eitan et al., 2013).

But not only valence of the processed stimuli is an important factor for STN-DBS effects. Also the arousal of a stimulus is of relevance in its processing, and the STN has been shown to be responsive to the stimulus´ arousal (Sieger et al., 2015). While valence implies the qualitative measure of emotions, arousal refers to the quantitative measure of emotional intensity from calm to excited. Possibly, the arousal of the stimuli used in the presented studies play a role for individual DBS outcome; however, this is a confounding variable that was not systematically tested in the

studies. But for the investigations of the emotional processing under STN-DBS (Chapter 6, with the two preceding studies in Chapters 4 and 5), the emotional stimulus words used in the experimental setting were taken from the "DENN-BAWL" (Briesemeister et al., 2011b). This is a standardized word list containing words with different emotional valence and arousal values. For the presented studies only those words were chosen as stimuli that achieved an emotional intensity score of at least 3 on a Likert-scale and hence are suggested to hold a certain emotional arousal for patients. In future studies, systematic investigations of the influence of arousal on STN-DBS outcome would be generally endorsed.

Previous research has proposed quite unsteady and heterogeneous findings concerning the influence of STN-DBS in cognitive and emotional domains in PD patients. It is difficult to constitute globally valid results, since study designs and testing procedures as well as methods occasionally differ in considerable ways. Moreover, it was recently postulated that "what is consistently reported as a group effect seems to be mainly driven by a small, but substantial subgroup of DBS-treated patients" (Foki et al., 2018; Højlund et al., 2017). Effects of treatment may be small and specific to certain individuals. Thus, results after stimulation have should be regarded with respect to inter-individual characteristics and intensities as well as to possible heterogeneous gains and losses from DBS. To face this problem, I applied DBS outcome difference parameters as well as correlations with possible confounding variables in a part of the calculations of the presented studies. By doing this, I could demonstrate the potential of DBS to operate differently in distinct behavioral ranges.

With respect to the reported findings in this thesis, I provide further insights into cognitive and emotional post-operative mechanisms and consequences of STN-DBS in PD patients, despite well-known motor improvements. The decision to undergo DBS surgery should be taken in view of possible side effects and implications after surgery. Informed consent that DBS may result in several ancillary effects on cognitive, affective and behavioral domains, is necessary and essential for each patient. The prospect of expectable motor improvements should be balanced and

traded against possible constraints on other functional levels pre-operatively, but also after surgery, depending on patients´ subjective and individual preferences and well-being. Patients should be aware that STN-DBS can involve detriments in non-motor areas of life, like impulsive behaviors or problems in recognizing negative emotions in others, as for instance disgust-connoted facial expressions. Contrastingly, simplifications in action control, reward anticipation and difficult decision-making – next to a variety of other aspects improving under stimulation – clearly count as advantages caused by STN-DBS and can lead to better independence and autonomy for patients. Appropriate examinations in advance are important and can contribute to a facilitated surgery decision in patients and their relatives.

Moreover, effects of DBS might depend on baseline characteristics of special features, and prior motor and cognitive functions are predictive for the stimulation-related performance changes in patients. The long-lasting DBS outcome should be considered in dependence from potential pre-determining factors like age, gender, early vs. late disease onset, disease duration before surgery etc. Such pre-existing factors may pre-dispose patients toward a given outcome of stimulation. These factors may have considerable impact on the effectiveness of DBS and are regarded as pre-operative predictive factors for the long-term outcome of DBS (Fukaya et al., 2017). In the presented studies, I could accordingly demonstrate that individual factors can influence DBS outcome post-operatively and can affect the behavioral results. For instance, I found the factor baseline impulsivity to be crucial in perceptual decision-making (Project B). In impulsive PD patients, DBS increased the default bias, whereas in less impulsive patients, stimulation reduced this bias. Among the limbic functions that involve the STN, impulse control disorders and impulsivity have been the most intensely studied recently, and my study on perceptual decision-making in risky options (Project B) complements this growing body of research quite well.

Certainly, further research is needed to elucidate such pre-defining factors in cognitive and emotional outcomes to ameliorate subjective well-being and post-operational care of patients after STN-DBS.

Limitations

While this thesis provides an important contribution to the current body of literature on the modulating influence of STN-DBS on cognitive and emotional domains, the studies presented here yet underlie some methodological limitations. Most of them have already been addressed in each experimental project (Chapters 2-6), but I would like to outline some further limiting aspects in conclusion.

Generally, it would have been desirable to conduct all experiments with one constant patient sample. This would have allowed to draw conclusions about individual alterations through DBS on different cognitive domains. Due to organizational and time-dependent reasons, this was not possible. General neuropsychological and psychiatric testing was performed before surgery and post-operatively at regular time intervals, but further pre-operative behavioral data of interest was not constantly assessed. This would have been advantageous to draw comparisons over the course of surgery and implantation, and to detect possible long-term developments. Further research should aim to include such measures in both pre- and post-surgical assessments. Generally, a homogeneous patient sample with respect to age, gender, disease duration etc. is recommended. These factors may all contribute to behavioral, emotional and cognitive alterations after stimulation.

Another possible constraining factor that may have interfered with the observed results is verbal deterioration. Worse semantic and phonematic verbal fluency was often reported after STN-DBS in patients. The studies in this thesis all underlie semantic instructions and execution. Particularly the experimental setting investigating implicit and explicit emotional processing (Project C) is subject to semantic understanding, processing and answering which was demanded from the patients. Verbal fluency and understanding was tested regularly during neuropsychological assessments in patients, so I can exclude general verbal detriments in patients. However, beginning changes in verbal processing after STN-DBS might still have developed undetected.

Concluding, this thesis demonstrated considerable STN-DBS influence on three different cognitive and emotional domains of human behavior and thereby contributes to the growing evidence showing impact of STN stimulation on non-motor aspects in PD patients.

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Ehrenerklärung

Ich versichere hiermit, dass ich die vorliegende Arbeit ohne zulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; verwendete fremde und eigene Quellen sind als solche kenntlich gemacht.

Ich habe insbesondere nicht wissentlich:

- Ergebnisse erfunden oder widersprüchliche Ergebnisse verschwiegen,

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Mir ist bekannt, dass Verstöße gegen das Urheberrecht Unterlassungs- und Schadensersatzansprüche des Urhebers sowie eine strafrechtliche Ahndung durch die Strafverfolgungsbehörden begründen kann.

Ich erkläre mich damit einverstanden, dass die Arbeit ggf. mit Mitteln der elektronischen Datenverarbeitung auf Plagiate überprüft werden kann.

Die Arbeit wurde bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form als Dissertation eingereicht und ist als Ganzes auch noch nicht veröffentlicht.

Bernburg, 26.02.2019

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