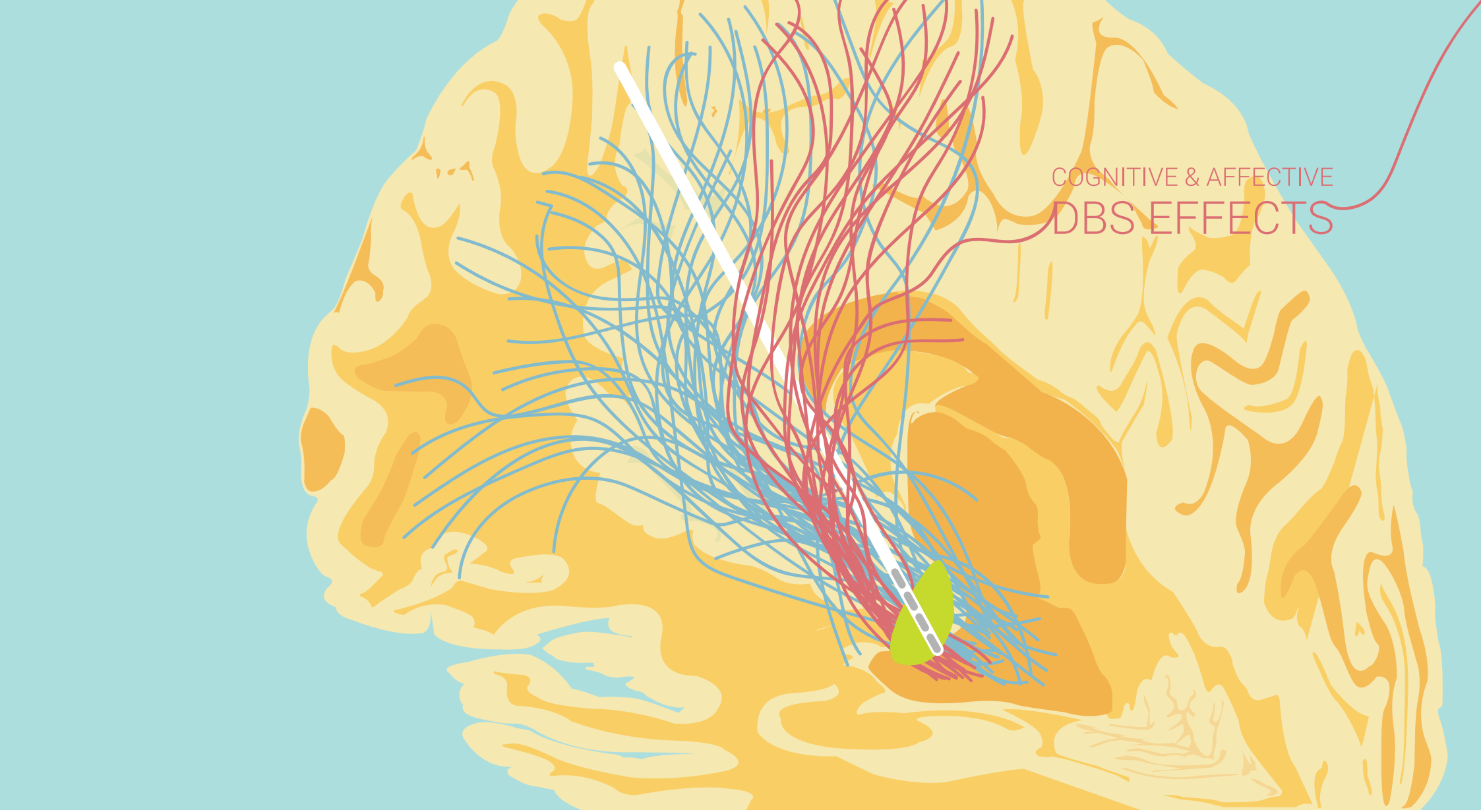

COGNITIVE & AFFECTIVE DBS EFFECTS

UNDERSTANDING THE IMPACT OF SUBTHALAMIC DEEP BRAIN STIMULATION ON COGNITIVE AND AFFECTIVE PROCESSING

Friederike Irmen

UNDERSTANDING THE IMPACT OF SUBTHALAMIC DEEP BRAIN STIMULATION ON COGNITIVE AND AFFECTIVE PROCESSING

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Vorblatt

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List of Abbreviations

ACC	Anterior Cingulate Cortex
ANOVA	Analyses of variance
BDI	Beck's Depression Inventory
BER	Berlin
CE	Certainty equivalent
CGN	Cologne
DBS	Deep brain stimulation
DiODe	Directional Orientation Detection
dlPFC	Left dorsolateral prefrontal cortex
DRN	Dorsal raphe nucleus
FEM	Finite Element Method
fMRI	functional Magnetic Resonance Imaging
GPe	External globus pallidus
GPi	Internal globus pallidus
LEDD	Levodopa Equivalent Daily Dosis
LTP	Long-term potentiation
LTD	Long-term depression
MOCA	Montreal Cognitive Assessment
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridin
MRI	Magnetic Resonance Imaging
MSN	Medium spiny neurons
PD	Parkinson's disease
QU	Queensland
rTMS	repetitive Transcranial Magnetic stimulation
SEM	Standard error of the mean
SMA	Supplementary motor area
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
SPM12	Statistical Parametric Mapping software
STN	subthalamic nucleus
STN-DBS	Subthalamic nucleus deep brain stimulation
STN-THS	Tiefe Hirnstimulation des Nucleus subthalamicus
UPDRS-III	Unified Parkinson's Disease Rating Scale-III
VTA	Volume of tissue activated

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt,

- dass ich die vorliegende Arbeit selbstständig und ohne unerlaubte Hilfe verfasst habe,
- dass ich mich nicht bereits anderwärts um einen Doktorgrad beworben habe,
- keinen Doktorgrad in dem Promotionsfach Psychologie besitze,
- und dass ich die zugrunde liegende Promotionsordnung vom 08.08.2016 kenne.

Berlin, den 25.08.2019

Friederike Irmen

List of Original Publications

Included in dissertation

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Friederike Irmen, Andreas Horn, David Meder, Wolf-Julian Neumann, Philip Plettig, Gerd-Helge Schneider, Hartwig Roman Siebner, Andrea A. Kühn (2018). Sensorimotor subthalamic stimulation restores risk-reward trade-off in Parkinson's disease. *Movement Disorders, 34*: 366-376.

Friederike Irmen*, Andreas Horn*, Philip Mosely, Alistair Perry, Jan Niklas Petry-Schmelzer, Haidar S. Dafsari, Michael Barbe, Veerle Visser-Vandewalle, Gerd-Helge Schneider, Dorothee Kübler, Gregor Wenzel, Andrea A. Kühn (2019). Left prefrontal connectivity links subthalamic stimulation with depressive symptoms. *bioRxiv, 665976. (*These authors contributed equally to this work)*

Andreas Horn, Gregor Wenzel, **Friederike Irmen,** Julius Hübl, Ningfei Li, Wolf-Julian Neumann, Patricia Krause, Georg Bohner, Michael Scheel, Andrea A. Kühn. Deep brain stimulation induced normalization of the human functional connectome in Parkinson's disease (2019). *Brain*, *awz239*.

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Further publications

Anke Ninija Karabanov, **Friederike Irmen,** Kristoffer Hougaard Madsen, Brian Numelin Haagensen, Svend Schulze, Thue Bisgaard, Hartwig Roman Siebner. Getting to grips with endoscopy - Learning endoscopic surgical skills induces bi-hemispheric plasticity of the grasping network (2019). *NeuroImage; 189*:32-44.

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Summary

As neuromodulatory treatment, subthalamic nucleus deep brain stimulation (STN-DBS) for Parkinson's disease (PD) undergoes a current paradigm shift, away from being seen as mainly a therapy to improve motor symptoms toward being a window to better understanding of nonmotor networks converging in the basal ganglia. Since the STN is a hub for the integration of cognitive and affective processes into the motor response, DBS impacts interaction of basal ganglia with motor, associative and affective brain regions. STN-DBS leads to cognitive and affective changes that either classify as improvements or disturbances of behaviour when compared to the baseline bias that PD has on nonmotor function per se.

This thesis attempted to improve the understanding of mechanisms underlying DBS effects on cognitive and affective processing by assessing nonmotor DBS-effects in understudied domains like decision-making and emotional processing and to relate the findings to computational or anatomical reconstructions of basal ganglia-cortex interactions or STN functional anatomy. To this end, five studies are presented, the results of which are complementary in understanding local and global impact of DBS on the brain and associated nonmotor behavioural changes.

Study 1 assessed impact of STN-DBS on emotional conflict processing in a perceptual decision-making task and found that DBS lead to the disability to slow down responses when cognitive control was required and at the same time to a blunting of a PD-inherent bias to process positive information more slowly than negative information. Coherently, Study 4 of this thesis compared response times in automatic movement versus movement that require cognitive control and found that DBS induced a disinhibition that was related to a disruption of cortex-STN coupling via the hyperdirect pathway. Study 2 also assessed changes in decision-making under DBS but in the domain of risk-reward trade-off decisions. Here, it was again found that a PD-specific bias, namely, to take too little risks, could be altered by STN-DBS. Specifically, when motor STN territory was stimulated, risk attitude normalized to a healthy level. This nonmotor benefit of effective STN-DBS is coherent with the results of Study 3 and 4, where impact on the STN motor territory was related to a normalization of depressive symptoms and a functional connectivity that was similar to that of healthy controls.

Together, these studies imply that DBS of the STN motor territory induces improvements in value-based decision-making, depression and functional connectivity, while causing impairments in cognitive inhibition during the recruitment of cognitive control. Electrode misplacement however can lead to behavioural disturbances through impact on nonmotor networks like the left prefrontal cortex, the connectivity to which, if disrupted by DBS, explains worsening of depression.

The results of this thesis are of high clinical value since they can aid refinement of DBS programming, inform tailored DBS therapy and help to better understand and in the future avoid DBS side effects.

Zusammenfassung

Die Tiefe Hirnstimulation des Nucleus subthalamicus (STN-THS) wird bei Morbus Parkinson (PD) zur Verbesserung der motorischen Symptome eingesetzt. Als neuromodulatorische Behandlung bietet sie jedoch auch Zugang zu verbessertem Verständnis nichtmotorischer Netzwerke in den Basalganglien. Da der STN einen Konvergenzpunkt für die Integration kognitiver und affektiver Prozesse in die motorische Reaktion darstellt, beeinflusst die THS die Interaktion der Basalganglien mit motorischen, assoziativen und affektiven Hirnregionen. STN-THS kann daher auch zu kognitiven und affektiven Veränderungen führen, die verglichen mit den krankheitsbedingten nichtmotorischen Veränderungen bei PD entweder als förderlich oder störend für das Verhalten klassifiziert werden können.

Diese Dissertation versucht, das Verständnis der Mechanismen zu verbessern, die den Effekten, die THS auf die kognitive und affektive Verarbeitung hat, zugrunde liegen. Hierzu wurden nichtmotorische THS-Effekte in Bereichen wie Entscheidungsfindung und emotionaler Verarbeitung erfasst und die Ergebnisse mit computationalen Modellen, anatomischen Rekonstruktionen von Basalganglien-Kortex-Wechselwirkungen oder der funktionellen Anatomie des STN in Beziehung gesetzt. Es werden fünf Studien vorgestellt, deren Ergebnisse zum Verständnis der lokalen und globalen Auswirkungen von THS auf das Gehirn und der damit verbundenen nichtmotorischen Verhaltensänderungen beitragen.

In Studie 1 wurde die Auswirkung von STN-THS auf die Verarbeitung emotional-perzeptiver Konflikte in einer Entscheidungsaufgabe erhoben und festgestellt, dass THS dazu führte, dass die motorischen Reaktionen nicht adäquat verlangsamt werden, wenn kognitive Kontrolle erforderlich ist. Gleichzeitig schwächte STN-THS eine PD-inhärente Tendenz ab, positive Informationen langsamer zu verarbeiten als negative Informationen. Ergänzend dazu wurden in Studie 4 dieser Dissertation Reaktionszeiten bei automatischen Bewegungen mit jenen verglichen, die kognitive Kontrolle erforderten. Hier konnte die DBS-induzierte Disinhibition in kontrollierten Bewegungen mit einer Störung der Cortex-STN-Kopplung über den hyperdirekten Pfad erklärt werden. In Studie 2 wurden auch Änderungen in der Entscheidungsfindung unter THS erhoben, jedoch wurden speziell Entscheidungen betrachtet, in denen zwischen Risiko und Belohnung abgewogen werden musste. Es zeigte sich, dass die PD-spezifische kognitive Einschränkung, in Entscheidungssituationen zu wenig Risiko einzugehen, durch STN-THS ausgeglichen werden konnte. Interessanterweise war der Effekt abhängig von der Elektrodenposition: Wenn der motorische Teil des STN stimuliert wurde, normalisierte sich das Risikoverhalten auf ein gesundes Niveau. Dieser nichtmotorische Nutzen einer motorisch wirksamen STN-THS steht in Einklang mit den Studien 3 und 4, in denen Stimulation des motorischen STN zu einer Normalisierung der depressiven Symptomatik und der funktionellen Konnektivität führte. Zusammengenommen deuten die Ergebnisse der Studien dieser Dissertation darauf hin, dass die THS des motorischen STN zusätzlich zu ihrem motorischen Effekt auch positive Auswirkungen auf nichtmotorische Fähigkeiten haben kann: Sie führt zu

einer Normalisierung von wertbasierten Entscheidungen, depressiver Symptomatik und funktioneller Konnektivität. Gleichzeitig vermindert die THS jedoch eine Inhibition der motorischen Antwort in Reaktionszeitaufgaben, die kognitive Kontrolle bedürfen. Zudem kann eine Fehlplatzierung der THS-Elektroden dazu führen, dass nichtmotorische Netzwerke beeinträchtigt werden. Beispielsweise zeigt Studie 3, dass Stimulation von Fasern, die mit dem linken präfrontalen Kortex verbunden sind, zu einer Verschlechterung der depressiven Symptomatik bei PD Patienten führen können.

Die Ergebnisse dieser Dissertation haben einen großen klinischen Wert, da sie zu einer Verfeinerung der THS-Programmierung verhelfen und den Weg zu einer individualisierten THS-Therapie, die basierend auf Anatomie und patientenspezifischer Symptomatik eingestellt wird, aufzeigen. Außerdem leisten sie einen Beitrag zum Verständnis der Hintergründe kognitiver und affektiver THS-Effekte und dadurch zur potenziellen Vermeidung von THS-induzierten Nebenwirkungen.

1. Theoretical and empirical foundations

We used to think of motor and motivational processing in the brain as being segregated. In the past two decades however, increasing understanding of subcortical structures and their interaction with the cortex have led to a paradigm shift. On the basis of current knowledge, substrates like the basal ganglia that have traditionally been associated with motor control, are now also assigned a role in cognitive and affective processing. There is not only evidence of parallel functional motor, associative and limbic cortico-basal ganglia pathways but at the same time evidence for interactions, overlap and convergence in these loops. Relatedly, diseases of the basal ganglia often cause a combination of movement, emotional and cognitive symptoms; and hence, therapeutic interventions like deep brain stimulation (DBS) affect all aspects of basal ganglia functioning including cognitive and affective processing. Importantly, DBS offers a rare opportunity to study brain structures integrating motor and motivational processing, the understanding of which finds translational application in the treatment of basal ganglia diseases.

1.1. Subthalamic stimulation for Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting 6.1m individuals worldwide in 2016, resulting in a prevalence of 1.7 % in men and 1.2 % in women (Dorsey et al., 2018). It is associated with a progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) (Ehringer & Hornykiewicz, 1960), which supplies dopamine to the basal ganglia, a complex set of deep brain nuclei primarily engaged in motor control with further roles in learning, executive functions and emotion processing. The biggest risk factor for PD is age, and prevalence peaks at the ages 85 to 89. The disease manifests with motor symptoms including rigidity, bradykinesia, tremor and postural instability as well as in nonmotor symptoms affecting autonomic function, sleep, apathy, cognition and mood (Chaudhuri & Schapira, 2009). Patients motor symptoms are usually first treated with dopaminergic replacement therapy via the dopaminergic precursor Levodopa or dopamine agonists. As the disease progresses, advancing dopaminergic denervation may lead to reduced efficacy of dopaminergic drugs and therefore to ON-OFF-fluctuations and dyskinesias (Jankovic, 2005).

Deep brain stimulation of the subthalamic nucleus (STN-DBS) has become a guideline therapy for the treatment of motor symptoms in patients with advanced PD and severe On-Off-fluctuations. It was the discovery of Bergman, Wichman and DeLong in 1990 that demonstrated that lesions of the STN alleviated experimental parkinsonism in the MPTP monkey model of PD

(Bergman, Wichmann, & DeLong, 1990), that paved the way to stimulate that nucleus with high frequency electric current in humans. Nowadays, over 150,000 patients worldwide have been treated with DBS (Hariz, 2017), in Berlin approximately 50 patients are newly treated each year (2019). The treatment is achieved by stereotactic implantation of deep brain electrodes (Figure 1A,B) into the target structure, which in PD is commonly the STN (Figure 1C). During the surgery, microelectrode recordings and stimulation tests are conducted while the patient is awake to assure the correct placement of electrodes which is further confirmed by postoperative imaging. In the following, the stimulator is implanted in the patient's torso, sending high-frequency stimulation to the deep brain electrodes via subcutaneous cables (Figure 1A). The stimulation parameters are adjusted within three to 12 months post-surgery, achieving the optimal stimulation profile for the individual patient, maximizing symptom control and minimizing side effects. For the purpose of research, the effects of STN-DBS and therefore the underlying cortico-basal ganglia network can be studied for example by switching the device on and off (hereafter referred to as ON DBS and OFF DBS) to measure effects on cognitive and affective processing. Furthermore, pre- and postoperative behavioural and cognitive states can be compared offering insights into longer-term network modulations. Patients treated with STN-DBS thus provide a unique window to study the role of the basal ganglia in cognition and affect.

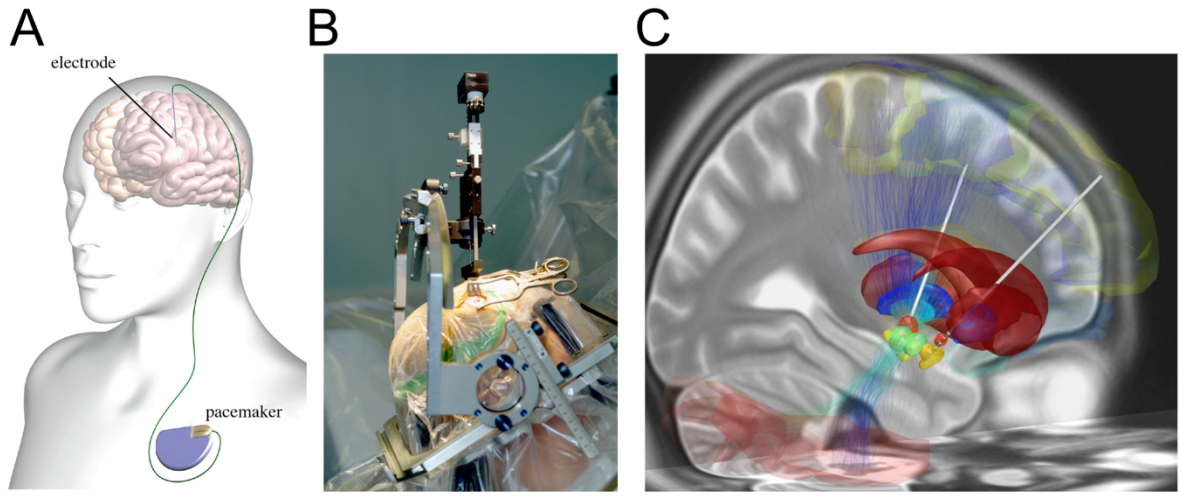

Figure 1. Overview on deep brain stimulation. A) Deep brain stimulation setup: The electrode is placed in the brain and connected to a neurostimulator permanently placed under the skin of the chest (Source: Shamir R, Noecker A and McIntyre C (2014) Deep Brain Stimulation. Front Young Minds. 2:12); B) Insertion of an electrode during stereotactic surgery for deep brain stimulation (Source: https://commons.wikimedia.org/wiki/File: Parkinson_surgery.jpg; Uploaded by Thomasbg); C) Bihemispheric DBS electrodes that have been surgically placed into the most common target structure for treatment of Parkinson's Disease, the subthalamic nucleus (orange). Other subcortical structures include the red nucleus (green), the substantia nigra (yellow), the internal (cyan) and external (blue) pallidum and the striatum (red). A stimulation volume is modeled by applying 2V (at 1000Ω impedance) to the second-uppermost contact of the left electrode. Structural fibertracts traversing through this volume are visualized and cortical regions that are connected with the stimulation volume are selected from an automatic anatomical labeling atlas and visualized (www.lead-dbs.org) (Source: Andreashorn - CC BY-SA 4.0, https://commons.wikimedia.org)

1.2. Nonmotor effects of subthalamic stimulation

Despite the great therapeutic effect of STN-DBS, a number of undesirable side effects on cognition, behaviour and emotion have been noted that typically occur within the first postoperative months during the adjustment of stimulation and medication (Le Jeune et al., 2010; Maillet et al., 2016; Mallet et al., 2007; Péron, Frühholz, Vérin, & Grandjean, 2013; Volkmann, Daniels, & Witt, 2010; Voon et al., 2008; Witt et al., 2008). In particular, STN-DBS has been frequently associated with impulsivity and disinhibition (Brandt et al., 2015; Florin et al., 2013; Green et al., 2013; Hälbig et al., 2009). This manifests for example during decision-making: STN-DBS seems to interfere with response-slowing in the face of decision conflict, that is when faced with a difficult decision where an evaluation of their choice options is naturally required, PD patients with STN-DBS actually speed up their response instead of slowing it down and therefore also make more errors (Cavanagh et al., 2011; Frank, Samanta, Moustafa, & Sherman, 2007; Herz, Zavala, Bogacz, & Brown, 2016; Jahanshahi, Obeso, Baunez, Alegre, & Krack, 2015). Computational models formalizing this process predict that conflict-induced impulsive behavior under STN-DBS relates to disturbed STN inhibitory activity (Cavanagh et al., 2011; Green et al., 2013; Obeso et al., 2014) and underline the role of the STN in inhibitory executive control (Jahanshahi et al., 2000; Zavala et al., 2015).

The effects of STN-DBS also manifest in the affective domain: in some patients, STN-DBS can induce hypomania (Volkmann et al., 2010); and there are also (fewer) cases in which it can induce acute depression (Bejjani et al., 1999; Funkiewiez et al., 2006, 2003) or lead to suicide (Voon et al., 2008). This evidence is complemented by physiological data that suggests a modulation of STN activity by affective content (Brücke et al., 2007; Huebl et al., 2011; Kühn et al., 2005) thus implying a role of the STN in affective processing.

Adding to the complexity, there are large variations in the effect of STN-DBS: it can be beneficial, improving mood, anxiety and cognitive performance (Daniele et al., 2003; Ehlen, Schoenecker, Kühn, & Klostermann, 2014; Funkiewiez et al., 2003; Frank Schneider et al., 2003; Witt et al., 2008, 2004) or result in worsening of patients' cognitive-affective state (Castelli et al., 2006; Ehlen et al., 2014; Smeding et al., 2006; Voon, Kubu, Krack, Houeto, & Tröster, 2006; Welter et al., 2014; Witt et al., 2008; Xie, Meng, Xiao, Zhang, & Zhang, 2016). Reasons for this variability include varying stages of neurodegeneration, symptom-specific effects, comorbidities, premorbid personality traits, pharmacological interactions as well as stimulation parameters and electrode positioning (Volkmann et al., 2010; Witt, Daniels, & Volkmann, 2012). Of all these variables, the latter is especially interesting to research since latest development of software for DBS electrode reconstructions based on pre- and postoperative imaging (Lead-DBS, https://github.com/leaddbs/leaddbs) facilitates the estimation patient-specific stimulation effects within the anatomical surrounding.

Taken together, STN-DBS has been understood to create a new phenotype, leading to motor and cognitive-affective alterations that vary between patients. To better understand and predict these outcomes, local and global network effects of the stimulation need to be investigated.

1.3. Interaction of DBS effects with nonmotor PD symptoms

When researching the effects of STN-DBS on cognition and affect in PD patients, it is important to take disease-specific effects into consideration. For example, when regarding the effect of STN-DBS on emotional processing it has to be considered, that PD-inherent nonmotor symptoms include emotional blunting, depression and apathy (Chaudhuri & Schapira, 2009; Maillet et al., 2016) and that therefore affective processing *per se* is changed through the disease (Gray & Tickle-Degnen, 2010). The same is true for decision-making deficits, which in PD have been described to include altered cost-benefit judgements and outcome evaluation (Ryterska, Jahanshahi, & Osman, 2014), high risk aversion (Baig et al., 2017), low novelty seeking and altered sensitivity to reward (Brandt et al., 2015; Kaasinen et al., 2001; McNamara, Raymon, & Harris, 2008; Menza, 2000). These disease-inherent cognitive and affective changes have been mainly associated with dopaminergic denervation leading to associated disbalances in cognitive and reward-processing networks (Chaudhuri & Schapira, 2009). This entails, that the effects of dopaminergic medication also have to be taken into account when running experiments with PD patients ON and OFF stimulation. It has been shown that DBS mimics the effect of dopaminergic replacement therapy on cognition (Castrioto, Lhommée, Moro, & Krack, 2014) but the medication itself distinctly affects cognitive and affective processing (Chaudhuri & Schapira, 2009; Clark & Dagher, 2014; Norbury, Manohar, Rogers, & Husain, 2013). A true limitation to experiments run with patients treated with STN-DBS, is that cognitive-behavioral tests often have to be carried out ON medication to render patients motor impairments bearable.

1.4. A role of the STN in cognition and affect

The accumulating evidence on nonmotor effects of STN-DBS, together with neuroimaging and physiological evidence (Brücke et al., 2007; Cavanagh et al., 2011; Eitan et al., 2013; Herz et al., 2014; Huebl et al., 2014; Le Jeune et al., 2010; Péron, Frühholz, Ceravolo, & Grandjean, 2015; Sieger et al., 2015; Siegert et al., 2014; Zénon et al., 2016) all suggest a role of the STN in the integration of cognitive and affective aspects of behaviour into the motor response. This role is best understood when being considered within the context of the basal ganglia network.

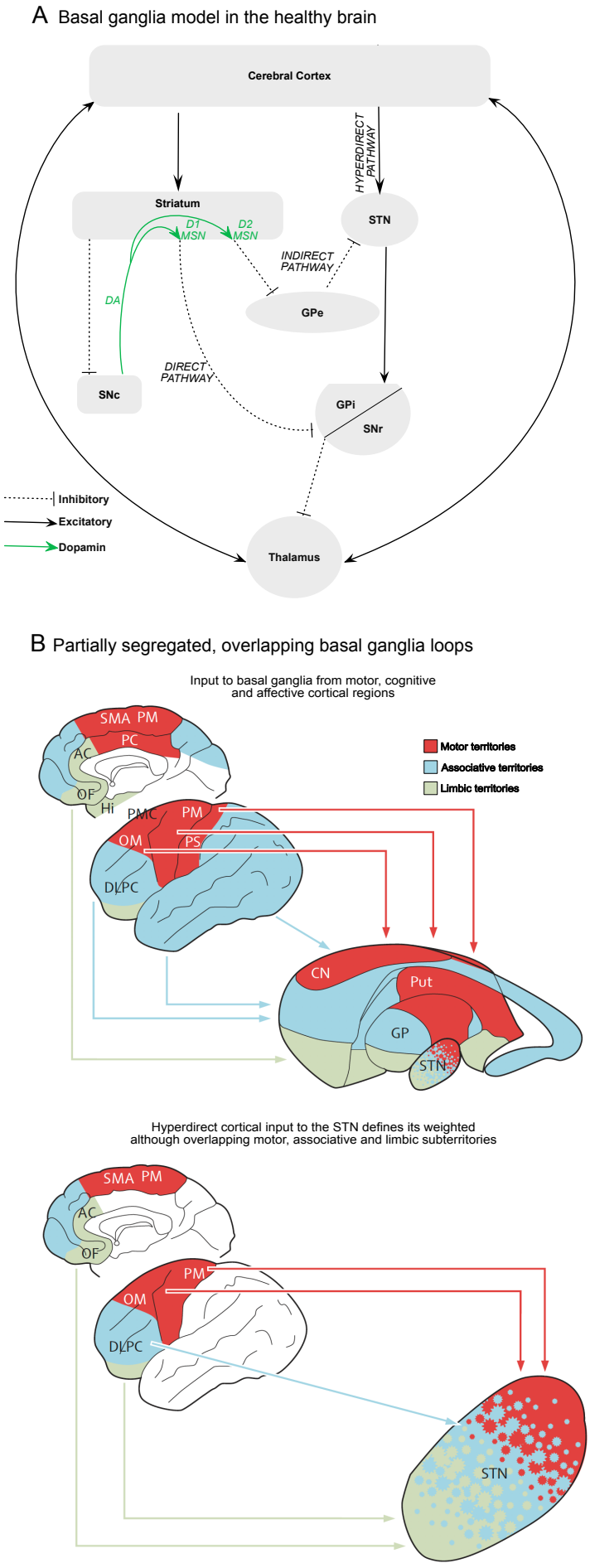

Figure 2. Simplified diagram of (A) the basal ganglia functional connectivity and (B) basal ganglia motor, associative and limbic loops.. A) Cortical inputs enter the basal ganglia through the striatum and STN while the internal globus pallidus (GPi) and substantia nigra pars reticulata (SNr) are the primary output nuclei conveying inhibition to thalamo-cortical loops. GABAergic projections from the striatum monosynaptically inhibit GPi/SNr output via a *direct pathway*, which leads to movement facilitation. As a counterpart, motor output is inhibited via the *indirect pathway* where striatal projections relay at the external pallidum (GPe) and the STN. A *hyperdirect pathway* from cortex to STN enables a fast inhibition of motor output. Dopaminergic projections from substantia nigra pars compacta (SNc) to striatal medium spiny neurons (MSN) convey a reinforcement signal that is important for a balanced functioning of direct and indirect pathways.
B) The basal ganglia and the STN receive input from motor (red), associative (blue) and limbic/affective (green) regions in partially-segregated yet overlapping pathways (Panel B was adapted from Castrioto et al., 2014).

The basal ganglia nuclei compose a complex system of interlinked motor, associative and affective pathways that guide the selection, facilitation and inhibition of movements, emotions, behaviours and thoughts (Volkmann et al., 2010). Their functional organization has been described in a classic model focussing on motor control (Figure 2A) which has been adapted multiple times as understanding of microcircuits in the basal ganglia increases (Singer, Mink, Gilbert, & Jankovic, 2016). In brief, the basal ganglia modulate motor output to selectively facilitate a desired motor programme while inhibiting competing or interfering ones (Mink, 2003). This modulation is guided by the facilitation of the selected motor programme via the interplay of a direct pathway (cortex to striatum to internal pallidum [GPi]) and the parallel continuous inhibition of competing movements through an indirect pathway (cortex to striatum to external pallidum [GPe] to STN to GPi) (Albin, Young, & Penney, 1989; Alexander & Crutcher, 1990). The appropriate functioning of these pathways requires dopaminergic input and dopaminergic denervation in PD results in severe deficits in the control of voluntary movement (Redgrave et al., 2010; Singer et al., 2016). In this system, the STN is not only a modulatory relay of the indirect pathway, but also receives direct cortical input via a hyperdirect pathway (Nambu, Tokuno, & Takada, 2002). It is thus assigned a central regulatory role being able to induce a fast and strong global suppression of motor output via centre surround inhibition (Singer et al., 2016). This "braking" function of the STN on movement seems to transfer to cognitive functions like decision-making, too. Here, local field potential recordings from STN electrodes in PD patients show, that the STN synchronizes with prefrontal cortical areas in low frequency oscillations while subjects are evaluating competing or conflicting responses (Cavanagh et al., 2011; Herz et al., 2016). It is presumed, that based on this low frequency synchronization the STN pauses motor output of the basal ganglia until the appropriate motor plan is set (Frank et al., 2007) at which point prefrontal areas and the STN would desynchronize again.

Since cortical input to the basal ganglia is projected topographically, three partially-segregated yet overlapping functional circuits have been defined in the basal ganglia: a motor, an associative and a limbic/affective loop, referenced accordingly by their respective cortical projections (Accolla et al., 2014; Lambert et al., 2012; Mallet et al., 2007) (Figure 2B). Within these loops, the role of the STN is understood to be that of an integration hub of cognitive and affective information into the motor response (Accolla et al., 2016). In this sense, the STN coordinates and weights input from motor and nonmotor regions to regulate behaviour (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Baunez & Lardeux, 2011; Péron et al., 2013).

Anatomical atlases of the STN that are based on manual segmentation, structural connectivity and brain tissue properties assume a tripartite organization of the STN (Accolla et al., 2014; Ewert, Plettig, Chakravarty, Kuehn, & Horn, 2016). Since electrode positions can now be estimated based on pre- and postoperative imaging (Horn & Kühn, 2015; Horn et al., 2019) and the volumes of brain issue activated by the stimulation can be estimated (Horn et al., 2017;

2019), the effects of STN-DBS on local and global (i.e. wide-spread) brain networks can be predicted. On the one hand, one can calculate the weighted local impact of the stimulation on motor versus nonmotor STN territories and correlate it to behavioural change observed under STN-DBS (Mosley et al., 2018) or even measure global connectivity changes under stimulation in relation to symptom change (Horn et al., 2017). Finally, impact on brain networks can be modelled computationally. Importantly, the impact of STN-DBS on local and global neural networks can aid to explain and predict the effect of STN-DBS on cognitive and affective processing.

2. Research questions and hypotheses

Based on the current literature, the understanding of the effect of STN-DBS on cognition and affect and the underlying mechanisms remains vague. There is a tremendous clinical need in refining concepts of basal ganglia motor and nonmotor functions which can directly advance translational efforts in adjusting deep brain stimulation to patients' individual symptoms. With this thesis I aimed to answer a number of questions aiding the understanding of the impact of STN-DBS on cognitive and affective processing and, relatedly, the role of the STN in these processes.

The first study I conducted concerned the role of STN-DBS in emotional processing and decision-making. A growing range of literature suggests the involvement of the STN in emotion recognition and expression through connections to affective processing regions like the basolateral amygdala and orbitofrontal cortex (Eitan et al., 2013; Lambert et al., 2012; Le Jeune et al., 2008; Péron et al., 2010; Schneider et al., 2003; Sieger et al., 2015). Moreover, the STN has a role in decision-making, inhibiting basal ganglia output when cognitive control is required in the presence of conflict, i.e. ambiguous or competing information (Cavanagh et al., 2011; Frank, Samanta, Moustafa, & Sherman, 2007; Herz et al., 2016; Zavala et al., 2014; Zavala et al., 2016). Hence in this study, I was specifically interested in whether under STN-DBS, patients would show deficits in i) processing emotional content or ii) response inhibition during decision-making or iii) both. It was hypothesized that the integration of emotional content in the STN occurs relative to a conflict signal. Thus, response-slowing in emotionally conflicting trials was predicted to be present in healthy controls and PD patients OFF STN-DBS but impaired in patients ON STN-DBS. To integrate our results in the computational background of the paradigm, the effects were modelled using an adapted version of the well-known Stroop model (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Cohen, Dunbar, & McClelland, 1990).

My second study also addressed the role of the STN in decision-making. Previous work assessing the effects of STN-DBS has mainly focussed on motor inhibition, were DBS is

consistently reported to induce impulsive, premature and erroneous decisions in high-conflict scenarios (Ballanger et al., 2009; Cavanagh et al., 2011; Coulthard et al., 2012; Frank et al., 2007; Green et al., 2013; Hälbig et al., 2009; Herz et al., 2016). Very little work investigated STN involvement in value-based decisions, which resemble decisions we constantly make in our everyday lives where we have to weigh a reward against potential risks. Thus, in this study, it was investigated whether STN-DBS would influence patients' behaviour in risk-reward trade-off decisions and whether the relative stimulation of motor and associative/limbic STN territories might explain this effect. Based on a previous study suggesting STN influence in the applied paradigm (Meder et al., 2016), it was presumed that STN-DBS would increase risky decision behaviour in our sample and that this effect would relate to activation of motor versus nonmotor territory.

The final study conducted for this thesis regarded the change of depressive symptoms that occurs with STN-DBS treatment. One of the common side effects of STN-DBS is postoperative depression with a prevalence of 20-25% (Witt et al., 2012). Interestingly, symptoms of depression have been reported to improve (Campbell et al., 2008; Daniele et al., 2003), worsen (Follett et al., 2010; Temel et al., 2006) or not to change (Deuschl et al., 2006; Weaver et al., 2009) under STN-DBS. I was interested in the predictive and explanatory value of electrode position and associative connectivity. Thus, this study assessed whether structural connectivity determined by the electrode position explains changes in depressive symptoms after 6 to 12 months of STN-DBS. Here, it was assumed that it would be primarily connectivity to associative and limbic cortical regions that would explain and predict postoperative changes in depression.

In addition to the three primary studies described in this dissertation, two further studies where I was co-author are included: First, in Neumann et al. (2018), we assessed the disentangled modulation of basal ganglia indirect versus hyperdirect pathways using computational modelling of behavioural changes with STN-DBS as well as fiber connectivity mapping. It was hypothesized that cognitive disinhibition under DBS would specifically relate to a decoupling of STN and cortex through disruption of the hyperdirect pathway. Second, the study by Horn et al. (2019) investigated the network effects of STN-DBS more closely. Here, the main research interest was to study the effect of DBS on functional resting-state connectivity using functional Magnetic Resonance Tomography (fMRI). It was hypothesized that DBS impact on motor networks would depend on the individual electrode placement and that well-placed electrode would tune network activity more toward that of healthy controls. Since I did not count those two studies as primary parts of the dissertation, they were excluded from the Methodology section.

In sum, this dissertation aimed to comprehensively assess behavioural markers of STN-DBS impact on cognition and affect, link them with local and global network effects depending on

electrode placement and generate predictive models for behavioural change. A broad scope of experimental approaches was applied for this purpose of which Figure 3 provides an overview.

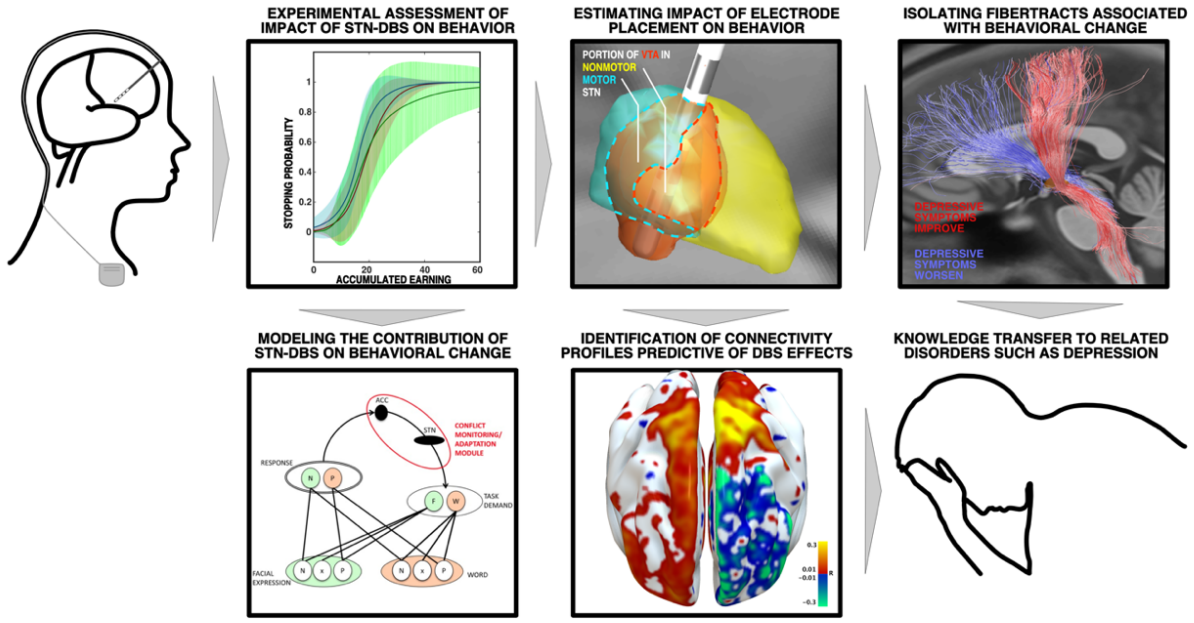

Figure 3. Overview over Research approach. Nonmotor effects of STN-DBS are still poorly described. In this dissertation work I aimed to gather behavioural markers for STN-DBS impact on behaviour by measuring e.g. emotional conflict processing, risk attitude and depression symptoms under STN-DBS. To add explanatory value, I either modelled the contribution of STN-DBS on behavioural change using renown computational models (here the impact of STN-DBS on the emotional Stroop effect); or estimated the impact that electrode placement would have on behaviour. Based on the electrode position, I could furthermore identify connectivity profiles, that were predictive for behavioural change (here improvement of depressive symptoms after DBS surgery) and isolate fibertracts that when stimulated would be associated with the given behavioural change. The knowledge that is gained through this research is not only important for understanding STN-DBS effects but can also be transferred to related disorders such as depression.

3. Methodology

3.1. Experimental samples

Studies 1 – 3 of this dissertation all required the recruitment of a separate set of patients and healthy controls. For Studies 1 – 2 the experiments were conducted in the laboratory in a standardized set-up applying computerized tasks. All PD patients tested in Studies 1 – 2 and the Berlin sample (n = 32) in Study 3 had undergone stereotactic neurosurgery for bilateral STN-DBS at the Department of Neurosurgery, Charité Universitätsklinikum Berlin. Intraoperative microelectrode recordings, intraoperative macrostimulation and postoperative imaging confirmed correct placement of DBS electrodes. Presurgical MRI and neuropsychological examinations were run in all patients to exclude anatomical or psychiatric comorbidities. For Study 1, all patients of Study 1 were implanted the electrode Model 3389®, Medtronic,

Minneapolis, MN, USA. In Study 2, 13 patients had Model 3389®, Medtronic, Minneapolis, MN, USA; and 4 patients had Boston Scientific Vercise Cartesia Directional electrodes. In Study 3, DBS electrodes of the study sample (n = 121) were either Model 3389®, Medtronic, Minneapolis, MN, USA (n = 42), Boston Scientific Vercise (n = 31), Boston Scientific Vercise Cartesia Directional (n = 36) or St Jude Infinity Directional model 6172 (n = 7). Subjects included in these studies gave written informed consent and all studies were approved by the local ethics committee to be in accordance with the declaration of Helsinki.

3.1.1. Study 1

Eleven PD patients (two females, mean age 62 ± 6.4 years, Table 1) and eleven age-matched healthy controls (two females, mean age 63.5 ± 7.4 years) were recruited for this study. In the PD sample, none of the patients had any major cognitive or affective disorders or clinically relevant depressive symptoms (Beck's Depression Inventory [BDI] < 19 indicates minimal/moderate depressive symptoms; Beck et al., 1961). Healthy controls had no history of neurological or psychiatric disease, were under no psychoactive medication and no cognitive impairments (as assessed with the Montreal Cognitive Assessment [MOCA] test). None of the participants had difficulties recognizing facial expressions in the Benton Facial Recognition Test (Benton, 1990). PD patients had a mean disease duration of 11.5 ± 4.2 years and showed significant improvement in their motor symptoms by effective STN-DBS (Unified Parkinson's Disease Rating Scale-III [UPDRS-III] indicated an average reduction of motor symptoms of 57.55 ± 17.58 % ON vs. OFF) which was associated with a reduction of dopaminergic replacement therapy (reduction of Levodopa Equivalent Daily Dosis [LEDD] of 61.42 ± 26.80 % pre- versus post-surgery). Patients completed the experiment while on their usual antiparkinsonian medication.

Table 1. Study 1 – Patients' sample demographics and clinical characteristics

Case/sex	Age	Disease duration	BDI prior to surgery	BDI time of study	Benton FRT	UPDRS-III score OFF DBS	UPDRS-III score ON DBS	LEDD pre-OP	LEDD post-OP	Contacts used for continuous STN-DBS	
1/f	50	6	5	1	49	40	13	1175	600	L:-1;+2	R: -1;+2
2/m	69	20	15	9	45	56	16	1260	400	L:-1	R:-1
3/m	64	7	-	-	39	45	23	1250	200	L:-1	R: -2: -3
4/m	65	12	8	14	-	30	7	1450	240	L:-1;-3	R:-1;-3
5/m	60	7	0	0	49	23	19	900	800	L:-0	R:-0
6/m	69	10	4	4	-	30	8	1400	0	L:-1	R:-1
7/m	66	14	3	1	43	34	14	1400	600	L:-1	R:-1
8/f	63	14	17	17	39	28	18	1080	140	L:-1	R:-1
9/m	56	15	13	6	39	44	11	750	300	L:-2;-3	R: -1
10/m	70	14	14	7	43	30	14	600	500	L:-0;-1	R:-1;-2
11/m	53	7	-	-	41	40	18	1100	450	L:-1;-2	R:-1;-2
M(SD)	62 (6.4)	11.5 (4.2)	8.7 (5.8)	6.5 (5.6)	43 (3.8)	36.4 (9.1)	14.6 (4.6)	1124.09 (263.32)	384.54 (224.23)		

M(SD) – Mean (Standard deviation), BDI – Beck Depression Inventory, Benton FRT – Benton Facial Recognition Test, UPDRS-II – United PD rating scale, LEDD – Levodopa equivalent daily dosage; SD – standard deviation

3.1.2. Study 2

Seventeen patients (six females, mean age 64.94 ± 7.03 years, Table 2) with idiopathic PD (mean disease duration 14.23 ± 7.5 years) that were treated with STN-DBS and 17 age-matched healthy controls (mean age 65.64 ± 6.78 years) were included in the study. PD patients completed the experiment while on their usual antiparkinsonian medication (LEDD was 504±375.68 in total with dopamine agonists contributing 110.76±85.43). STN-DBS lead to an effective reduction in motor symptoms of PD patients of 51.68±21.00 % (assessed ON medication) and compared to preoperative LEDD, patients showed an average postoperative LEDD reduction of 62.12±26.64 % which also indicates effectivity of the stimulation. None of the participants had any major cognitive or affective disorders or clinically relevant depressive symptoms (BDI < 19) No monetary reimbursement was given to PD patients, while healthy controls received 15 EUR as compensation.

Table 2. Study 2 – Patients' sample demographics and clinical characteristics

Case/ sex	Age	Disease duration	LEDD (total/daily)	LEDD (DA agonists/daily)	Relative LEDD reduction post-OP	Abs. change UPDRS-III OFF-ON DBS	Pct. Change UPDRS-III ON/OFF DBS	BDI	BIS 11 Attentional Impulsiveness	BIS 11 Motor Impulsiveness	BIS 11 Non-planning Impulsiveness	Contacts used for continuous STN-DBS	
1/m	69	10	457	157	35.63	12	40	14	17	21	32	L: -10	R: -2
2/m	54	10	0	0	100.00	31	67.39	8	13	21	26	L: -9	R: -1
3/f	67	31	466	210	72.97	15	71.43	1	11	25	20	L: -9	R: -1
4/f	61	16	1090	200	28.99	17	34.69	6	16	22	21	L: -7, -6	R: -3
5/f	65	10	518	52	58.19	8	23.53	7	12	17	20	L: -1	R: -9
6/f	63	14	715	315	27.97	15	68.18	15	21	18	25	L: -11	R: -3
7/m	75	10	960	30	25.52	9	32.14	12	13	21	25	L: -11	R: -3
8/m	69	20	157	157	90.84	24	66.67	7	16	17	22	L: -9, -8	R: -1
9/m	75	16	460	160	77.70	13	56.52	8	13	20	23	L: -10	R: - 3
10/m	56	9	170	120	92.16	28	73.68	4	12	18	22	L: -5 (50%), -4 (50%)	R: -12 (66%), -13 (34%)
11/m	52	8	0	0	100.00	31	83.78	2	11	22	24	L: 5/6/7 (33%)	R: 13/14/15 (33%)
12/m	57	5	352	52	50.77	33	73.33	4	14	21	20	L: 4	R: 12
13/m	68	16	1338	140	63.87	9	32.14	6	12	16	22	L: 10, 8, -9	R: 4, 0, -2
14/f	60	11	520	70	23.53	27	65.85	12	17	21	29	L: -11, -10	R: -2
15/m	71	11	785	160	41.42	4	25	9	18	21	22	L: -9	R: -1
16/m	73	16	0	0	100.00	24	61.54	13	21	21	27	L: -2 (54%), -3 (23%), -4 (23%)	R: -10 (54%), -11 (23%), -12 (23%)
17/f	69	11	580	60	66.24	7	11.86	13	17	21	18	L: 3, -1	R: 4, -5
M(SD)	64.94(7.03)	14.23(7.50)	504(375.68)	110.76(85.43)	62.10(26.64)	18.06(9.31)	52.22 (21.30)	8.29(4.15)	14.94(3.13)	20.18(2.02)	23.41(3.49)		

M(SD) - Mean (Standard deviation), BDI – Beck Depression Inventory, BIS 11 – Barratt Impulsiveness Scale , DA – Dopamine, UPDRS-III – United PD rating scale; LEDD – Levodopa equivalent daily dosage; SD – standard deviation; post-OP – postoperatively; Abs./Pct. Change – absolute/percentage change

3.1.3. Study 3

This retrospective study included 121 PD patients from three DBS centers (Berlin [BER]: n = 32; Queensland [QU]: n = 49; Cologne [CGN]: n = 40) with a mean age 62 ± 0.84 years and 43 females (Table 3). Five patients had to be excluded from the analyses. One patient from Queensland had to be excluded due to incomplete data. Of the CGN dataset, two patients had unilateral VIM (instead of STN) stimulation due to a tremor-dominant PD syndrome and two patients showed clinically relevant psychiatric symptoms before surgery that were pharmacologically treated (thus distorting BDI measurements). The final cohort consisted of 116 PD patients (mean disease duration 9.55 ±4.45 years; see Appendix C for detailed tables of the sample).

In all patients, depressive symptoms were recorded pre- and postoperatively (after 7.56 ± 2.9 months) using BDI. On average, BDI scores decreased from 9.94 ±0.50 to 8.96 ±0.60 (on average by 0.97 ±0.54 points = absolute BDI change) postoperatively, i.e. there was an overall reduction in BDI of 3.34 ± 8.12% but the difference was not significant (Appendix B). Importantly, scores in some patients improved while they worsened in others (with an absolute BDI change in single patients of up to 19). Furthermore, LEDD reduced pre- to postoperatively by 56.55 ± 2.77 % and motor improvement (UPDRS-III) with DBS was significant although it was measured ON medication reaching an average DBS response of 27.56 ± 8.37 %.

Table 3. Study 3 Patients' sample demographics and clinical characteristics

Cohort	N	Age (yrs)		Sex		Disease duration (yrs)		Months postop	BDI (Baseline)		BDI (Postop)		UPDRS-III (Baseline, MED ON)		UPDRS-III (Postop, MED ON)		LEDD-Reduction (%)	
		M	SEM	f	m	M	SEM	M	M	SEM	M	SEM	M	SEM	M	SEM	M	SEM
Berlin	32	61	2	10	22	10	1	12	11.56	1.11	11.56	1.32	20.78	1.82	19.26	2.47	46.06	7.32
Queensland	48	62	1	15	33	8	1	6	11.06	0.68	8.45	0.82	37.46	2.23	33.95	1.89	68.98	3.32
Cologne	36	62	8	18	18	10	1	6	7.00	0.71	7.00	0.97	18.00	1.65	17.00	1.53	48.27	3.15
Total	116	62	1	43	73	9	0	7	9.94	0.50	8.96	0.60	26.75	1.43	24.85	1.35	56.32	2.77

BDI – Delta change in Beck's depression inventory (Baseline = pre; Postop = post DBS surgery); UPDRS-III –Unified Parkinson's disease rating scale III (Baseline = pre; Postop = post DBS surgery ON Medication); LEDD – Levodopa-equivalent daily dosage; M – mean; SEM – Standard error of the mean

3.2. Experimental Paradigms and parameters

This section describes the tasks and parameters used in Study 1 and 2. Study 1 employed an emotional Stroop task to assess the effect of STN-DBS on perceptual decision-making with affective content, while Study 2 used a sequential decision-making task to assess impact on risk-reward trade-off. Study 3 did not employ any experimental paradigm, but its outcome variables are detailed in the next section.

3.2.1. Study 1: Emotional Stroop task

This study employed an adapted version of the emotional Stroop paradigm by Etkin et al. (2006). Black and white photographs of faces with happy or sad expressions (Figure 4) were displayed with superimposed emotion words (German "Freude" for happiness, and "Trauer" for sadness) that were either congruent or incongruent to the facial expression. Trials were defined as being conflicting, when face and word were incongruent while in non-conflicting trials face and word were congruent. More details on the experimental stimuli and their properties can be found in the supplementary methods section of Study 1 (Appendix A).

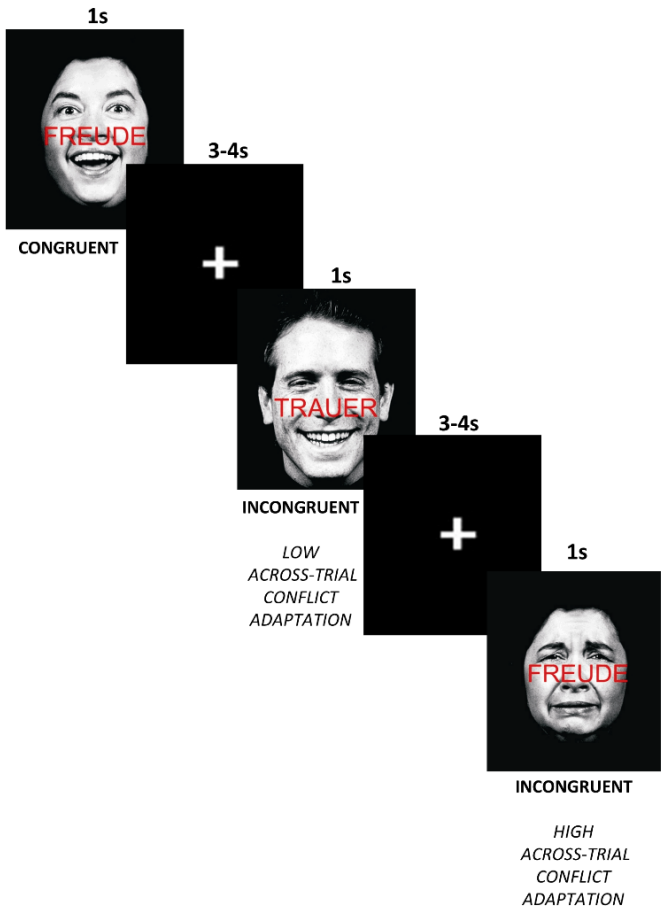

Figure 4. Study 1 - Emotional Stroop paradigm. Stimuli were presented for 1 second, followed by a black screen with a white fixation cross presented for a jittered interval of 3–4 seconds. Figure by Irmen et al., 2017

Subjects completed the computerized task while seated, using left and right button presses on a joystick to react to sad or happy facial expressions (button valence assignment was pseudo-randomized). Patients performed the task ON and OFF DBS (order pseudo-randomized) with a 30-minute waiting interval after switching OFF the stimulation. One run of the experiment took approximately 20 minutes.

3.2.2. Study 2: Dice Game Task

The computerized task in this study instructed subjects (seated, a joystick in each hand) to roll a die repeatedly by pressing a button. With each time of rolling the die the round-gain would accumulate by the number of pips on the die. When rolling a '1' however, subjects lost the accumulated sum. Thus, at each trial, subjects had to decide whether to continue rolling the die or to stop the round and bank the accumulated round-gain (the choice was manifested with a button press, continue and stop button were pseudo-randomized across subjects). The aim of the game was to maximize the average gain over all rounds (at least 200 rounds were performed). One run of the task took around 30 minutes. HC completed the task routine once, whereas PD patients performed the task twice, ON and OFF STN-DBS, in a pseudo-randomized order with a 30 minutes delay after switching off the DBS device.

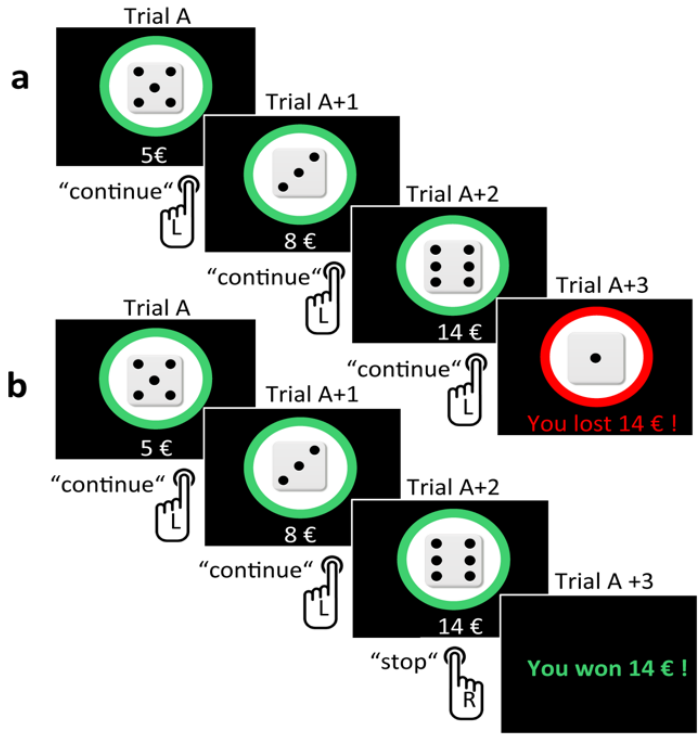

Figure 5. Study 2 - Dice Game paradigm. A prototypical loss (a) and win round (b) in the task. At each trial, subjects decided whether to "continue" (here left button [L]) rolling the die to add the amount of pips to their accumulated sum; or to "stop" (here right button [R]) to bank the current amount. Rolling a '1' meant the current amount was lost (b). Figure by Irmen et al., 2018

3.3. Outcome variables

This section briefly describes the outcome variables in the applied paradigms, outlining the focus of the experimental approach and data analysis. While Study 1 and 2 are behavioural studies with a computational (Study 1) and anatomical (Study 2) focus, Study 3 concentrates on the global network impact of STN-DBS and its relation to change in depressive symptoms.

3.3.1. Study 1

Since in the emotional Stroop task, error rates are typically very low (Etkin et al., 2011), the analysis of the task data concentrates on reaction time comparisons of congruent and incongruent trials. I also compared trial-to-trial adaptation, that is, whether cognitive control recruited in a conflict trial would lead to faster responses in a following conflict trial. Moreover, to further describe the data in this study, a well-known computational model was applied, that explains the emergence of the Stroop effect and its blockage by STN-DBS (Botvinick et al., 2001; Cohen et al., 1990).

3.3.2. Study 2

In this study, I aimed to assess risk-reward integration and the impact STN-DBS had on it. Therefore, I ran within-subject (ON–OFF DBS) and between-subjects (ON/OFF DBS – healthy controls) comparisons for three behavioural parameters: (i) Stopping probability usually increases with accumulated sum as utility of ending the round increases. I used the certainty equivalent (CE) to quantify risk attitude, which is the accumulated sum at which a subject's utility of the risky 'continue' choice is equivalent to the safe 'stop' choice (Figure 6). Subjects can be risk-averse, risk-seeking or risk-neutral depending on their CE. Subjects' stopping probability at each trial *n* was modelled using a logistic regression:

$$p(\text{stop}|x_n) = \frac{1}{1 + \exp(-w_1 x_n - w_0)}.$$

The accumulated sum x_n in trial *n* is modulated by free parameters w_0 and w_1. The CE was defined as the amount at which stopping probability was 0.5 (i.e. subjects are equally likely to stop and to continue the trial). I correlated CE change ON vs. OFF DBS with DBS response (relative change in UPDRS-III ON vs. OFF DBS), LEDD and postoperative LEDD reduction. Consistency of stopping strategy was represented by the slope of the logistic regression, i.e. the steeper the slope, the more consistent subjects' stopping behaviour.

The second behavioural parameter measured was (ii) response time as an index of impulsivity. Here, I calculated response slowing with increasing accumulated sum, and characterised

subjects with a lower degree of response slowing as being more impulsive. I fit a linear regression of RTs on accumulated sum and compared the slope of the regression line between groups.

The final behavioural measure was (iii) outcome: Subjects' mean gain and percentage of loss trials was calculated over all rounds and compared between conditions and groups.

As a final variable, I assessed, whether the relative activation of STN segments by the stimulation would explain changes in risk attitude. To this end, I localized the electrodes (detailed in the section 3.4.2.) and calculated the ratio of motor and nonmotor STN (defined by subzones in DISTAL subcortical atlas; Ewert et al., 2017) impacted by the volume of tissue activated (VTA) surrounding active contacts of the left and right electrodes of each patient. The ratio index was also correlated with clinical DBS response (UPDRS–III change OFF–ON).

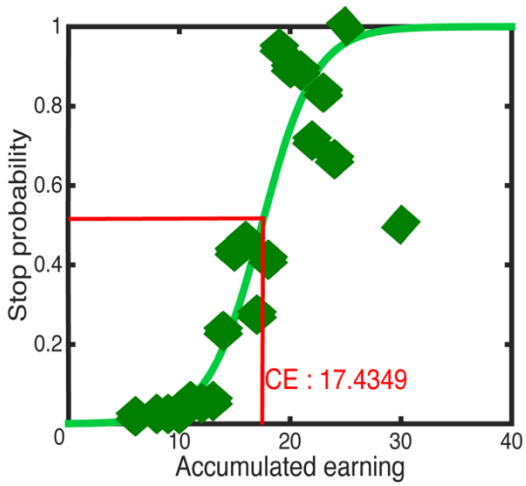

Figure 6. Study 2 - Stopping probability and certainty equivalent. A prototypical stop probability function, each dime represents a stop amount. The certainty equivalent (CE) is the amount at which the subject is equally likely to "stop" or to "continue". Figure by Irmen et al., 2018

3.3.3. Study 3

In Study 3, depressive symptoms before and after long-term STN-DBS were assessed to study underlying network effects. Here, I used data of depressive symptoms that were recorded pre and post (after 7.56 ± 2.9 months) STN-DBS implantation using the BDI scale. Using information on electrode position and individual's structural connectivity profile that were estimated based on a normative connectome, change in depressive symptoms was predicted (see section on Data analysis for details). As covariates, pre- to postoperative reduction of LEDD and UPRDS-III were included.

I used three cohorts from three different DBS centers, trained a model on two datasets, cross-validated it, and predicted data of the third independent dataset: Data from Charité

Universitätsmedizin Berlin (BER) and University of Queensland (QU) were used to form the training and cross-validation datasets to identify structural connectivity predicting mood changes after DBS surgery. Data from the University Hospital Cologne (CGN) was used as a test dataset to validate the established model.

3.4. Data analysis

In this section, I provide an overview of the applied data analyses in the dissertation work. I describe the methods used for inference statistics in Study 1 and 2 as well as DBS electrode localizations and VTA modelling (Study 2 and 3) and the structural connectivity analyses applied in Study 3. All data were analysed using MATLAB (The Mathworks,Natwick,MA).

3.4.1. Statistical analyses

3.4.1.1. Study 1

In Study 1, behavioural data was analysed using analyses of variance (ANOVA). After standardizing reaction times of PD patients to the mean of the control group (to establish how much conditions differed from the control group), the difference of conflict and no-conflict trials, i.e. the Stroop effect, was compared for trials of negative and positive valence using a repeated-measures ANOVA and by testing for significance of the intercept, I tested whether mean reaction times in PD patients differed from the mean of the control group. Across-trial adaptation of reaction times was assessed in the same manner.

To further describe the mechanisms behind patients' altered Stroop effects under STN-DBS, a well-established computational model was applied (Botvinick et al., 2001; Cohen et al., 1990), consisting of five modules. Applied to the emotional Stroop task, two sensory modules, one for facial expression and one for word processing compete for control of the response module. A task demand module biases the sensory modules to favour facial expression input over word input while at the same time receiving distracting input from the sensory word module. If the trial is conflicting, incongruent face and word information compete for access to the response unit, and the conflict monitoring (ACC) and adaptation (STN) module biases the task demand module to strengthen focus on faces, which delays reaction times. Conversely, responses are fast and correct for congruent stimuli when congruent face and word information adds up.

We fit the model to represent a Parkinsonian initial bias: since our results indicated a response bias for negative stimuli, we increased the weight for these respective stimuli to reproduce the

Stroop effects observed in the PD OFF DBS state. The detailed equations of the model adapted from Botvinick et al. (2001) can be found in Appendix A.

To test in which way STN-DBS interferes with emotional conflict processing, three assumptions were tested: i) STN-DBS elevates baseline activity inducing increased activation of STN neurons' axons; ii) STN-DBS leads to a reduction of input from the ACC to the STN; iii) STN-DBS increases both STN baseline activity and reduces ACC input to the STN. Simulations were run for all three assumptions and assumption i) was found to hold true, which is detailed in the next section on the study results.

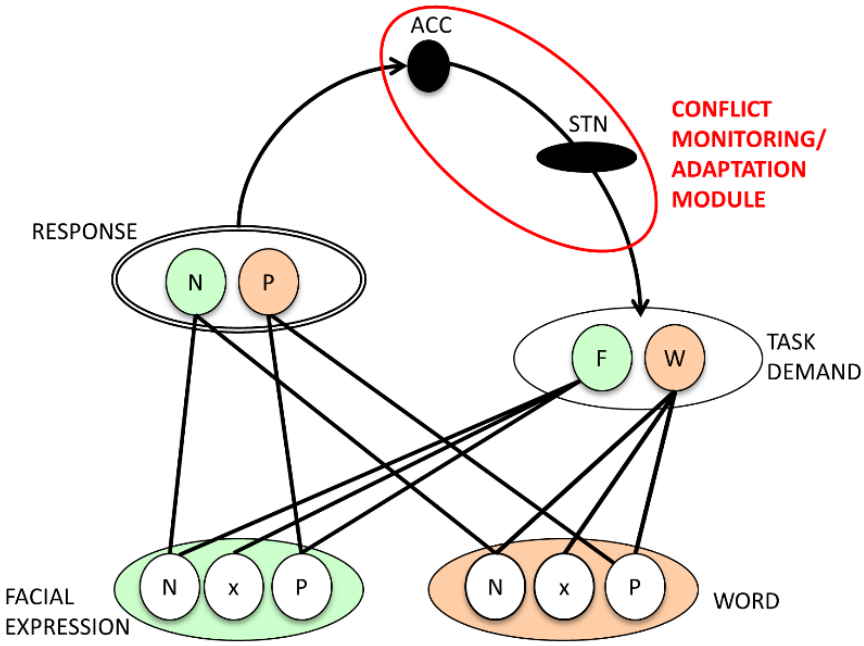

Figure 7. Study 1 - Computational model of STN involvement in emotional conflict monitoring and adaptation. Small circles represent units, large ovals represent modules. Arrows represent unidirectional connections while lines represent bidirectional connections. P represents positive stimulus features, N represents negative features. X represents the assumed representation of features of neutral valence. F: Facial expression naming; W: Word naming. Figure by Irmen et al., 2017

3.4.1.2. Study 2

Within-subject (ON–OFF DBS) and between-subjects (ON/OFF DBS – healthy controls) comparisons were run for the behavioral parameters detailed above: CE (stopping probability indexing risk attitude), impulsivity (reaction time slowing) and outcome. Non-parametric tests were used to describe group differences since data was not normally distributed as Kolmogorov Smirnov tests indicated. Reported p-values are the result of planned randomised permutation test using 10,000 permutations. Paired tests were used to compare ON and OFF DBS assessments. Planned comparisons were FDR-corrected and p-values were classified significant at a 5% level.

3.4.1.3. Study 3

We used randomized permutation tests (5000 permutations) to test for significance and Spearman's correlation coefficients throughout all analyses. Details on the Structural connectivity analysis, modelling of connectivity-driven mood changes and isolation of fibre tracts are detailed below.

3.4.2. Electrode localizations and VTA modelling (Study 2 and Study 3)

In all patients, DBS electrodes were localized using the Lead-DBS toolbox (www.lead-dbs.org; Horn & Kühn, 2015) in Matlab (The Mathworks, Natwick, MA). Specifically, the advanced processing pipeline illustrated in Horn et al. (2019) was applied (Horn et al., 2019a). In short, postoperative CT or MRI were linearly coregistered to preoperative MRI using advanced normalization tools (ANTs; stnava.github.io/ANTs/; Avants et al., 2008). Coregistrations were visually inspected and refined if needed. A brainshift correction step was applied as implemented in Lead-DBS. All preoperative volumes were used to estimate a precise multispectral normalization to ICBM 2009b NLIN asymmetric ("MNI") space applying the ANTs SyN Diffeomorphic Mapping method (Avants et al., 2008) using the preset "effective: low variance default + subcortical refinement" implemented in Lead-DBS. In some patients where this strategy failed, a multispectral implementation of the Unified Segmentation approach (Ashburner & Friston, 2005) implemented in Statistical Parametric Mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm) was applied. These two methods are available as presets in Lead-DBS and were top-performers to segment the STN with precision comparable to manual expert segmentations in a recent comparative study (Ewert et al., 2019). DBS contacts were automatically pre-reconstructed using PaCER (Husch et al., 2018) or the TRAC/CORE approach (Horn & Kühn, 2015) and manually refined if needed. For segmented leads, the orientation of electrode segments was reconstructed using the Directional Orientation Detection (DiODe) algorithm (Hellerbach et al., 2018; Sitz et al., 2017).

Based on the clinically applied stimulation parameters, the VTA was calculated using default settings in Lead-DBS applying a Finite Element Method (FEM) -based model (Horn et al., 2017a), which estimates the E-field on a tetrahedral mesh that differentiates four compartments (grey and white matter, electrode contacts and insulation). Grey matter was defined by key structures (STN, internal and external pallidum, red nucleus) of the DISTAL atlas (Ewert et al., 2016). The resulting gradient vector magnitude was thresholded at a heuristic value of 0.2 V/mm. This analysis thus resulted in a VTA object which could be used for further analysis. In Study 2, the ratio of VTA in STN motor and nonmotor subzones defined using the DISTAL atlas (Ewert et al., 2016) was calculated in each patient for left and right electrodes.

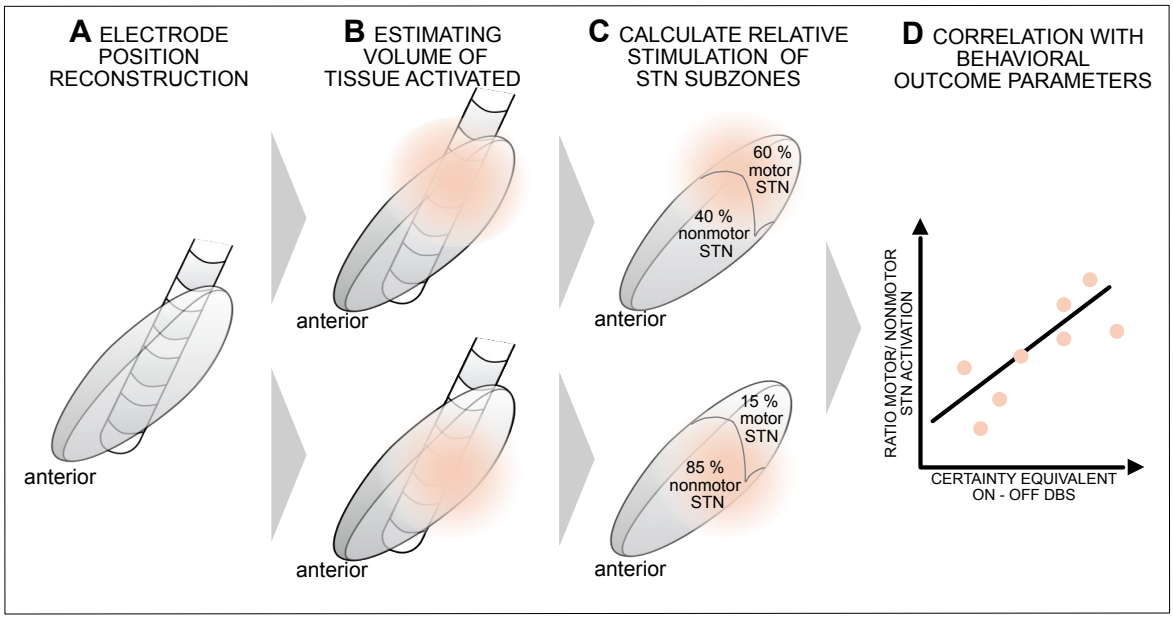

Figure 8. Study 2 - Research approach. (A) Electrode positions for each patient were reconstructed using Lead-DBS. (B) The volume of tissue activated was estimated applying a finite element approach. (C) Subzones of the STN were identified using the DISTAL atlas (Ewert et al., 2017) and relative stimulation of motor and nonmotor STN-subzones was calculated. (D) The ratio index for each patient was correlated with the patients' change in risk attitude ON vs. OFF STN-DBS.

In Study 3, the VTA as well as the unthresholded E-field (to control for limitations of the VTA concept such as assumption of type of axon diameter/orientation and the anatomical complexity of the subcortex as described by e.g. Forstmann et al., 2016) were used as seeds in further structural connectivity analysis (see next section).

3.4.3. Structural connectivity analyses (Study 3)

Whole-brain structural connectivity profiles seeding from bilateral VTAs or E-Fields were estimated using a Parkinson's Disease group connectome that is based on publicly available data (Marek et al., 2011; Parkinson's Progression Markers Initiative; www.ppmi-info.org; n = 90; mean age 61.38 ± 10.42 years, 28 female). For each patient, fibers that passed through the VTA or a non-zero voxel of the E-Field were selected from this normative connectome and projected onto a voxelized volume in standard space (1mm isotropic resolution) while keeping count of the fibers traversing each voxel. In the binary (VTA) analyses, the number of fibers traversing each voxel was denoted (resulting in classical fiber-density map), in the E-Field based analyses, each fiber received the weight of the maximal E-Field magnitude of its passage and fiber densities were weighted by these values.

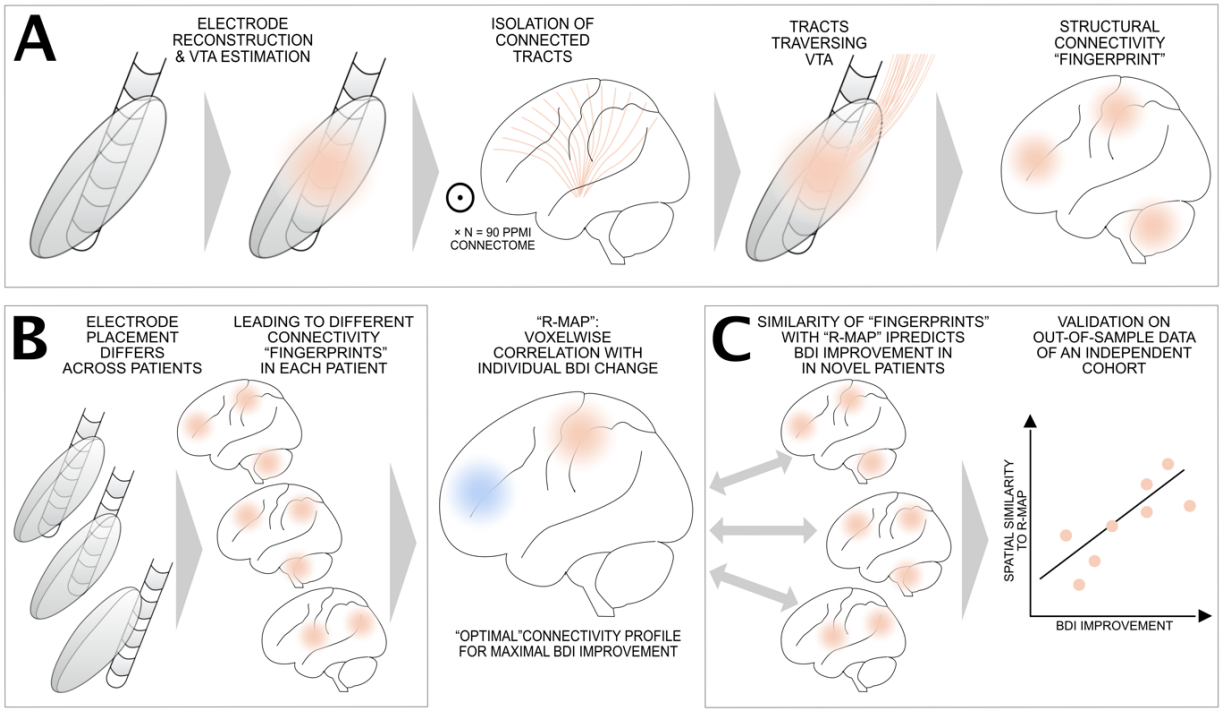

Figure 9. Study 3 - Research approach. A) In each patient, electrodes were localized and VTAs were calculated in standard stereotactic space using Lead-DBS software. From a normative Parkinson's Disease connectome (N = 90 PPMI datasets), tracts that traversed through each patient's VTA were selected and projected to the brain as fibre density maps. These maps represent the structural connectivity "fingerprint" seeding from each VTA. B) Varying electrode placement leads to different connectivity "fingerprints" in each patient. Across the group of patients, these fingerprints are used to generate a model of connectivity that is associated with maximal BDI improvement by voxel-wise correlation ("R-Map"). C) The R-Map represents a model that denotes how electrodes should be connected to result in maximal BDI improvement. When comparing each novel patient's "fingerprint" with this model (by means of spatial correlation), individual BDI improvement can be predicted. Crucially, this is done to predict improvement in out-of-sample data, i.e. across cohorts or in a leave-one-out fashion throughout the manuscript. This means that the R-map is never informed by the predicted patient's structural connectivity "fingerprint". Figure by Irmen et al., 2019

3.4.4. Modelling of connectivity-driven mood changes (Study 3)

Structural connectivity strength, i.e. number of fibers between VTA and each voxel was Spearman rank-correlated with BDI change (preoperative - postoperative), which resulted in a map that codes for regions, a connectivity positively or negatively associated with BDI improvement ("R-maps" denote Spearman's correlation coefficients for each voxel). Spearman's correlation was used since tractography results are highly non-Gaussian distributed and rather follow an exponential distribution (e.g. Horn et al., 2014). In this process, one R-map for each subset (BER, QU) and a joint map for the entire training/cross-validation set (BER+QU) was calculated. R-maps were then used to predict BDI changes in out-of-sample data (i.e. cross-predicting between QU ↔ BER cohorts and predicting from QU/BER → CGN) by spatial correlation between the R-map (model) and the connectivity profile seeding from an electrode in each patient. This was done across voxels with an absolute Spearman's R-value of

> 0.1 on each R-map. For example, the R-map (model) was calculated across the BER sample and voxels with an absolute R > 0.1 were spatially correlated with connectivity maps in the QU sample. For each patient in the QU cohort, this led to one R-value that coded for spatial similarity to the model. These R-values were then correlated with empirical BDI changes. In the same fashion, BDI change in patients of the test dataset (CGN) was predicted based on the joint R-map of the whole training set.

Three subanalyses were included to further validate the results: i) I assessed a potential lateralization of the connectivity profile that allows prediction of BDI change in the test cohort based on the training dataset. ii) I tested how robustly our R-maps were, by solving the applied prediction in a leave-one-out fashion across the whole dataset, i.e. data from patients 1-115 was used to predict patient 116 and so on. iii) Finally, to control for the effect of LEDD reduction and UPDRS-II change postoperatively, those variables were included in the prediction models as covariates.

3.4.5. Fibertract analyses (Study 3)

In order to identify tracts that could discriminate patients with positive from negative BDI change, fibertracts were isolated: For each fibertract in the normative connectome (PPMI 90, see above), its accumulative E-Field vector magnitude while passing by each patient's electrode was denoted. This value was then Spearman rank-correlated with each patient's clinical change in depressive symptoms. Thus, a fibertract that passed proximally to active contacts of patients that had BDI improvement but far from active contacts in patients that had BDI worsening would receive a high Spearman's R value (and tracts exhibiting the inverse property received a low and negative R-value). These R values were used to color-code tracts that were positively and negatively predictive of BDI improvement. This analysis was expected to show identical (or highly similar results) as the "R-map" method explained above but has the advantage of working on a tract-by-tract basis (instead of a voxel-wise fashion). Thus, it is ideal to visualize the actual fibertracts that were predictive of change in depressive symptoms.

4. Dissertation studies

This chapter provides a brief overview over the three empirical studies constituting the main work of this thesis. The following summaries are largely based on excerpts from the manuscripts.

4.1. Subthalamic nucleus stimulation impairs emotional conflict adaptation in Parkinson's disease

This study aimed to assess and model the impact of subthalamic stimulation on emotional conflict processing. Specifically, since STN-DBS has been shown to interfere with conflict processing and respective slowing of responses (Brittain et al., 2012; Frank et al., 2007; Green et al., 2013; Herz et al., 2016; Zavala et al., 2015, 2016), I was interested in assessing its impact on emotional conflict processing. Given the above-detailed putative role of the STN in the integration of cognitive and affective content into the motor output, I hypothesized that STN-DBS would disrupt response-slowing for conflicting emotional stimuli, and I was interested whether such effect would differentiate between valence of these stimuli. To test this hypothesis an emotional Stroop paradigm was applied where subjects categorized face stimuli according to their emotional expression while ignoring emotionally congruent or incongruent word labels. Because reading is automatized (MacLeod, 1991), labelling the emotion of a face that is superimposed by an incongruent word elicits cognitive control. This cognitive effort is needed to suppress a response to the word, which slows down reaction times (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006).

Eleven PD patients ON and OFF STN-DBS and eleven age-matched healthy controls conducted the task in our laboratory. PD patients were on their usual antiparkinsonian medication and completed the task ON and OFF DBS in a pseudo-randomized order with a 30-minute waiting interval between conditions.

The results indicated that STN-DBS induced a defect in the processing of conflicting emotional input: PD patients ON STN-DBS did not slow down their reactions in trials where a conflict signal should have been detected. Conversely, healthy controls showed the expected response slowing for incongruent emotional stimuli reflecting intact emotional conflict processing and, at the first glance, PD patients OFF DBS slowed down their responses equally when facing conflict. Yet, when looking at stimuli of different valence separately, it became clear that OFF DBS, PD patients showed much stronger response slowing for negative incongruent stimuli while little for positive stimuli, thus exhibiting a valence bias in conflict processing. In particular, conflict-induced response slowing was stronger, if a negative face was superimposed by a positive word, than vice versa. STN-DBS erased this valence bias and lead to a lack of response slowing in both negative and positive conflict trials.

Using an adapted version of the well-known Stroop model by Cohen et al. (1990) and Botvinick et al. (2001), we modelled the valence-biased Stroop effect in our data: the model was modified to include

the STN in the conflict monitoring and adaptation module which modulates motor output based on given conflict information. Testing three sets of assumption on how STN-DBS might disrupt emotional conflict processing, the model suggested that it was increased baseline activity, i.e. a higher baseline noise level in the STN, that best explained a reversal of the valence-biased conflict processing to no conflict adaptation under STN-DBS.

Taken together, this study provides evidence for an interference of STN-DBS with emotional conflict processing. In addition, it shows that there is a PD-inherent bias in processing emotional information with a higher conflict signal elicited by positive words and a low conflict signal elicited by negative words in incongruent trials. This finding complements previous research (Beck, 2008; Gotlib, Krasnoperova, Yue, & Joormann, 2004; Gray & Tickle-Degnen, 2010) and fits the depressive clinical symptoms that are often part of the disease (Maillet et al., 2016). The findings are discussed in more details in the discussion section of this thesis.

Statement of contribution: The task was set up and the PD patients were recruited at Charité - Universitätsmedizin Berlin by a team of neurologists at the Neuromodulation Unit, Julius Huebl and Christopf Brücke. I recruited the cohort of age-matched healthy controls, conducted the data analysis, and was responsible for data interpretation and writing of the paper. For the application of the computational model, I was supported by a Postdoc of the Neuromodulation Unit, Henning Schroll.

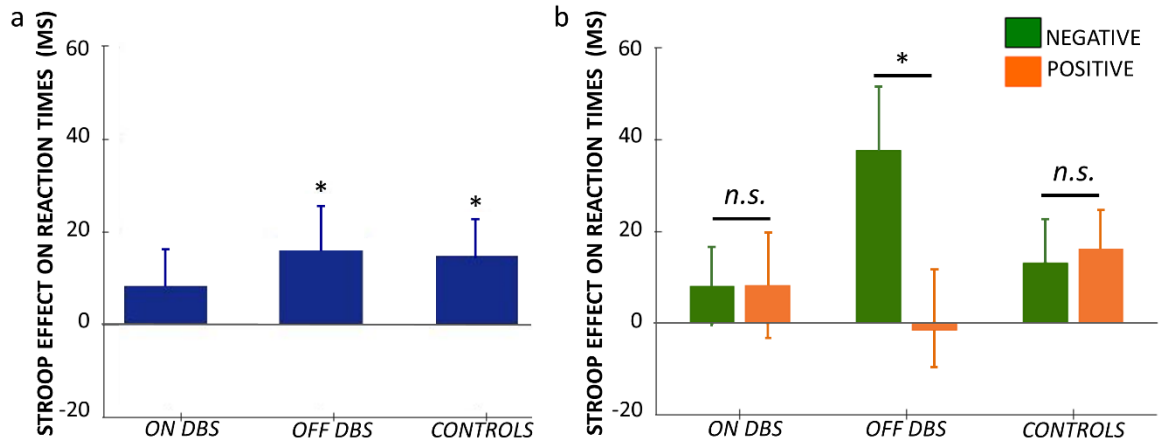

Figure 10. Study 1 - Emotional Stroop effect on reaction times. (a) Over both valences, the Stroop effect of reaction times (delta of conflict – no conflict trials) is significantly different from zero in PD patients OFF DBS and healthy controls. No such difference is present ON DBS. (b) PD patients OFF DBS show a strong Stroop effect only for conflicting negative stimuli whereas no valence difference is found ON DBS and in healthy controls. Mean reaction times and standard error of the mean (SEM) are displayed (*P < 0.05). Figure by Irmen et al., 2017

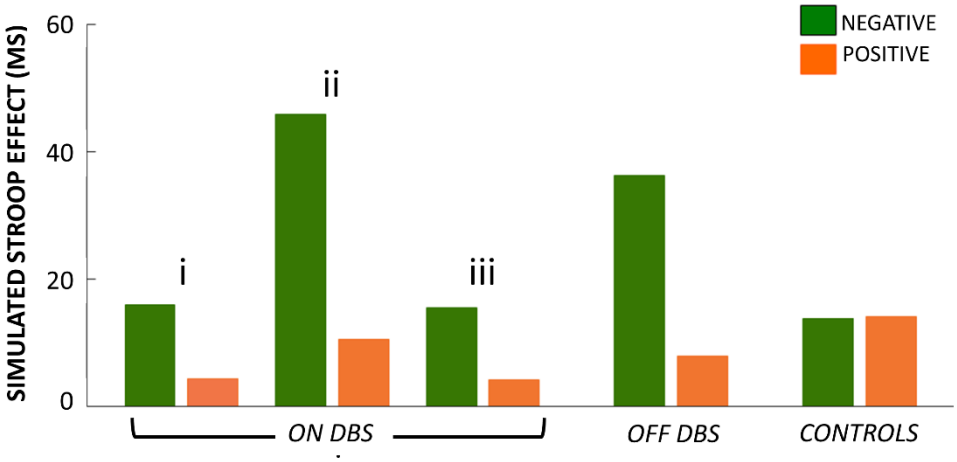

Figure 11. Study 1 - Results of computational modelling of STN-DBS interference with the Stroop effect. STN-DBS is modelled with (i) a reduction in inputs from the ACC to the STN and increased STN baseline outputs, (ii) a reduction in STN inputs, and (iii) a reduction in STN outputs. Figure by Irmen et al., 2017

4.2. Sensorimotor subthalamic stimulation restores risk-reward trade-off in Parkinson's disease

Plenty of evidence suggests an impact of STN-DBS on decision-making. Especially the role of the STN in motor inhibition is well described and stimulation-induced increased impulsivity is consistently reported (Ballanger et al., 2009; Cavanagh et al., 2011; Coulthard et al., 2012; Frank et al., 2007; Green et al., 2013; Hälbig et al., 2009; Herz et al., 2016). Yet, some studies suggest an impact of risk attitude and judgement of reward on STN activity, suggesting that information on these variables is integrated into motor output (Meder et al., 2016; Zénon et al., 2016). Yet, the effect of STN-DBS on risk-reward trade-off decisions is still unknown, despite these decisions having high real-life impact because the accumulation of reward often comes with a gradual increase in risk, for example when foraging for more nutritious food requires climbing dangerously high on a tree or getting very close to a hungry predator.

Interestingly, when regarding nonmotor STN-DBS effects, the direction of nonmotor behavioural change varies: STN-DBS can be beneficial, improving mood, anxiety and cognitive performance (Daniele et al., 2003; Ehlen et al., 2014; Funkiewiez et al., 2003; Frank Schneider et al., 2003; Witt et al., 2008, 2004) or result in worsening of patients' cognitive-affective state (Castelli et al., 2006; Ehlen et al., 2014; Smeding et al., 2006; Voon et al., 2006; Welter et al., 2014; Witt et al., 2008; Xie et al., 2016). A possible explanation for these mixed findings lies in the effect of electrode position within the STN: depending on the weighted stimulation of STN subterritories (and relatedly basal ganglia motor and nonmotor loops), cognitive performance might improve or worsen (Accolla et al., 2014, 2016; Accolla, Horn, Herrojo-Ruiz, Neumann, & Kühn, 2017; Castrioto et al., 2014; Ehlen et al., 2014; Højlund, Petersen, Sridharan, & Østergaard, 2017; Mallet et al., 2007; Okun et al., 2009; Ulla et al., 2011; Welter et al., 2014; Witt et al., 2013). In this study, I aimed to assess the impact of STN-DBS on risk-reward trade-off

decision-making and link VTA and weighted stimulation of STN motor versus nonmotor territories to differential DBS effects.

A total of 17 PD patients ON and OFF STN-DBS and 17 age-matched healthy controls conducted a sequential decision-making task with escalating risk and reward in which STN involvement had previously been implicated (Meder et al., 2016). Risk attitude, impulsivity and other behavioural parameters were compared within PD patients ON and OFF STN-DBS and between-groups to healthy controls. Further, bilateral electrodes were localized for all patients and the predictive value of the ratio of VTA in STN motor and nonmotor territories on behavioural change was analyzed.

The results showed that STN-DBS not only improves PD motor symptoms but also normalizes overly risk-averse decision behavior in PD patients: PD patients were overly cautious in their decisions leading to a smaller outcome gain and DBS elevated patients' risk attitude to a healthy level.

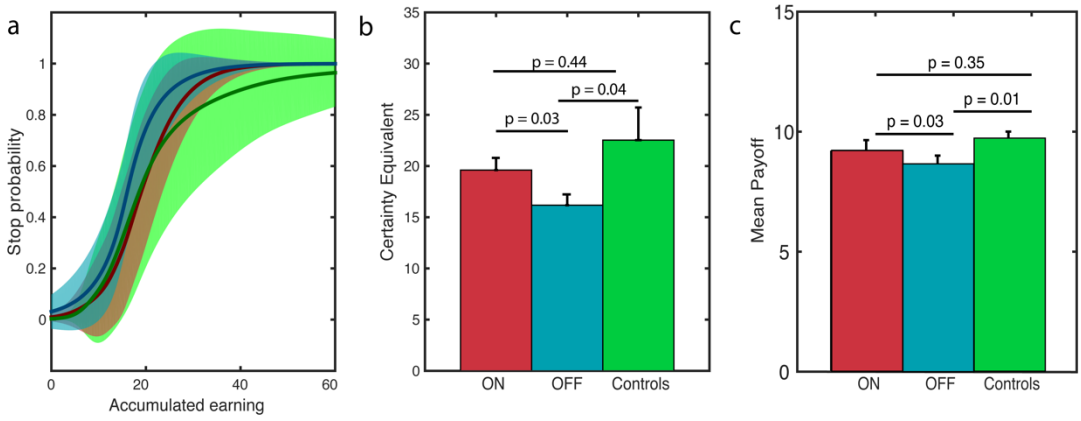

Figure 12. Study 2 – Effects of STN-DBS on stopping probability and certainty equivalent. (a)Stopping probability increases over accumulated sum in all three groups (M(SD)). (b) PD patients had a lower certainty equivalent than healthy controls and DBS normalized risk-reward trade-off (M(SE)). (c) PD patients OFF DBS earned less money and DBS increased their payoff (M(SE)). Figure by Irmen et al., 2018

Since a previous study employing the same paradigm had found STN-to-cortex coupling during the gradual build-up of action inhibition in the task (Meder et al., 2016), it can be speculated that STN-DBS may restore an adequate risk-reward trade-off by disrupting excessive STN-to-cortex coupling in PD (which manifests in a cautious risk-attitude). Indeed, a current theory suggests PD patients may be caught up in an overly strong bias to maintain the status quo (Fleming, Thomas, & Dolan, 2010) relating to their neuropathological enhancement of beta activity (Engel & Fries, 2010; Little & Brown, 2018) which biases them to rather accept the suboptimal default than to take more risk to increase their gains. Because STN-DBS disrupts excessive beta-activity (Oswal et al., 2016), patients are released from the enhanced status quo bias allowing for gain-maximizing risk-reward trade-off decisions.

Interestingly, inter-subject variance in electrode and VTA location was predictive for this behavioral change: if STN-DBS activated preferentially STN motor territory, patients' risk-reward trade-off decisions more resembled those of HC. This suggests a positive impact of well-placed STN-DBS

electrodes on cognitive improvement. While an effect of STN-DBS of cognition might prompt the suggestion that it was induced by stimulation of nonmotor STN territory, it is again the direction of change that matters: stimulation of STN nonmotor territories has been related to disturbance of cognitive function (Mosley et al., 2018) while the relation of cognitive improvement to relative motor and nonmotor STN stimulation had ben disregarded prior to this study.

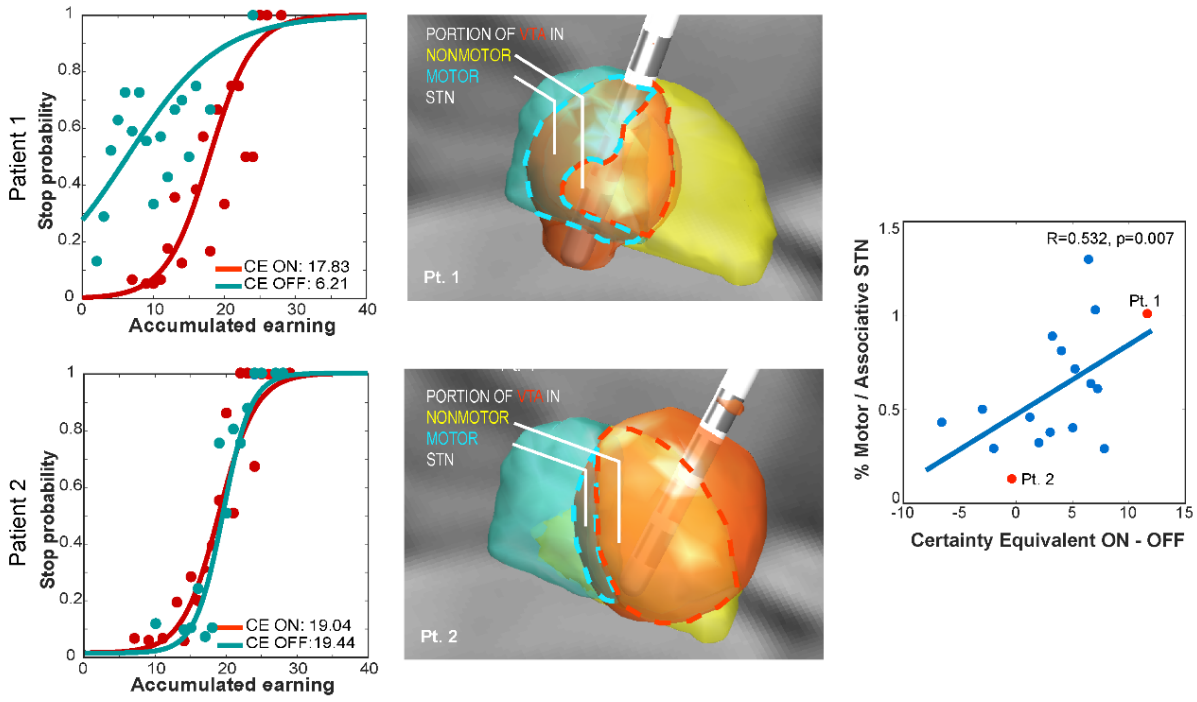

Figure 13. Study 2 - Impact of electrode placement on behavioral change. Individual stopping probabilities over accumulated sum in two exemplary patients are depicted together with VTA location stimulating motor and nonmotor STN territories. DBS-induced behavioural change in the certainty equivalent correlates with the ratio of motor over nonmotor STN activation by the VTA. Figure by Irmen et al., 2018

Moreover, there is plenty of evidence that the functional segregation of STN territories is not clear-cut: there is a convergence of motor, associative and limbic basal ganglia loops in transient STN sub-zones with a gradient distribution of neurons responding to motor, associative and limbic content (Accolla et al., 2014, 2016, 2017; Haynes & Haber, 2013; Lambert et al., 2012). In the STN motor segment, neurons with primary motor association may interact with neurons connected to prefrontal areas or the same neuron may receive shared projections from both motor and associative targets (Aron, Herz, Brown, Forstmann, & Zaghloul, 2016; Haynes & Haber, 2013). There is thus evidence for intertwined STN and basal ganglia loops and converging projections from associative prefrontal areas in the motor STN (Carmichael & Price, 1998; Joel & Weiner, 1994; Lynd-Balta & Haber, 2004) which could explain the observed positive effect of well-placed STN-DBS on nonmotor cognitive functioning in PD.

Statement of contribution: Data acquisition and analysis was conducted by me at Charité - Universitätsklinikum Berlin. The task was designed by David Meder and used in a previous publication during an fMRI experiment at the Danish Research Centre of Magnetic Resonance (Meder et al., 2016).

The adaptation of the task for the use in our PD sample was done with help of Wolf-Julian Neumann. I wrote the paper and got feedback by my coauthors.

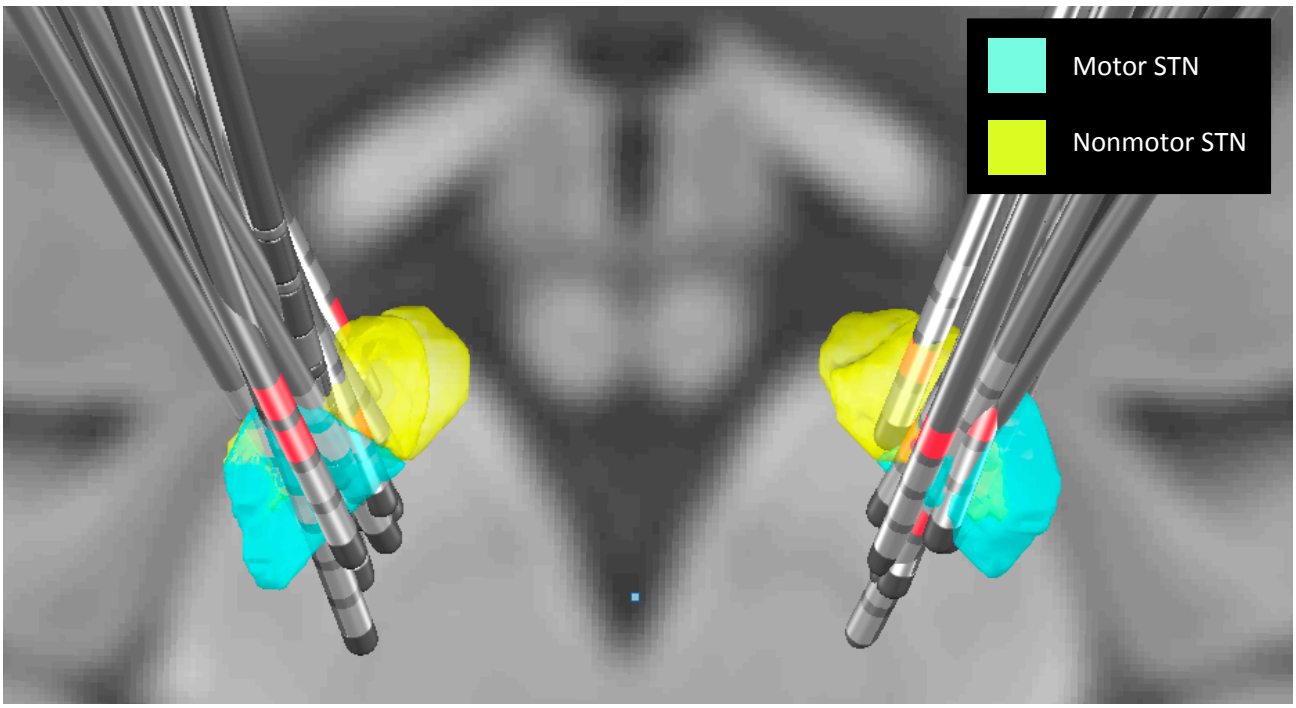

Figure 14. Study 2 - Electrode placement in study cohort. STN motor and nonmotor territories are marked in blue and yellow, respectively. Active contacts for each electrode are marked in red. Figure by Irmen et al., 2018

4.3. Left prefrontal connectivity links subthalamic stimulation with depression

As detailed in the introduction, it is currently accepted that STN-DBS leads to changes in nonmotor symptoms by modulating overlapping cortex-basal ganglia motor and nonmotor loops (Haynes & Haber, 2013). Nonmotor symptoms of PD include depression (Chaudhuri & Schapira, 2009) and STN-DBS can induce affective changes such as postoperative hypomania (Volkmann et al., 2010) but also acute depression (Bejjani et al., 1999; Funkiewiez et al., 2006, 2003), the latter has an estimated prevalence of about 20-25% (Witt et al., 2012). Interestingly, STN-DBS has been reported to improve (Campbell et al., 2012; Daniele et al., 2003), worsen (Follett et al., 2010; Temel et al., 2006) or to have no effect (Deuschl et al., 2006; Weaver et al., 2009) on symptoms of depression or anxiety.
There is evidence, that the precise local placement of DBS electrodes has an effect on nonmotor DBS effects (Irmen et al., 2019; Mallet et al., 2007; Mosley et al., 2018; Witt et al., 2013) and modulation of distant brain regions involved in affective processing might play a crucial role on how affective symptoms develop after surgery. In this study, I thus sought to investigate the impact of electrode placement and associated structural connectivity on changes in depressive symptoms with STN-DBS. To this end, I retrospectively collected data on depressive symptoms recorded with the BDI before and 6-12 months after STN-DBS surgery in a sample of 116 PD patients (Appendix B). In all patients, based on pre- and postoperative imaging, electrode placements were reconstructed using Lead-DBS

software. Next, using a finite element approach the VTA was estimated and combined with normative connectome data to identify structural connections passing through VTAs. This way each patient's individual structural connectivity profile to other regions in the brain could be estimated.

The total sample was divided into (i) a training and cross-validation set of 80 PD patients from two DBS centres (BER, QU), and (ii) a test data-set from an independent DBS center (CGN, n = 36). Using the training set, I calculated models that explained and cross-predicted change in depressive symptoms and cross validated them between DBS centers.

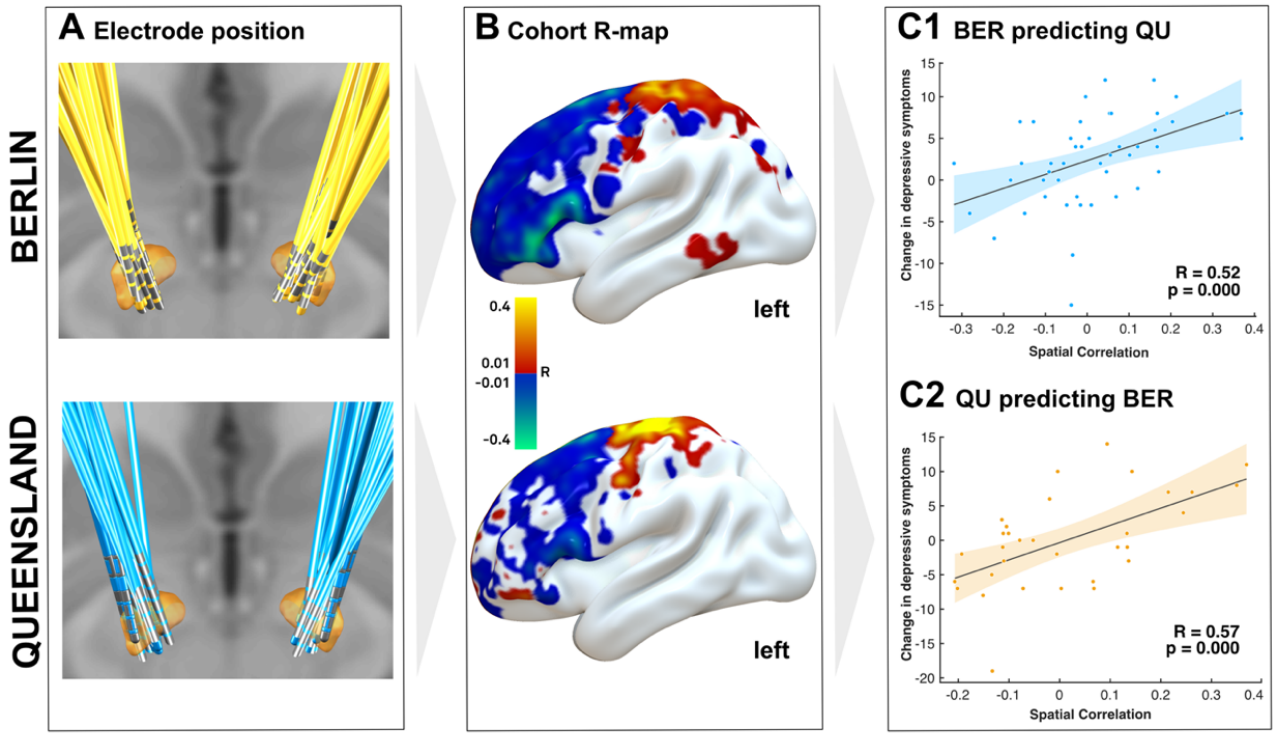

Figure 15. Study 3 - Results Training dataset. A) Electrode position for the two cohorts from Berlin and Queensland. B) Each cohort's R-Map represents the association with change in depressive symptoms under STN-DBS. Negative (blue) areas of the left hemisphere shown here relate to worsening of depressive symptoms. R-Maps revealed a significant association between worsening of depressive symptoms after STN-DBS and connectivity to left dorsolateral PFC. C1) Based on the R-Map from the Berlin cohort, depressive symptoms in the Queensland Cohort could be significantly predicted and vice versa (C2). R-Maps are presented smoothed with a 3mm full-width half-maximum Gaussian kernel to increase signal-to-noise ratio. Figure by Irmen et al., 2019

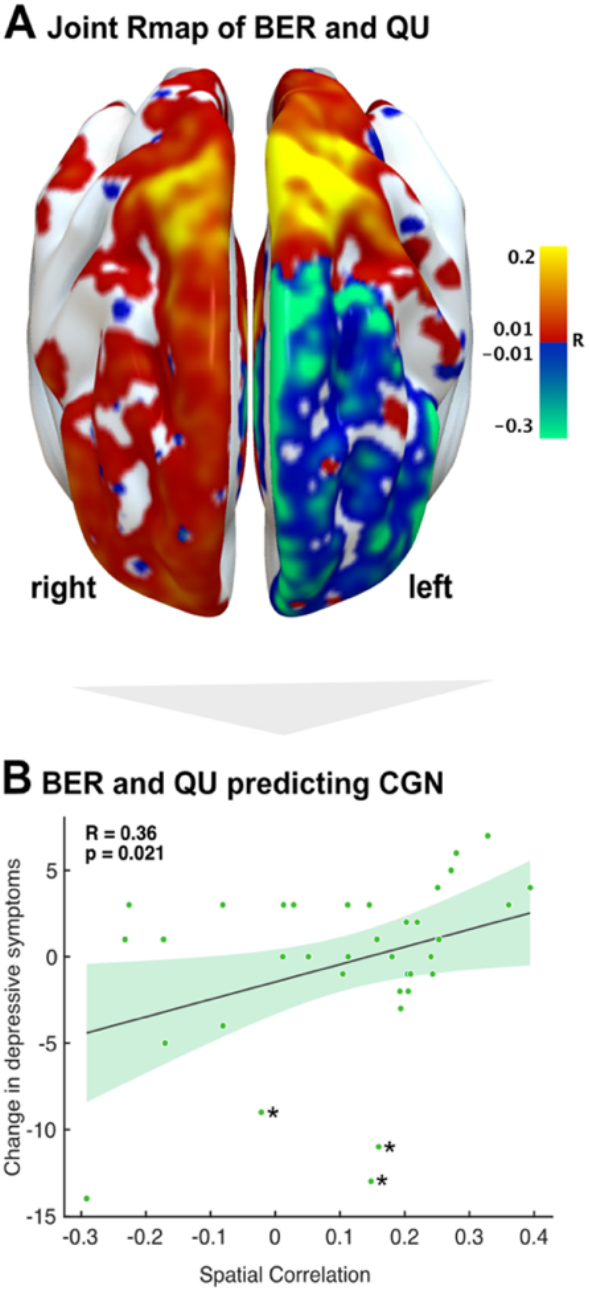

Figure 16. Study 3 - Structural connectivity predicting change in depressive symptoms in the test dataset. A) R-Map of the training dataset. Negative (blue) areas represent association with worsening of depressive symptoms while positive (red) areas represent association with improvement of depressive symptoms under STN-DBS. The R-Map is presented smoothed with a 3mm full-width half-maximum Gaussian kernel to increase signal-to-noise ratio. B) The R-Map of the training dataset (BER-QU model) significantly predicted change in depressive symptoms in the test-dataset (CGN). Patients marked with asterisks showed moderate worsening in depressive symptoms with comorbidities and pain, which remained stable over the period of assessment; hence patients were not excluded from the test dataset. C) Electrode positions of the test dataset within the STN. Figure by Irmen et al., 2019

Subsequently, I predicted changes in depressive symptoms in the test set based on the previously cross-validated model. The analysis identified a robust model linking structural connectivity to depression under STN-DBS. An optimal connectivity map trained on the Berlin cohort could predict changes in depressive symptoms in patients from Queensland ($R=0.52$, $p<0.0001$) and vice versa ($R=0.57$, $p<0.0001$). Furthermore, the joint training-set map predicted changes in depressive symptoms in the independent test-set ($R=0.36$, $p=0.021$). The results remained significant when controlling for motor improvement and dopaminergic medication withdrawal.
Crucially, worsening of depressive symptoms was consistently associated with connectivity to left dorsolateral prefrontal areas. This area is also the prime target for non-invasive stimulation in depression (Pascual-Leone et al., 1996) and the common clinical targets of repetitive Transcranial Magnetic stimulation (rTMS) in depression that have been summarized by Fox et al. (2013) precisely lie within the clusters we find negatively associated with BDI improvement under STN-DBS. There is plenty of evidence linking depression to hypoactivity and dysfunction of the left frontal cortex (Chang et al., 2011; Egorova et al., 2017; Fedorof, Starkstein, Forrester, Geisler, Jorge, Arndt & Robinson, 1992; Grajny et al., 2016; Grimm et al., 2007; Hama et al., 2007; Hamilton et al., 2012; Jorge et al., 2004; Koenigs et al., 2008; Leung et al., 2018; Mayberg et al., 2005; Shi, Yang, Zeng, & Wu, 2017; Thomas et al., 2003). This has been explained by involvement of the left dorsolateral prefrontal cortex (dlPFC) during negative affect regulation, e.g. reappraisal and voluntary suppression (Koenigs et al., 2010; Lévesque et al., 2003; Ochsner et al., 2004; Phan et al., 2005) which is exceeded via the frontoparietal cognitive control network (Pan et al., 2018). With rTMS, excitation of hypoactive frontal regions can be increased leading to symptom amelioration (Pascual-Leone et al., 1996).
An additional analysis conducted in this study could show that depressive symptom worsening under DBS is associated with stimulation of fibers reaching from prefrontal areas via zona incerta to the dorsal mesencephalon and brainstem (where they might terminate in the dorsal raphe nucleus, a key part of the serotonergic system (Michelsen et al. , 2008; Politis et al., 2010; Wei et al., 2018). STN-DBS may lead to artificial lesioning and blockage of connecting fibers between prefrontal areas and the brainstem. Indeed, dysconnectivity of the dorsal raphe nucleus (DRN) and prefrontal areas is related to depression (Ikuta et al., 2017) and abnormal serotonergic neurotransmission has been – albeit inconsistently – linked with depression in PD (Politis et al., 2010; Qamhawi et al., 2015). Thus, accidental disruption of the serotonergic communication between DRN and left prefrontal cortex may be a likely pathophysiological candidate to foster depressive states after STN-DBS.
Taken together, on the left hemisphere, high-frequency stimulation of fibers anteromedial to the STN is associated with worsening of depressive symptoms while stimulation of dorsolateral STN leads to improvement of depressive symptoms in PD patients. The connectivity profile described in this study may be used to inform surgeons and clinicians in the placement and settings of STN-DBS, depending on the patient's individual connectivity that could be studied before surgery.

Statement of contribution: Data of the Berlin dataset was gathered and electrodes were localized by me. I also reran localization for the dataset from Cologne. The Queensland dataset was localized by the team of Philip Mosley. BDI scores in Berlin were assessed by Gregor Wenzel and Dorothee Kübler as representatives of the team of neurologists in the Neuromodulation Unit of the Clinic of Neurology. Analysis was conducted by me with essential help of Andreas Horn who also supported me in writing the manuscript.

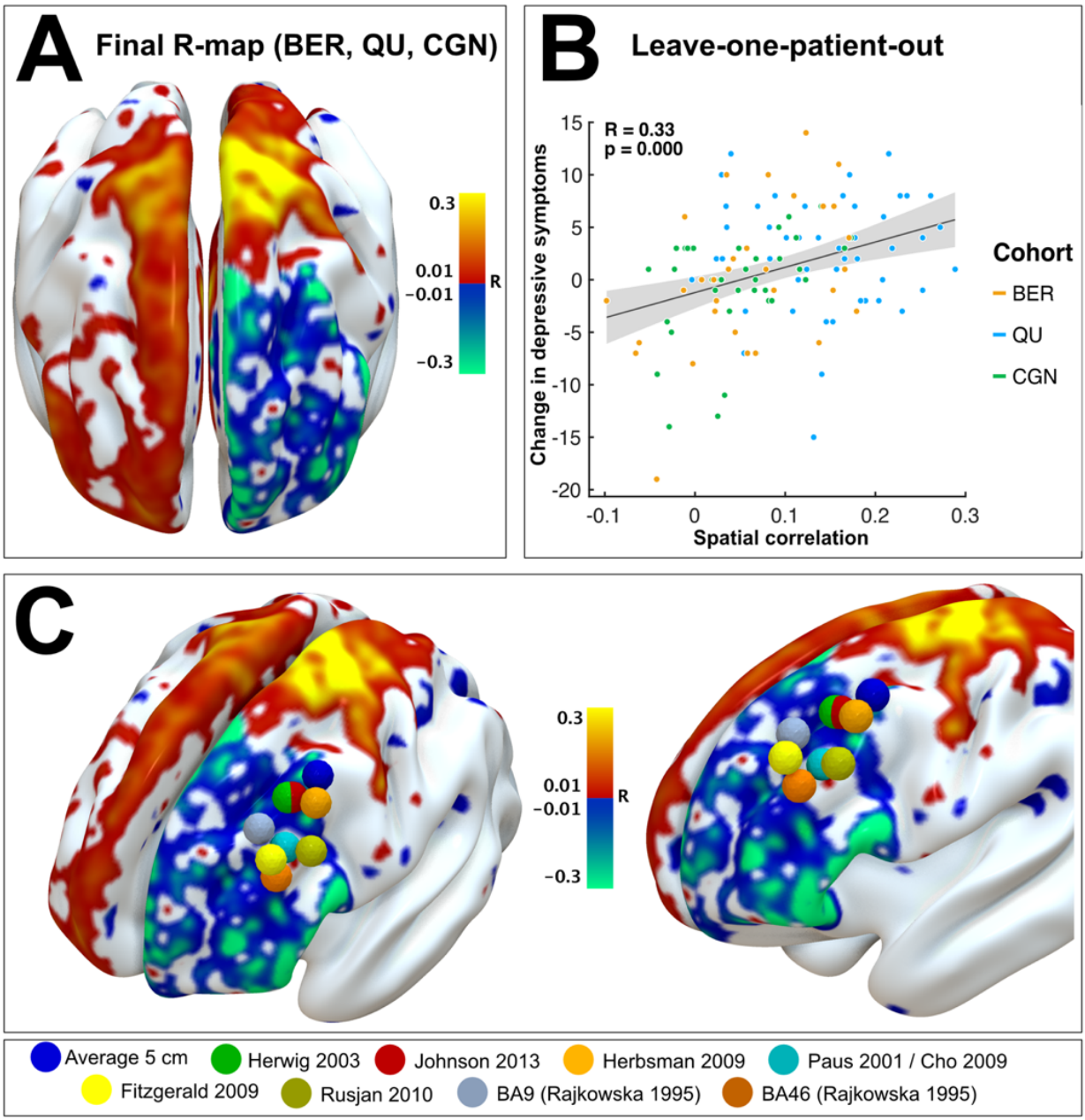

Figure 17. Study 3 - Final R-Map validation across all patients and proximity to TMS targets. A) R-Map associated with change of depressive symptoms over all patients (n = 116). B) Validation of the model using a leaving-one-out design. C) rTMS targets for treatment of depression superimposed on final R-Map. R-Maps are presented smoothed with a 3mm full-width half-maximum Gaussian kernel to increase signal-to-noise ratio. Figure by Irmen et al., 2019

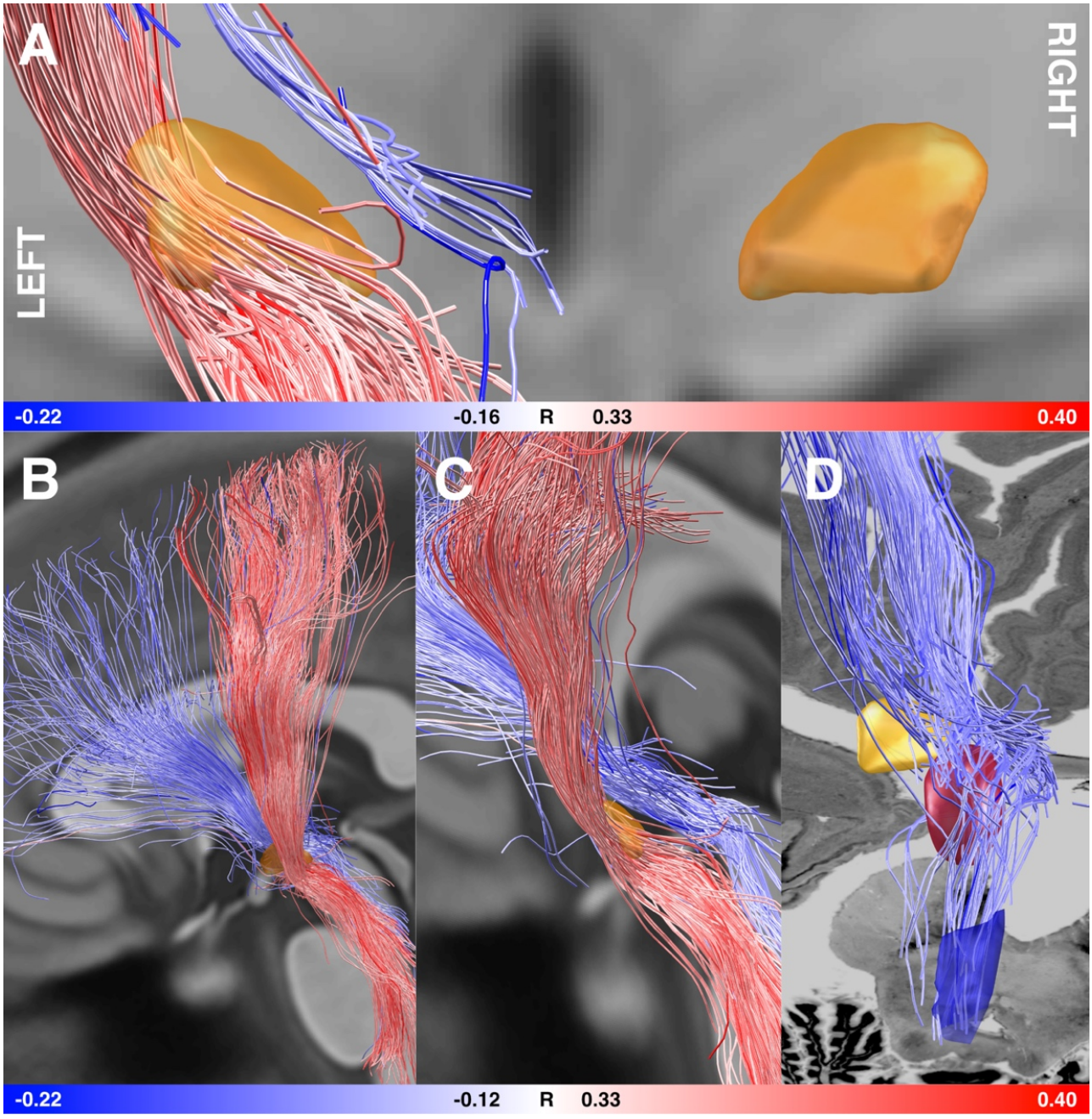

Figure 18. Study 3 - Fibertracts discriminative of BDI improvement when modulated. Red tracts are positively, blue tracts negatively correlated with BDI improvement. STN shown in orange. A) Coronal view from posterior with both hemispheres. At this threshold level, no fibers on the right hemisphere were associated with clinical improvement but a strong set of both positive and negative fibers were found on the left hemisphere. B) View from the left and C) view parallel to the longitudinal axis of the left STN. Positively and negatively correlated fibertracts seem to be distinct tracts, the positive one passing through the STN and lateral to it, the negative one medial and anteriorly. D) At the level of the brainstem, the negative tract seems to traverse around the red nucleus and may connect to (or originate from) brainstem nuclei such as the left DRN (shown in dark blue as defined by the Harvard Ascending Arousal Network Atlas; Edlow et al., 2012). Figure by Irmen et al., 2019

4.4. Further work on impact of subthalamic stimulation on cognition and affect

In addition to the three studies described above, I also contributed to two other projects which are briefly summarized here but do not count as main parts of the dissertation work and thus were not included in the Methodology section.

4.4.1. Study 4 - Functional segregation of basal ganglia pathways

This study focused on studying the complex interplay between converging basal ganglia pathways by measuring and modelling behavioral change induced by STN-DBS in a visuomotor adaptation task. This task was designed to disentangle the role of the inhibitory basal ganglia pathways in cognitive and kinematic aspects of automatic and controlled movements while studying the effect of STN-DBS on behaviour. Healthy subjects (n =20), PD patients ON and OFF STN-DBS (n = 20) and ON and OFF antiparkinsonian medication (n = 10; no DBS) participated in a visuomotor tracking task requiring normal (automatic) and inverted (controlled) reach movements.

PD patients ON and OFF STN-DBS presented complex patterns of reaction time and kinematic changes, when compared to healthy controls. Specifically, STN-DBS reduced reaction times in the condition with higher cognitive inhibitory demand (controlled condition), while movement velocity is globally increased independently of task difficulty (in controlled and automatic conditions).

To gather a mechanistic explanation for this behavioral change, fiber-tracking was performed which established that stimulation of cortico-subthalamic fibers (between the supplementary motor area [SMA] and STN) was associated with reduced reaction time adaptation to task demand, but not with kinematic aspects of motor control or alleviation of PD motor signs. As a final step, based on clinical and fibertracking data, the behavioral effect was computationally modelled to test differential effects of STN-DBS on hyperdirect and indirect pathways. The analysis revealed, that the DBS-induced loss of cognitive adaptation could be attributed to modulation of the hyperdirect basal ganglia pathway, while kinematics depended on suppression of indirect pathway activity.

The findings suggest that hyperdirect and indirect pathways, converging in the STN, are differentially involved in cognitive aspects of cautious motor preparation and kinematic control during motor performance. STN-DBS modulates but does not restore these functions. Intelligent stimulation algorithms could re-enable flexible motor control in PD when adapted to instantaneous environmental demand. Thereby, these results may inspire new innovative pathway-specific approaches to reduce side effects and increase therapeutic efficacy of neuromodulation in patients with PD.

Statement of contribution: For this project, I collected data of 10 subjects with PD without STN-DBS, that conducted the task while ON and OFF their usual antiparkinsonian medication. Furthermore, I gave input to the manuscript.

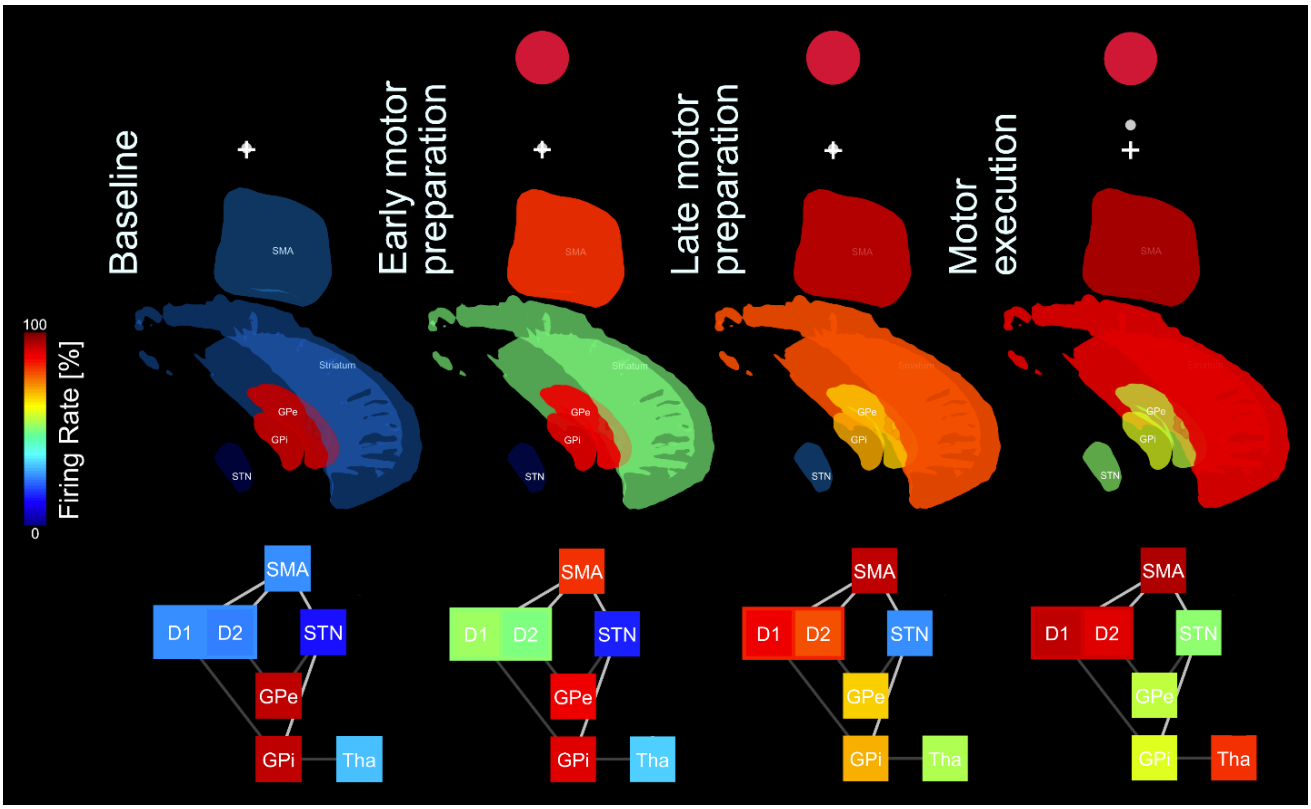

Figure 19. Study 4 - A firing rate model that can perform the visuomotor adaptation task. A representative trial performed by the healthy basal ganglia model illustrates the core elements and network dynamics [task stage depicted on top as baseline (500 ms in relation to cue onset), early motor preparation (250 ms), late motor preparation (500 ms) and during motor execution (1500 ms)]; 3D representations of model elements in the middle, 2D representations below, colour depicts relative baseline corrected firing rate. Figure by Neumann et al., 2018

4.4.2. Study 5 - Deep brain stimulation induced normalization of the human functional connectome in Parkinson's disease

This study focussed on studying the effects of STN-DBS on the functional human connectome. As detailed above, STN-DBS broadly modulates distributed brain networks. The aim of this study was to better understand this modulation.

Resting-state functional MRI was acquired in 20 PD patients with STN-DBS switched ON and OFF. An age-matched control cohort of 15 subjects was acquired from an open data repository. For the scanned patients, DBS electrodes were localized using Lead-DBS and the VTA was estimated using a finite element method approach. Based on minor differences in DBS electrode placement, different amounts of motor STN volume were stimulated in each patient. As a result, corresponding differing changes in motor cortical activation were expected that should be stronger or weaker as a function of electrode placement: an optimally placed lead would result in strong modulations in the motor network, normalizing toward the network properties found in healthy controls. In contrast, poorly placed leads would not result in strong motor network changes.

The results implicate that STN-DBS had a significant effect on brain connectivity throughout the sensorimotor network, specifically on its cortical and cerebellar subparts. Interestingly, DBS attenuated specific couplings that are known to be pathological in PD. Namely, coupling between motor thalamus and sensorimotor cortex was increased and striatal coupling with cerebellum, external pallidum and STN was decreased by DBS.

Crucially, electrodes with strong impact (i.e. VTA) on the motor STN induced larger changes than the ones with weak or no impact on the motor STN ($R = 0.7$, $p < 0.001$). Moreover, STN-DBS had the effect of "normalizing" both connectivity profiles of the electrodes but also average connectivity profiles toward profiles found in age-matched healthy control subjects. Again, this effect was dependent on electrode location – well placed electrodes shifted the overall connectivity profiles more strongly toward controls than poorly placed electrodes ($R = 0.713$, $p < 0.001$).

Taken together, this study demonstrates that effective DBS increases overall connectivity in the motor network, normalizes the network profile toward healthy controls and specifically strengthens thalamo-cortical connectivity while reducing striatal control over basal ganglia and cerebellar structures.

Statement of contribution: In this project, I conducted a literature review, where I summarized all studies that conducted resting-state fMRI ON and OFF DBS. With this, I could contribute to the manuscript in form of a table and furthermore gave input and feedback to the rest of the manuscript.

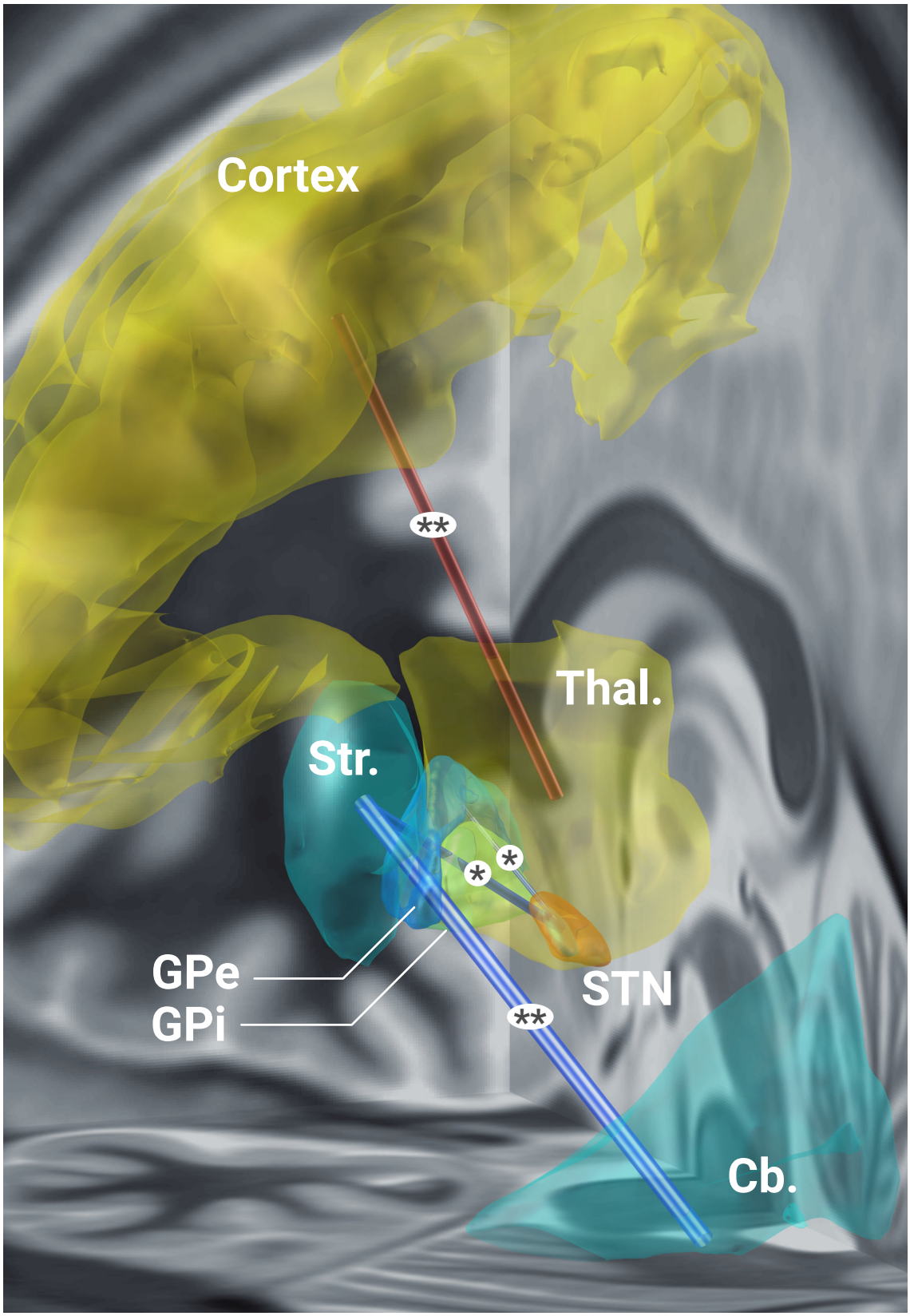

Figure 20. Study 5 - Specific connections in the sensorimotor network are modulated by effective STN-DBS. Functional connectivity between motor thalamus (sensorimotor functional domain) and sensorimotor cortex (SMA, M1, S1) increased as a function of DBS impact on the motor STN. Instead, connectivity between motor striatum and cerebellum, motor striatum and motor STN as well as motor STN and motor GPe decreased. For exact definition of ROI within the motor network see table 2. ** = $p < 0.005$, * = $p < 0.05$ corrected for multiple comparisons using the network based statistics approach as implemented in the GraphVar toolbox . Figure by Horn et al., 2019.

5. Discussion

Translational research in the field of clinical neuroscience has the potential to immediately impact understanding, adaptation and development of current therapies thereby improving patient care. Especially in the field of DBS of basal ganglia targets like the STN, where researchers still face many open questions, better understanding of mechanisms underlying DBS-induced effects on behaviour are valuable. This dissertation aims to make a modest contribution to this growing field of science by identifying behavioural markers for the influence of STN-DBS on behaviour that can be modelled computationally or by estimating local or global DBS impact on basal ganglia-cortical networks.

5.1. Discussion of research questions

The overall goal of the studies presented in this thesis was to aid the understanding of STN-DBS on cognition and affect, which determines the role of the STN within the basal ganglia motor and nonmotor circuits.

In Study 1, the influence of STN-DBS on emotional conflict processing was measured in patients with PD and in healthy controls using an emotional Stroop paradigm. Here, subjects needed to name the emotion of the face while ignoring the superimposed congruent or incongruent emotion word. Because reading is automatized (Stroop, 1935), naming the face requires cognitive control that involves detection of the incongruent stimulus by conflict monitoring modules in the Anterior Cingulate Cortex (ACC) and associated slowing of responses (Etkin et al., 2011; Etkin et al., 2006). Since it is established that STN-DBS impairs this conflict-induced slowing (Cavanagh et al., 2011; Frank, Samanta, Moustafa, & Sherman, 2007; Herz, Zavala, Bogacz, & Brown, 2016; Jahanshahi, Obeso, Baunez, Alegre, & Krack, 2015) but also affective processing (Drapier et al., 2008; Le Jeune et al., 2008; Péron, Grandjean, et al., 2010) we expected patients' responses ON DBS to be modulated by conflict, emotional content or both. Indeed, the main result suggested that PD patients were unable to ordinarily slow down their responses when facing emotional conflict while DBS is ON. Previous assessments of performance of PD patients under STN-DBS in the traditional Stroop paradigm reported no effect of DBS on behavior, however, their outcome parameters were different (total time needed to complete the task in Jahanshahi, 2000 and Witt et al., 2004 versus trial-by-trial reaction times in this study) or they lacked the waiting time in between ON and OFF DBS assessments (Schroeder, 2002). It is likely that the results also differed since the use of faces and emotion words in the applied task engaged affective brain regions such as the orbitofrontal cortex or amygdala not involved in the traditional Stroop task (Etkin et al., 2011).

The second important result of Study 1 was that emotional valence of the face was meaningful to the behavioral response of PD patients OFF DBS: here, conflict-related slowing was much stronger, if a negative face was superimposed by a positive word, than vice versa. This finding suggests a selective attentional or working-memory bias toward negative and away from positive information that is

present in PD patients. Since STN-DBS alleviated this bias, it can be presumed that the stimulation reduced this "negativity bias" in PD, but to an extend that emotional conflict information was literally ignored, and no response-slowing was present. In order to model the mechanism behind the reported DBS-effect, the computational Stroop model (Botvinick et al., 2001) was adapted and applied to emotional content. In this model, the STN was conceptualized to be part of the conflict module, contributing to the modulation of the behavioral response during conflict. The Parkinsonian state with a stronger Stroop effect for negative faces/positive words was modelled by increasing the "conflict weight" for positive words, i.e. by assuming that positive words elicit stronger conflict (see Appendix A for details). It was found that the reduction of conflict-induced slowing is best modelled by an increased baseline activity in the STN. This is of particular interest as DBS has been shown to modulate both input and output of the target structure (Agnesi, Connolly, Baker, Vitek, & Johnson, 2013; Dorval, Kuncel, Birdno, Turner, & Grill, 2010; Dorval et al., 2008). This data suggests that higher axonal output of STN neurons best explains the behavioral deficits of reaction time slowing under emotional conflict in PD patients treated with DBS.

Taken together, this study could show that PD patients have an inherent bias by which positive stimuli elicit stronger conflict signals, leading to greater response slowing. STN-DBS alleviates this bias but blunts emotional conflict processing altogether leading to equally fast responses for conflicting and non-conflicting stimuli. This effect is steered by an increased baseline activity in the STN, which might override physiological STN-activity during the task that would normally pause the motor output (Brittain et al., 2012; Chen et al., 2006; Garcia, Audin, D'Alessandro, Bioulac, & Hammond, 2003).

The second study conducted for this dissertation investigated the effect of STN-DBS on decision-making. While STN-DBS has been shown to alter the decision threshold and induce impulsivity in *perceptual* decision-making (Cavanagh et al., 2011; Frank et al., 2007; Green et al., 2013; Herz et al., 2016), its effects on *value-based* decision-making are only poorly described. Thus, in this study I investigated, whether STN-DBS impacts decisions where risk and reward are traded off against each other using the dice game, a sequential gambling task.

The first finding of this study was that PD patients OFF DBS were highly risk averse in their decisions – more so than healthy controls in their age. This is perhaps unsurprising, since high risk aversion, low novelty seeking, reduced reward sensitivity, altered cost-benefit judgements and outcome evaluation have previously been linked to PD (Baig et al., 2017; Kaasinen et al., 2001; McNamara et al., 2008; Ryterska et al., 2014; Van Der Vegt et al., 2013). Indeed, PD patients seem to lack cognitive flexibility, being caught up in the status quo (Fleming et al., 2010): that is, in the dice game task, they tended to rather bank the current sum of money than to take more risk and increase their gains (which would be more beneficial). This might relate to the pathophysiological increase in beta activity in the basal ganglia which enhances maintenance of the status quo (Engel & Fries, 2010; Little & Brown, 2018). Our finding that STN-DBS makes patients more risk-seeking is in line with the understanding that STN-

DBS suppresses the amplified beta activity (Kühn et al., 2005; 2008). Interestingly however, the results of this study did not suggest an increase in impulsivity but rather a normalization toward healthy decision behavior: under STN-DBS patients' decisions more resembled those of healthy controls. This likely relates to the fact that conflict was stable in this task, i.e. evidence did not accumulate over time until a decision-threshold was reached as in perceptual decision making tasks (Herz et al., 2016). This methodological difference might explain why in this study no DBS-induced impulsivity was reported.
As an approach to a mechanistic explanation of the behavioral changes, the alterations in decision-making behavior were correlated with the estimated stimulation of STN motor versus nonmotor territory based on the reconstructions of patients' electrodes and the volume of brain tissue activated by the stimulation. Interestingly, the normalizing (towards healthy behavior) effects of DBS were larger, if the electrode stimulated primarily motor STN territory. This suggests a healthy impact of STN-DBS as long as the stimulation is effectively placed in the STN motor target. It can however not be ruled out that stimulation of nonmotor STN territories might lead to a deterioration of value-based decision-making as has been shown in cohorts where DBS leads targeted the limbic STN subzone (Voon et al., 2017).
The fact that motor STN-DBS alters cognitive functions supports the increasing evidence for overlap of cortical input reaching the basal ganglia, resulting in converging rather than strictly segregated pathways (Haynes & Haber, 2013). Gradient transitions between STN subzones mean that neurons with primarily motor associations might interact with neurons that have prefrontal connections (Castrioto et al., 2014). Such convergence of motor, associative and limbic information in the STN highlights its role in the integration of motor and nonmotor information during action selection and initiation. The findings of this study thus contribute to the understanding of STN function and link behavioral performance in a cognitive task to local stimulation impact on basal ganglia motor and nonmotor territories.

The third study conducted for this dissertation investigated the impact of electrode placement and the associated structural connectivity on changes in depressive symptoms 6-12 months after STN-DBS surgery. The main incentive for this study was the current paradigm shift towards investigating DBS effects on distributed brain networks rather than only local targets (Accolla et al., 2016; Horn, 2019; Lozano & Lipsman, 2013). This approach already helped to explain motor outcome with STN-DBS in PD (Horn et al., 2017) or clinical improvement with DBS in patients with obsessive compulsive disorder (Baldermann et al., 2019). DBS-effects on cognition and affect as described above relate to the modulation of overlapping motor, associative and limbic basal ganglia circuits (Haynes & Haber, 2013). Thus, the assessment of global network alterations induced through STN-DBS can aid the understanding and potentially the control of these nonmotor DBS-effects. One of the most common affective side effects of STN-DBS is depression (Funkiewiez et al., 2006, 2003; Witt et al., 2012). Thus,

this study focused on this specific DBS-effect and aimed to demarcate associated network changes under DBS.

The results strongly suggest a left-lateralized impact of STN-DBS on prefrontal regions that explains worsening of depressive symptoms. Within a training dataset consisting of two cohorts form two international DBS centers (BER, QU, n = 80) the connectivity map of the BER sample could significantly predict worsening of symptoms in the QU cohort and vice versa. Moreover, data from an independent test-set (CGN, n = 36) could be predicted by the training-set connectivity map. Taken together, this evidence suggests that worsening of depressive symptoms occurs when DBS electrodes target fibers connected to the left dlPFC which is also the primary target for rTMS in major depression (Fox, Liu, & Pascual-Leone, 2013) where left prefrontal regions are hypoactive (Chang *et al.*, 2011; Grimm *et al.*, 2007; Hamilton *et al.*, 2012; Koenigs *et al.*, 2008; Mayberg *et al.*, 2005; Thomas *et al.*, 2003). Indeed, dlPFC connectivity seems to play a major role in depression (Hwang *et al.*, 2015; Kaiser *et al.*, 2015; Sheline *et al.*, 2010) as this region has been linked to affective reappraisal and voluntary suppression of negative affect (Koenigs *et al.*, 2010; Lévesque *et al.*, 2003; Ochsner *et al.*, 2004; Phan *et al.*, 2005). Thus, DBS impacting left prefrontal territories may disrupt this process leading to increased depressive symptoms. In contrast, patients with less STN-prefrontal connecting fibers stimulated improved in their depressive symptoms. Importantly, the streamlines between STN and left prefrontal cortex were not directly connected to STN territory but bypassed the STN anteriomedially descending to the brainstem. A candidate seed for these fibers could be the DRN, which as part of the serotonergic system impacts mood states (Michelsen *et al.* , 2008; Politis *et al.*, 2010; Wei *et al.*, 2018). In depression, the DRN is hypoactive (Michelsen *et al.*, 2007) and shows an altered connectivity with prefrontal areas (Ikuta *et al.*, 2017). Hence, accidental disruption of the serotonergic communication between left dlPFC and DRN through stimulation of fibers running anteriomedial to the STN may be a pathophysiological candidate to foster depressive states after STN-DBS. Importantly, since the current data result from analyses using a normative connectome, these findings should be replicated with patient-specific structural connectivity. Based on this study, new directions can be developed to avoid harmful side effects of STN-DBS in PD patients by considering connectivity to networks guiding these side effects, which has high potential therapeutic value. A potential follow-up study could monitor changes in depressive symptoms in patients with directional (segmented) electrodes, where the electric current can be steered away versus towards fibertracts connected to left prefrontal areas. One would expect depressive symptoms to occur (long-term) if current is directed anteriomedially but not if it is directed posteriolaterally away from the fibers connected to the left prefrontal cortex. Furthermore, functional resting-state connectivity changes could be tracked and correlated with STN-DBS associated changes in depression. Here, functional connectivity changes of STN and left prefrontal regions would be expected in patients where the stimulated contact approaches the described fibertracts anteriomedially of the STN. Taken together, this study opens a lot of perspectives to further study

affective changes induced by DBS and brain networks involved in the evolution of depressive symptoms.

Additionally, my work in the two publications with co-authorship also contributed to the understanding of STN-DBS effects on basal ganglia pathways and the cortico-subthalamic resting-state interaction underlying DBS effects, respectively. The aim of Study 4 by Neumann et al. (2018) was to disentangle basal ganglia pathways involved in cognitive control and kinematics of movement. To this end, a visuomotor adaptation task was conducted with PD patients ON and OFF STN-DBS, where subjects had to make automatic versus controlled movements (the latter of which require cognitive control). DBS affected both movement preparation and execution: when stimulated, PD patients decreased their reaction times in controlled movements leading to more errors. This suggests that STN-DBS interfered with the coupling of STN-to-cortex, that has been hypothesized to delay movement execution via the hyperdirect pathway in tasks that demand cognitive control. Indeed, a computational model applied confirmed the reaction time effect to be guided through interference with hyperdirect pathway activity. Moreover, in this study, DBS decreased movement times, which based on the applied model related to suppression of indirect pathway activity. Importantly, indirect pathway activity has been related to motor symptom alleviation (Kahan, 2014) and in this study also correlated with motor symptom improvement. Thus, this study contributed to a better understanding of STN-cortex interaction during movement and provided a computational model for healthy, PD-specific and DBS-induced mechanism of basal ganglia functioning that guide behavioral changes.
Study 5 by Horn et al. (2019) focused on functional connectivity changes under STN-DBS. There have been a number of studies examining resting-state changes under DBS (see Horn, et al., 2019 for a comprehensive table) but none of them has taken electrode placement into account as a regressor. Importantly, even minimal variance in electrode position can impact clinical outcome and connectivity modulation (Baldermann et al., 2019; Neumann et al., 2018; Rorden et al., 2018). To this end, this study aimed to assess resting-state functional connectivity ON or OFF DBS in order to compare the change in functional network activity within subjects and to healthy controls. The results suggest that STN-DBS lead to an overall increase in functional connectivity throughout the sensorimotor network which might relate to reduction of basal ganglia output (which is inhibitory; hence, a reduction of output from GPi and SNr facilitates movement) and resulting stronger thalamo-cortical interaction. Moreover, this connectivity shift depended on electrode location: under DBS, average functional connectivity in motor regions more resembled that of healthy controls if the electrode was placed optimally in the motor STN subzone. If however, the electrode was placed outside the STN, little to no modulation of the sensorimotor regions was induced. Interestingly, DBS had a "normalizing" influence on functional brain connectivity. The better the placement of the electrode, the more functional connectivity "normalized" to resemble that of healthy controls. These results suggest that resting-state fMRI could potentially be

used to improve targeting of basal ganglia by quantification of the potential stimulation impact on the motor network.

Taken together, the studies included in this dissertation contribute to i) present evidence for nonmotor DBS effects in PD patients, and ii) provide mechanistic explanations for the observed alterations such as computational models or estimation of local and global network effects induced by DBS. Together, they provide insights into the role of the STN within the basal ganglia-cortical network, Parkinsonian features of change in this network and DBS-induced alterations within and across network hubs. The subsequent section embeds the results in the current understanding of the basal ganglia functional model.

5.2. A model of subthalamic stimulation impact on cognition and affect

Cognitive and affective changes induced by STN-DBS are best understood when put in context of the basal ganglia functional organization and PD-related functional changes. As outlined in the introduction, the basal ganglia are assumed to be functionally organised to facilitate a selected movement (via activation of the direct pathway) and at the same time inhibit competing movements (via the indirect pathway) (Albin et al., 1989). Additionally, a hyperdirect pathway allows for fast modulation of basal ganglia output by cortical input leading to a global inhibition of movement (Nambu et al., 2002).

The interplay of direct and indirect pathways is strongly relying on dopaminergic input. Dopamine conveys a reinforcement signal that may be crucial for adaptive behaviour, i.e. the following of actions with desired outcomes and the avoidance of actions with undesired ones. Thus, in the interplay of direct and indirect pathway, dopamine is a strong modulator, reinforcing behaviour based on outcome, and ensuring smooth control of action. In PD, the loss of dopaminergic input to the basal ganglia originating from degeneration of dopaminergic neurons in the SNc leads to a disbalance between these pathways resulting in the pathognomonic parkinsonian motor signs. At the same time or even before, nonmotor symptoms also occur in PD which in the cognitive and affective domain include a lack of cognitive flexibility and decision-making impairments (Baig et al., 2017; Brandt et al., 2015; Kaasinen et al., 2001; McNamara et al., 2008; Menza, 2000; Ryterska et al., 2014) as well as emotional disturbances such as depression, anhedonia and apathy (Chaudhuri & Schapira, 2009; Gray & Tickle-Degnen, 2010; Maillet et al., 2016). These nonmotor symptoms, can partly be explained by the crucial role of dopamine in cognition and affect, especially in reinforcement learning (Schultz, Dayan, & Montague, 1997). Here, PD nonmotor symptoms may arise from disturbed basal ganglia functional organization: the basal ganglia receive input from not only motor but also associative and affective processing cortical areas and therefore have been described to be organized along (partly overlapping) motor, associative and limbic loops (Figure 2A). They present a crucial inhibitory control network,

where motor and nonmotor signals collectively influence adaptive behavioural output (Jahanshahi, Obeso, Baunez, et al., 2015; Jahanshahi, Obeso, Rothwell, & Obeso, 2015; Volkmann et al., 2010). Consequently, the parkinsonian hypodopaminergic state may be associated with functional circuit alterations that result in concurrent and potentially interdependent motor and nonmotor symptoms. The following section considers PD-related circuit changes as an initial bias to the investigation of STN-DBS-induced changes.

5.2.1. The basal ganglia in PD and the initial bias

"Sometimes my brain 'freezes up,' kind of like my legs sometimes do. Finding the words I want to say is very hard, and my thoughts seem like they are blank." (Goldman et al., 2018)

This quote by a PD patient provides anecdotal insight into the disturbing nature of nonmotor symptoms, which strongly affect patients' quality of life (Goldman et al., 2018). Both limbs and thoughts slow down in PD and comparing motor and nonmotor symptoms makes sense when considering their common origin in pathophysiological changes of basal ganglia function (Figure 21). The loss of dopaminergic neurons in the SNc leaves striatal-thalamic-prefrontal and basotemporal limbic pathways without the reinforcing signal that guides synaptic plasticity to mediate behavioral adaptation (Obeso et al., 2017). In fact, it has been hypothesized, that the lacking dopaminergic reinforcement signal leads to progressively diminished synaptic strength (or long-term depression [LTD]) and consequently an increased inhibitory burden for input – output transfer through the basal ganglia circuit (Bar-Gad & Bergman, 2001) explaining chronic deterioration. This might lead to learning deficits in PD patients (de Almeida Marcelino, Horn, Krause, Kühn, & Neumann, 2019), disturbed emotion processing (Le Jeune et al., 2008; Péron, Biseul, et al., 2010; Péron, Grandjean, et al., 2010; Péron, le Jeune, et al., 2010) and affective disturbances such as depression (Volkmann et al., 2010), which was at the center of Study 3 of this dissertation. Furthermore, the dopamine deficit results in disturbed interaction with a range of other monoamines such as serotonin, and norepinephrine (Halliday, Leverenz, Schneider, & Adler, 2014; Obeso et al., 2017). Together with the disturbed reinforcement signal, this might contribute to the negative processing bias observed in PD patients in Study 1 (where positive valence stimuli induce a much higher conflict signal than negative ones).
On the local circuit level, this state may be caused by an electrophysiologically measurable hyper-activation of the indirect and a hypo-activation of the direct pathway (Albin et al., 1989; Redgrave et al., 2010) leaving PD patients in a constant state of hesitation as a potential immediate effect. Here, loss of pallidosubthalamic inhibition may increase subthalamic excitability, which could amplify the influence of net-inhibitory hyperdirect cortical drive on motor output in the presence of conflict or ambiguity (Neumann et al., 2018).

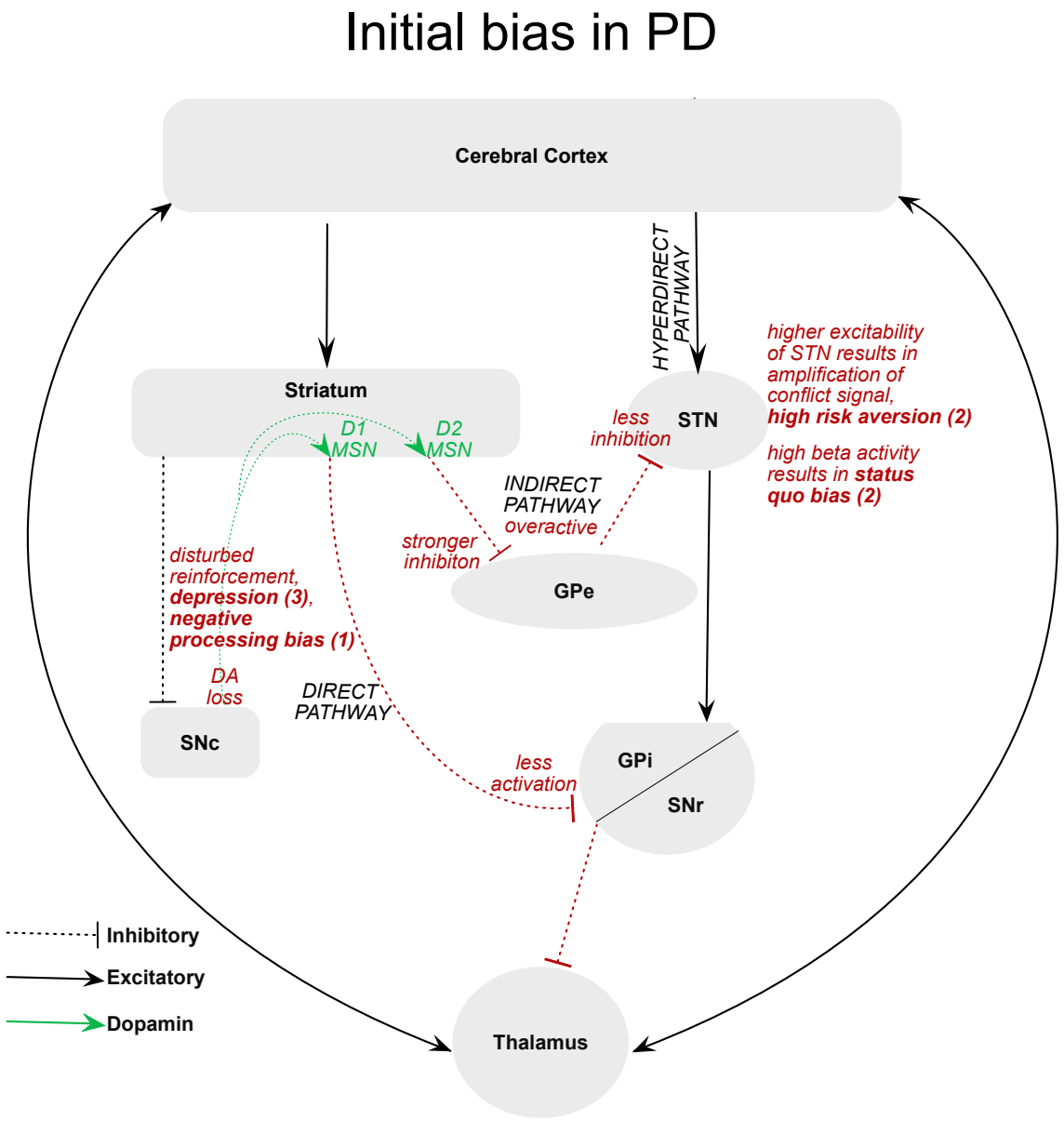

Figure 21. Modulation of basal ganglia systems by PD. Loss of dopaminergic neurons (which may be linked to depression and a negative information processing bias described in Study 1 and 3) leads to stronger activation of indirect and reduced activation of direct pathways, respectively, and renders the STN more excitable. Together with increased beta activity in the STN (Kühn et al., 2008; 2009; Neumann et al., 2016), this may induce high risk aversion and status quo bias as described in Study 2).

As a result from the abovementioned synaptic changes, the parkinsonian STN is spontaneously hyperactive, which is characterized by both an increased firing rate and temporally patterned oscillatory activity in the beta frequency (13 – 30 Hz), which has been identified as a biomarker for bradykinesia or rigidity in PD (Kühn et al, 2006; 2009; Neumann et al., 2016; Oswal et al., 2016). One explanatory approach suggests that high beta activity in the STN induces a status quo bias in PD patients, i.e. a deterioration of flexible behavioural and cognitive control (Engel & Fries, 2010; Fleming et al., 2010). Essentially, this theory relates PD patients' loss of variance in cognitive output (e.g. risk

aversion in Study 2) to the same mechanism resulting in hypokinetic symptoms and thus variance and amplitude in motor output (e.g. kinematic motor control in Study 4).
Importantly, there is still insufficient evidence to clearly link nonmotor symptoms of PD to underlying complex cellular changes and more research is needed to aid understanding of these processes. For the discussion of results of this thesis, it can be summarized that PD creates a phenotype that poses an initial bias characterized by chronic negative reinforcement and amplification of cortical conflict signalling, which modulates cognition and affect resulting in measurable behavioural (risk aversion, conflict related reaction time changes) and emotional effects (depressive symptoms, negativity bias).

5.2.2. Effects of motor STN-DBS on basal ganglia circuits alter cognition and affect

Within the basal ganglia network, the STN is part of the indirect pathway but also receives monosynaptic cortical input via the hyperdirect pathway. Its currently presumed role implies a direct delay of behavioural responses under uncertainty in order to optimize outcome (Aron et al., 2016). Although the functional mechanism of STN-DBS is not fully understood, there is evidence that high frequency stimulation affects the cortico-basal ganglia circuit computations on several layers (Figure 22).
STN-DBS disinhibits thalamo-cortical loops by decreasing basal ganglia output (which is inhibitory) in several ways. STN-DBS is hypothesized to suppress hyperdirect pathway cortical input to the STN depending on STN activity (Frank et al., 2007; Herz et al., 2018). Because the STN receives input from motor as well as associative and affective/limbic cortical regions (Accolla et al., 2016) and motor, associative and limbic basal ganglia pathways converge in the STN (Haynes & Haber, 2013; Mallet et al., 2007), STN-DBS simultaneously suppresses glutamatergic *input* from motor and nonmotor brain regions. Indeed, the observed suppression of the negative processing bias in Study 1 in PD patients OFF DBS might relate to a disturbed integration of input from emotional processing structures such as prefrontal areas or the amygdala (Péron et al., 2013).
At the same time, DBS decreases STN *output* (Milosevic, Kalia, Hodaie, Lozano, Fasano, et al., 2018; Steiner et al., 2019) and recent evidence shows that 130 Hz stimulation of axons of GABAergic GPe neurons projecting to the STN results in neural decoupling of pallidal processing from striatal indirect pathway activity which in turn facilitates motor output (as shown in the computational model by Neumann et al, 2018). This decreased indirect pathway activity results in a relative overactivity of the direct pathway. Downstream, this decrease of STN output induces a disbalance in the basal ganglia loops leading to thalamo-cortical disinhibition. In terms of behaviour, the altered basal ganglia-thalamo-cortical interaction manifests in the inability to slow down reaction times in the face of conflict (Cavanagh et al., 2011; Frank et al., 2007; Herz et al., 2016) as could also be observed in Study 1 of this thesis.

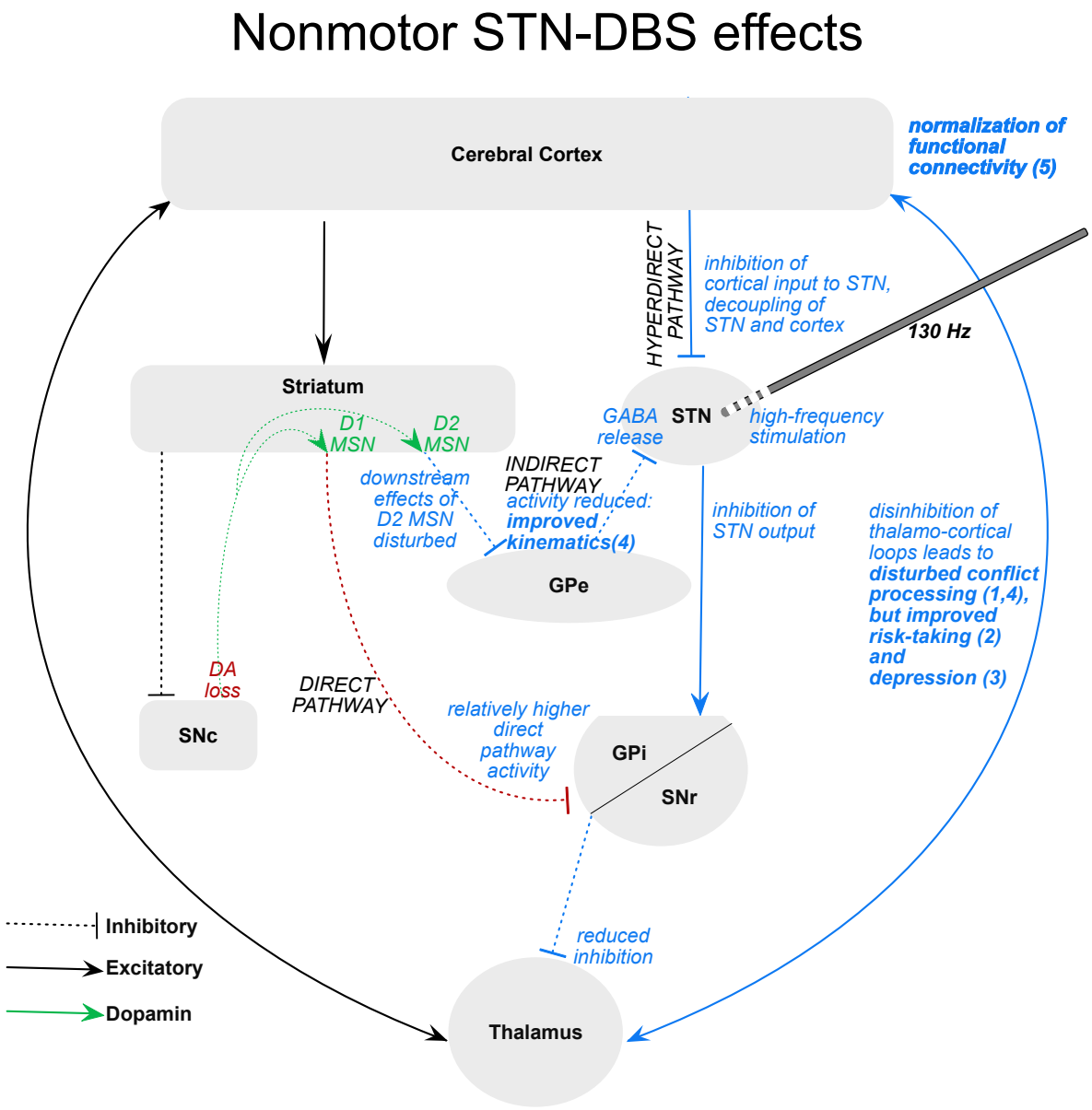

Figure 22. Modulation of basal ganglia systems by STN-DBS. (B) High-frequency stimulation of the motor STN inhibits cortical input to the STN (as modelled in Study 1) as well as STN output (Milosevic, Kalia, Hodaie, Lozano, Fasano, et al., 2018). Moreover, it may shift the release of GABA and Glutamate in the STN through continuous activation of GPe GABAergic neurons and synaptic silencing of glutamatergic input from cortex (Milosevic, Kalia, Hodaie, Lozano, Fasano, et al., 2018; Steiner et al., 2019), which may reduce and decouple STN output from the striatal indirect pathway D2-MSNs (resulting in improved kinematics as shown by Neumann et al., 2018 [Study 4]). Together, this modulates the basal ganglia inhibitory 'Stop' route conveying a relative higher weight of direct pathway activity, which in turn disinhibits thalamo-cortical loops resulting in decreased accounting of reaction time to conflict (Study 1 and 4), but normalized risk-taking (Study 2) and affect (Study 3) as compared to the initial PD-induced bias.

The complex DBS-induced network changes are complicated further by network modulations relating to the Parkinsonian increased beta synchronization (Eusebio et al., 2011; Kühn et al., 2008; Oswal et al., 2016). Increased beta activity in a PD animal model is associated with an increase in STN firing rates (Tachibana, Iwamuro, Kita, Takada, & Nambu, 2011). Consequently, artificial lesioning of the STN through DBS reduces both beta activity (Kühn et al., 2008; Neumann et al., 2016) and STN firing rates

through synaptic silencing of the STN (Milosevic, Kalia, Hodaie, Lozano, Fasano, et al., 2018). On the behavioural side, increased beta activity has been linked to a cognitive status quo bias (Engel & Fries, 2010; Fleming et al., 2010): PD patients rather accept the (less beneficial) default choice than continue to evaluate their options and take risks (Study 2). Since DBS downregulates beta activity (and therefore disinhibits thalamo-cortical loops), it releases PD patients from the cognitive status quo bias (Engel & Fries, 2010; Fleming et al., 2010). It thus makes sense that a suppression of beta activity would result in a change of risk-taking attitude in value-based decisions under STN-DBS as observed in Study 2.

The extent to which STN-DBS interferes with nonmotor function however seems to relate to its impact on STN subzones and associated distal brain regions. STN motor and nonmotor territory have been described as overlapping with a rather gradient distribution of neurons corresponding to motor, associative and limbic content (Accolla et al., 2014, 2016, 2017; Haynes & Haber, 2013; Lambert et al., 2012). Since DBS that targets the motor STN likely also impacts nonmotor STN territory, DBS-effects on associative and limbic brain regions driving nonmotor functions are to be expected. Indeed, Neumann et al. (2018) demonstrate in Study 4 that the impact on fibers connecting the STN and SMA relates to the observed reaction time effect. This means that under STN-DBS, prefrontal cortex and STN coupling may be suppressed leading to a lack of cognitive control via the hyperdirect pathway. This finding is in congruence with the results of Study 2 and 5 of this thesis that imply a stimulation of STN motor territory to have a beneficial (or normalizing) effect on risk-taking and functional connectivity, respectively. In Study 2, the specific modulation of motor STN territory led to a normalization of risk-taking behaviour while in Study 5 Horn et al. (2019) showed that whole-brain functional connectivity became more similar to that of healthy controls if STN-DBS primarily impacted the motor STN. It is not straightforward to draw conclusions on how targeted nonmotor STN-DBS would impact cognitive and affective outcome in PD, but there is sparse evidence, that stimulation of limbic-associative STN territory is linked to a *disturbance* of cognitive and neuropsychiatric function (Mosley et al., 2018) (rather than an improvement as observed in Study 2 under motor STN stimulation). Associative-limbic STN stimulation can in fact induce cognitive-affective adverse events such as hypomania (Mallet et al., 2007; Welter et al., 2014). The few studies suggesting stimulation of nonmotor STN induces *improvement* of cognitive function such as better executive function (Greenhouse, Gould, Houser, & Aron, 2013) or verbal fluency (Ehlen et al., 2014) base their evidence not on the estimation of local impact of DBS on brain tissue but rather the (more unspecific) selection of more ventral or antero-medial electrode contacts. The influence of DBS however might be more specifically estimated by the localization of the electrodes (Study 2,3,4,5) and by predicting DBS impact on local brain tissue within and surrounding the target or on global brain networks. Indeed, depending on stimulation impact, fibers running past the STN may accidentally be activated leading to network changes outside the basal ganglia loops. In Study 3 it was demonstrated that specifically the stimulation of fibers running anteromedially of the STN could predict worsening of depressive symptoms under STN-DBS. Yet, whether the worsening of depression reflects stimulation of the

described fibers or partially simply the PD-inherent worsening of depressive symptoms with disease progression, cannot finally be answered based on this data and should be addressed in future studies regarding structural connectivity in PD patients with and without DBS.

In summary, the impact of STN-DBS stretches from local modulation of input and output of STN neurons to shifting dynamics in global brain networks. Both may contribute to nonmotor effects.The results of the dissertation studies suggest that a placement of the DBS electrode in the motor STN not only improves motor performance (Study 4) but also improves cognitive and affective outcome by increasing risk attitude to a healthy level in value-based decisions (Study 2), by improving symptoms of depression (Study 3), by eliminating a negative perceptual processing bias that is present in PD patients (Study 1) and by normalizing functional connectivity (Study 5). On the other hand, STN-DBS induces cognitive disinhibition (Study 1 and 4), which is most likely related to the suppression of hyperdirect pathway activity (Study 4) and thalamo-cortical disinhibition. One further interesting focus for future research will be understanding the interaction of thalamus and cortex which changes through DBS and may thus induce long-lasting changes in cortical plasticity (Milosevic, Kalia, Hodaie, Lozano, Popovic, et al., 2018). There is room for a wide range of follow-up studies that is discussed in the following paragraph.

5.3. Open questions and current perspectives

This is an exciting time for clinical neuroscience and DBS research. The field is rapidly expanding and novel software and hardware developments as well as an increasing understanding of mechanisms underlying DBS effects spur on further research. One of the current foci of DBS research is the development of adaptive stimulation devices. Here stimulation is dynamically controlled by feedback from biomarkers such as pathophysiological increased beta activity in PD detecting optimal periods of stimulation in order to avoid side effects while maximizing clinical outcome (Little et al., 2013). Cognitive and affective side effects might be avoidable when stimulation would specifically decrease pathological oscillations leaving physiological activity untouched. However, the determination of times and thresholds for adaptive stimulation is extremely complex and a lot of work is needed until the theory is translated into hardware (Meidahl et al., 2017).

Furthermore, tailored therapy is a goal that is increasingly expressed among DBS researchers. In essence, improved pre- and intraoperative imaging and estimation of functional and structural connectivity profiles and associated sweetspot of stimulation for the individual patient can aid targeting of basal ganglia structures in order to maximize positive impact of STN-DBS on the sensorimotor network. For example, the impact of DBS on left prefrontal fibers running anteromedially past the STN (the stimulation of which is associated with worsening of depressive symptoms as shown in Study 3) could be avoided by directing lead placement on the left hemisphere away from these fibers. However, there should be more research done on the true impact of this fiber-stimulation

on behaviour: I would be interested in seeing if the relationship replicates when using patient-specific diffusion imaging data as the basis for tractography (rather than a normative connectome as used in Study 3) and also whether change in depressive symptoms occur based on directing the stimulation current towards versus away from these fibers which could be done based on directional electrode reconstruction in a single-blind study. In this context, it would be especially interesting to determine the true lateralization of the effect as well by recording DBS effects of left and right STN stimulation separately and controlling for laterality of symptom onset in the PD patients.

Another very important aspect is the time frame of assessment. DBS induces plasticity in the form of long-term potentiation (LTP) or LTD (Milosevic, Kalia, Hodaie, Lozano, Fasano, et al., 2018; Milosevic, Kalia, Hodaie, Lozano, Popovic, et al., 2018) shifting network dynamics across the cortex. Such strengthening versus weakening of basal ganglia-thalamo-cortical loops may evolve differentially for acute and long-term stimulation thus inducing differential effects in the short-term when assessing DBS effects ON and OFF stimulation (Study 1, Study 2, Study 4, Study 5) and in the long-term when quantifying affective processes before and after 6-12 months of chronic stimulation (Study 3). At the later stage, synaptic plasticity may have altered networks gradually, leading to a shift in structural connectivity. Thus, it is important to i) take the timeframe of assessed changes into account and ii) use control groups of PD patients and healthy controls that have not undergone DBS-induced synaptic plasticity.

A last central question that would aid understanding of DBS-induced effects on cognition and affect is whether there are specific physiological biomarkers, that through intraoperative microelectrode recordings could predict behavioural change under DBS thus supporting tailored approaches to DBS therapy, where stimulation of those foci could be avoided. In general, bringing together neurophysiological recording, behavioural investigation and imaging of electrode placement seems a promising approach to assess local and global DBS effects from a mechanistic perspective.

Taken together, increased understanding of the mechanisms underlying DBS effects on cognition and affect is important as it can directly be translated into improved clinical hardware and surgical planning.

5.4. Limitations

There are a couple of limitations when conducting studies that assess the effect of STN-DBS on cognition and affect. The first major limitation is that working with the severely impaired PD patients makes assessment of DBS effects challenging, since PD nonmotor effects such as altered states of cognition and affect pose an initial bias on the results (Figure 21). It is thus important to consider PD-inherent baseline changes when evaluating DBS influence on behaviour. In the studies included in this dissertation this was done e.g. in Study 1 through weight-shifting in the Stroop model to reflect the PD-inherent negativity bias; or in Study 3 by using a normative Parkinson connectome (PPMI, Ewert et

al., 2017). However, nonmotor symptoms originating from disease progression remain difficult to disentangle from pure DBS effects and between-patient variations in disease progression influence cognitive performance.

Relatedly, patients' medication intake and the state of dopaminergic denervation interact with DBS impact. In Studies 1 to 2 dopaminergic medication was kept stable between assessments and the LEDD was included in the analyses as a regressor to make sure the observed effects related to DBS. Unfortunately, often a medication ON and OFF state is not assessible next to the DBS ON and OFF testing since patients' motor impairments are too grave OFF DBS and OFF medication due to their advanced disease progression preventing them from completing the task. However, there should be more attempts comparing DBS and medication effects at earlier disease stages, since dopamine replacement may differentially alter behaviour through impact on reward processing areas such as the ventral striatum (Clark & Dagher, 2014; Norbury et al., 2013) which is especially interesting when investigating DBS effects on decision-making.

Furthermore, electrode types differed between patients in the study cohorts, which might imply a hardware-related differential effect on the VTA-model through the respective consideration of constant voltage versus constant current settings of DBS systems by Medtronic versus Boston Scientific. In Study 3 I controlled for this effect by repeating the analyses with an unthresholded e-field.

For Study 3 and Study 5, another limitation might be the use of a normative connectome, which assumes structural or functional connectivity to be approximately the same for patients of our sample. Although this assumption might not be true in all cases, there are several recent studies that have validated this approach (Al-Fatly et al., 2019; Baldermann et al., 2019; Horn et al., 2017; Neumann et al., 2018) and the normative connectomes are based on large samples and acquired on specialized MRI hardware providing the advantage of a high signal-to-noise ratio and robust data quality.

As another limitation to Studies 2-5 in this thesis the anatomical reconstruction of the STN and its subzones may be considered. However, the studies all used the newest version of the state-of-the-art Lead-DBS pipeline for electrode reconstruction (Horn, Li, et al., 2019) and a modern atlas cross-validated for healthy control and PD data (Ewert et al., 2016).

Lastly, a common limitation of clinical studies is the relatively small sample size that results from strict inclusion and exclusion criteria and the small number of patients eligible to perform cognitive and affective assessments OFF DBS or OFF medication, which for most patients is a real strain. At least in Study 3, I managed to maximize the sample size to N = 116, but in the other studies included in this thesis effect sizes were calculated, statistical comparison values were always corrected for multiple comparisons and still significant. Thus, despite this factor being a major limitation, I attempted to control for it in the current studies.

6. Conclusion

This dissertation assessed the effects of STN-DBS on cognition and affect based mainly on behavioural experiments with PD patients and healthy controls. In the dissertation studies motor STN-DBS improved PD-inherent cognitive and affective biases such as an overly cautious risk attitude, a bias to process negative stimuli faster than positive ones or a high level of depression. At the same time, STN-DBS induced a deterioration of cognitive inhibition. These effects are partially explained by electrode placement and associated modulation of the basal ganglia-thalamo-cortical loops. Specifically, if STN-DBS impacted mainly motor STN territory, risk-taking, depression and whole-brain functional connectivity normalized while the ability to slow down responses to execute cognitive control was disturbed. The latter effect was related to a disruption of cortex-STN coupling by DBS. The studies reported here also took an effort to computationally and anatomically reconstruct the impact of STN-DBS on global brain networks, e.g. by showing that stimulation of fibers associated with the left prefrontal cortex lead to a worsening of depression. The main goal of this work was to aid the understanding of DBS side effects in PD. Furthermore, the results of the presented studies may foster the refinement of brain stimulation targets and the development of personalized or tailored DBS therapy that is adjusted to the patient's individual symptoms, anatomy and connectivity.

Altogether, this thesis contributes to a translational understanding of the role of the basal ganglia, and specifically the STN in cognition and affect. The presented findings advance the knowledge on the influence that STN-DBS has on cognitive and affective processing. On the clinical side, this work may translate into fine-tuned DBS targeting and programming needed to optimize clinical outcome in PD patients.

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Appendices

Appendix A. Study 1 Methods

Model equations

The model consists of six modules, each containing between one and three individual units, as outlined in Figure 2. For each of these units, membrane potentials and firing rates are computed iteratively across time steps. For all modules except the ACC and STN, the membrane potential (mp^i_t) of unit i at time point t was computed via:

$$mp_t^i = 0.01 \bullet \left(B^i + I_t^i + \sum_{pre} w^{i-j} \bullet r_{t-1}^j + e_t \right) + 0.99 \bullet mp_{t-1}^i, \qquad \text{eq. 1,}$$

where B^i is the unit's baseline membrane potential as detailed in sub-section connection weights, I^i_t is its input at time t, w^{i-j} is the connection weight between unit i and its presynaptic unit j, r^j_{t-1} is the presynaptic neuron's firing rate at the previous time point t-1 and e_t is a random Gaussian noise term with a mean of 0.0 and a standard deviation of 0.15. Please note that for the response module, the noise term was set to zero in line with Botvinick et al. (2001).

The firing rate of unit i at time t (r^i_t) was then computed from its membrane potential via the sigmoidal function:

$$r_t^i = \frac{1}{1 + \exp\left(-mp_t^i\right)}. \qquad \text{eq. 2}$$

The ACC conflict module contains only one unit. Its conflict-related activity (r^{ACC}_{tr}) was re-computed only at the end of each trial tr via:

$$r_{tr}^{ACC} = 0.05 \bullet \left(10 \bullet e_{tr} - 6\right) + 0.95 \bullet r_{tr-1}^{ACC}, \qquad \text{eq. 3}$$

where e_{tr} is the energy for that trial tr as computed via:

$$e_{tr} = \left(-1\right) \bullet w^{resp(negative)-resp(positive)} \bullet r_{t(resp)}^{resp(negative)} \bullet r_{t(resp)}^{resp(positive)}. \qquad \text{eq. 4}$$

In eq. 4, $w^{resp(negative)-resp(positive)} = -2.0$ is the weight between the two response units, $r^{resp(negative)}_{t(resp)}$ is the activity of the negative response unit at the time of the response and $r^{resp(positive)}_{t(resp)}$ is the activity of the positive response unit at this time point.

The STN module's activity, finally, was computed via

$$r_{tr}^{STN} = \frac{r_{tr}^{ACC}}{D_{stim}} + B_{stim}, \qquad \text{eq. 5}$$

where D_{stim} may reduce inputs from the ACC to the STN in magnitude in the stimulation ON condition and B_{stim} may increase the STN's baseline output. D_{stim} was either set to 1.0 when regular ACC input was desired or to 2.0 when a reduced input was wanted as detailed in Material and Methods. Similarly, B_{stim} was set to 0.0 when regular STN output was simulated and to 3.0 when increased output was desired.

A response was assumed to be initiated in the model whenever one of the response units crossed an activity threshold of 0.7 (deviating from Botvinick et al., 2001, where a threshold of 0.6 was chosen). Our choice made the model more robust against any influences of noise and therefore against prepotent erroneous responses. We assume our choice to be reasonable as we intended to study Stroop effects in reaction times, not error rates.

Connection weights

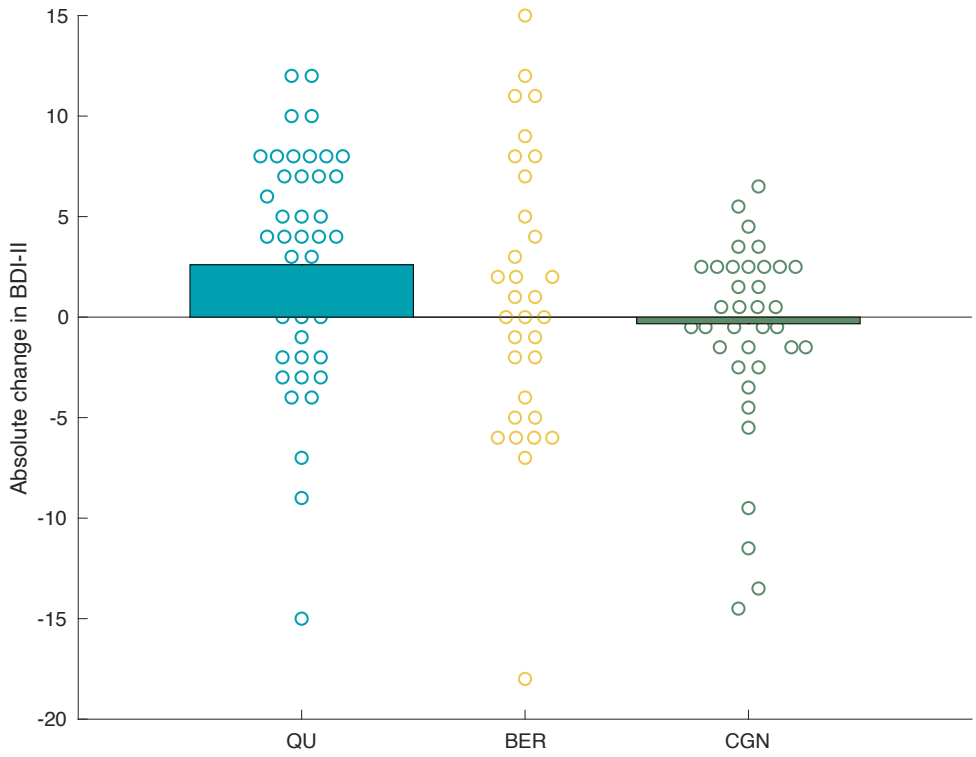
All connections between the model's units are given in Figure 2. For simulating the results of the healthy control subjects, all bidirectional connection weights between the task demand module and the stimulus modules were set to 4.0, in line with the original publication by Botvinick et al. (2001). For simulating PD patients ON and OFF stimulation, in contrast, we decreased the connection between the word processing unit of the task demand module and the negative unit of the sensory word module to 3.85 and increased the connection between the word processing unit and the positive unit of the sensory word module to 4.15. In line with Botvinick et al. (2001), all bidirectional connections between the response module and the sensory face module were set to 1.5 and all bidirectional connections between the response module and the sensory word module were set to 2.5. All uni-directional connections to and from the ACC and STN were set to 1.0. In line with Botvinick et al. (2001), moreover, the baseline membrane potentials of the units in the sensory modules were set -4.0. Additionally, we set the baseline membrane potentials of the two task demand units to -1.0 (deviating from Botvinick et al., 2001, where they were set to zero). The baseline membrane potentials of all other units were set to zero and all units within the same module were interconnected by inhibitory weights of strength -2.0, again in line with Botvinick et al. (2001).

Implementation of paradigm

We ran 11 networks for each of 72 trials per subject group to mirror empirical data (18 trials per condition). Networks were identical within groups except for the random noise terms introduced in eq. 1. All input stimuli were presented to the networks directly at the beginning of each trial. For inputs to the sensory face processing module, input strengths of 1.0 were used, while inputs to the sensory word processing module and to the task demand module were set to 0.25.

Appendix B. Study 3 BDI distribution

Heterogeneous distribution and mean absolute BDI change before and under STN-DBS for the three cohorts.



Appendix C. Study 3 Detailed sample characteristics

I. Berlin

PATIENT	AGE/ Gender	DiSEASE Duration (YRS.)	Type of iPS	months BETWEEN ASSESSMENTS	LEDD Reduction (%)	Dopamin Agonist Reduction (%)	ΔBDI-II (ABS.)	ΔBDI-II (%)	ΔUPDRS III (% DBS On vs. off – oN Medication)	Electrode Type	Contacts used for STN DBS	
											L	R
#1	63/m	15	trem.-dominant	12	70.4	0	10	66.7	14.3	Medtronic Activa PC 3389	10-	2-, 3-
#2	56/m	3	equivalent	12	36.1	100	6	66.7	46.7	Boston Scientific Vercise octopolar	12-	4-
#3	72/f	20	equivalent	12	69.1	85.9	-8	-400	88.9	Medtronic Activa PC 3389	9-	1-
#4	70/m	7	akin.-rigid rigid	12	70.7	100	0	0	70.8	Medtronic Activa PC 3389	9-/10-	1-/2-
#5	73/m	3	equivalent	12	67.8	-25	7	43.8	106.25	Medtronic Activa PC3389	8-	1-
#6	69/m	11	akin.-rigid	12	31.6	-	11	73.3	76.9	Medtronic Activa PC 3389	10-/11+	2-, 3-
#7	58/m	13	equivalent	12	88.4	-	0	0	68.2	Medtronic Activa PC 3389	11-	3-
#8	73/m	9	equivalent	12	39.1	100	3	30	33.3	Medtronic Activa PC 3389	11-	3-
#9	72/f	5	brady.-rigid	12	-26	-185.5	-7	-38.9	0	Medtronic Activa PC 3389	10-	0-
#10	65/m	14	akin.-rigid	12	44.4	46.7	4	66.7	77.1	Medtronic Activa PC 3389	8-/9+	0-/1+
#11	63/f	8	trem.-dominant	12	68.9	100	7	50	6.3	Medtronic Activa PC 3389	9-	1-
#12	63/f	8	equivalent	12	56.4	100	-1	-12.5	107.5	Medtronic Activa PC 3389	8-	0-
#13	58/f	8	trem.-dominant	12	18.4	8.9	14	51.8	20	Medtronic Activa PC 3389	9-, 10-	2-
#14	63/m	15	akin.-rigid	12	85.4	100	-5	-62.5	72.7	Medtronic Activa PC 3389	10-/11-	2-/3-
#15	52/m	5	akin.-rigid	12	100	100	-1	-6.7	-22.2	Boston Scientific Vercise Directed	13-/14-/15-	5-/6-/7-
#16	69/f	4	trem.-dominant	12	100	100	-7	-28	-66.7	Boston Scientific Vercise Directed	11-/14-	5-/6-/7-
#17	64/m	9	akin.-rigid	12	40.5	63.4	2	40	82.6	Medtronic Activa PC 3389	9-	1-
#18	50/m	6	akin.-rigid	12	16.3	0	1	8.3	-30	Medtronic Activa PC 3389	9-	1-
#19	61/f	-	equivalent	12	0	0	-3	-20	100	Medtronic Activa PC 3389	11-	3-
#20	63/m	16	akin.-rigid	12	45.6	40	-7	-100	69.2	Medtronic Activa PC 3389	9-	1-
#21	70/m	6	akin.-rigid	12	62.5	83.3	-6	-66.7	172.7	Medtronic Activa PC 3389	9-	1-
#22	61/m	6	akin.-rigid	12	-	-	-2	-66.7	-	Boston Scientific Vercise Directed	2(17%), 3(17%), 4(33%)	10(17%), 11(66%), 12(17%)
#23	41/f	14	trem.-dominant	12	64.3	-50	8	36.4	77.8	Boston Scientific Vercise Directed	3-	13-
#24	52/m	4	akin.-rigid	12	100	-	-7	-46.7	100	Boston Scientific Vercise Directed	3-/4-	11-/12-
#25	54/m	18	akin.-rigid	12	11.6	100	-6	-66.7	0	Boston Scientific Vercise Directed	4-	12-
#26	73/f	8	trem.-dominant	12	39.9	-	-1	-9.1	35	Boston Scientific Vercise Directed	5-/6-/7-	13- /14- /15-
#27	55/m	19	equivalent	12	61.2	100	10	47.6	-	Boston Scientific Vercise Directed	2- (53%), 3- (38%), 4- (9%)	10-(23%), 11-(54%), 12- (23%)
#28	77/m	7	akin.-rigid	12	13.7	100	-2	-25	-34.8	Boston Scientific Vercise Directed	14- (85%), 9- (15%)	1- (15%), 6- (85%)
#29	52/f	12	akin.-rigid	12	45	100	-19	-172.7	80.6	Boston Scientific Vercise Directed	2- (8%), 3- (6%), 4- (6%), 5- (28%), 6- (26%), 7- (26%)	10-(34%), 11-(33%), 12-(33%)
#30	60/m	14	equivalent	12	77.1	69.2	1	14.3	70	Medtronic Activa 3389	10-	2-
#31	61/m	15	equivalent	12	-100	-	-3	-100	67.6	Boston Scientific Vercise Directed	2- (33%), 3- (33%), 4- (34%)	13-(33%), 14-(33%), 15-(33%)
#32	32/m	15	akin.-rigid	12	29.7	36.8	1	20	64.3	Boston Scientific Vercise Directed	6-	11-/12-/13-

IPS – IDIOPATHIC PARKINSON'S SYNDROME; LEDD – LEVODOPA EQUIVALENT DAILY DOSIS; BDI-II – BECK'S DEPRESSION INVENTORY; UPDRS – UNIFIED PARKINSON'S DISEASE RATING SCALE; TREM.-DOMINANT – TREMORDOMINANT; AKIN.-RIGID – AKINETIC-RIGID

II. Queensland

PATIENT	AGE/ GENDER	DISEASE DURATION (yrs.)	TYPE OF IPS	MONTHS BETWEEN ASSESSMENTS	LEDD REDUCTION (%)	DOPAMIN AGONIST REDUCTION (%)	ΔBDI-II (abs.)	ΔBDI-II (%)	ΔUPDRS III (% DBS ON VS. OFF – ON MEDICATION)	ELECTRODE TYPE	CONTACTS USED FOR STN DBS	
											L	R
#1	71/m	6	akin.-rigid	6	65.2	0	0	0	28.3	Medtronic Activa PC 3389	1-	9-
#2	49/m	6	trem.-dominant	6	61.5	0	1	14.3	9.1	Medtronic Activa PC 3390	1+/2-	9+/10-
#3	69/f	4	akin.-rigid	6	66.2	0	8	80	-81.9	Medtronic Activa PC 3391	1-	9-
#4	76/f	15	akin.-rigid	6	59.7	50	7	36.8	28	Medtronic Activa PC 3393	0-	9-
#5	58/m	6	trem.-dominant	6	80.6	0	4	40	-155	Medtronic Activa PC 3394	1-	10-
#6	62/m	12	akin.-rigid	6	67.3	0	8	38	0	Medtronic Activa PC 3395	1-	9-
#7	47/m	7	akin.-rigid	6	71.9	0	3	33.3	-30	Medtronic Activa PC 3396	1-	9-
#8	66/m	6	trem.-dominant	6	78.4	33,33	-15	-125	72.3	Medtronic Activa PC 3397	2-	9-
#9	63/m	3	trem.-dominant	6	100	100	4	100	-12.5	Medtronic Activa PC 3398	1-	9-
#10	56/m	7	akin.-rigid	6	80.5	0	7	43.8	-97	Medtronic Activa PC 3399	1-	9-
#11	67/m	16	trem.-dominant	6	77.8	0	0	0	0	Medtronic Activa PC 3400	2-/3-	10-
#12	35/m	5	trem.-dominant	6	48.6	100	1	12.5	55.3	Boston Scientific Vercise octopolar	2-/5-	10+/11-/12+
#13	68/m	8	akin.-rigid	6	68.1	33,33	-2	-18.2	24.2	Medtronic Activa PC 3389	1-	9-
#14	66/m	16	trem.-dominant	6	59	0	-3	-27.3	-320	Medtronic Activa PC 3389	2-/3-	10-
#15	66/f	9	trem.-dominant	6	70.9	0	8	57.1	-14.3	Medtronic Activa PC 3389	1-/2-	9-
#16	65/m	10	akin.-rigid	6	71	0	-2	-33.3	-17.6	Medtronic Activa PC 3389	0-	10+/9-
#17	69/m	5	akin.-rigid	6	54.1	0	5	50	-26.9	Medtronic Activa PC 3389	1-	9-
#18	65/m	14	trem.-dominant	6	81.4	0	2	50	-21.4	Boston Scientific Vercise octopolar	3-	10+/11-
#19	69/m	12	akin.-rigid	6	49.9	0	12	92.3	-68.8	Boston Scientific Vercise octopolar	2-	10-
#20	72/f	20	trem.-dominant	6	55	0	-4	-44.4	-30.8	Boston Scientific Vercise octopolar	3-/5-	11-
#21	55/f	5	trem.-dominant	6	100	100	-1	-12.5	-69.2	Boston Scientific Vercise octopolar	3-	9-
#22	70/m	5	trem.-dominant	6	63.6	0	4	28.6	29.5	Boston Scientific Vercise octopolar	4-/5-	10+/11-
#23	57/f	2	trem.-dominant	6	100	0	-7	-100	-7.1	Boston Scientific Vercise octopolar	4-	12-
#24	64/m	8	trem.-dominant	6	74.4	-150	8	61.5	26.1	Boston Scientific Vercise octopolar	0+/1-	10-
#25	53/m	5	akin.-rigid	6	72.9	-193,33	12	75	-105.3	Medtronic Activa PC 3389	1+/2-	10+/11-
#26	65/m	6	trem.-dominant	6	0	0	1	6.7	7.4	Boston Scientific Vercise octopolar	3-	10+/11-/13-
#27	60/f	5	trem.-dominant	6	73.9	100	2	14.3	37.5	Boston Scientific Vercise octopolar	5-	12-
#28	61/m	21	akin.-rigid	6	55.8	-50	8	57.1	34.3	Medtronic Activa PC 3389	0-	9-
#29	42/m	3	akin.-rigid	6	85.7	0	7	77.8	-16.7	Boston Scientific Vercise octopolar	2-	10+/11-
#30	60/f	5	akin.-rigid	6	76.2	61,54	-4	-80	34.6	Boston Scientific Vercise octopolar	2-	11+/12-
#31	70/f	6	trem.-dominant	6	76.8	0	-3	-100	7.4	Boston Scientific Vercise octopolar	2-/3-	11-
#32	58/m	8	trem.-dominant	6	47.6	16,67	-9	-75	-34.3	Medtronic Activa PC 3389	2-	10-
#33	71/m	10	trem.-dominant	6	85.8	0	6	35.3	-30.2	Medtronic Activa PC 3389	1-	9-
#34	73/m	5	akin.-rigid	6	73.3	0	7	36.8	14.7	Boston Scientific Vercise octopolar	2-	10+/9-
#35	61/f	9	trem.-dominant	6	70.4	0	2	50	-3.7	Boston Scientific Vercise octopolar	4-	10-
#36	54/f	7	akin.-rigid	6	91	0	10	100	-70.8	Boston Scientific Vercise octopolar	3-	11-
#37	70/f	4	akin.-rigid	6	92	90	4	40	-19.6	Medtronic Activa PC 3389	1-	9-
#38	54/m	9	trem.-dominant	6	85.7	0	10	58.8	24.3	Medtronic Activa PC 3389	1-	9-

#39	54/m	8	akin.-rigid	6	79.5	0	5	41.7	42.9	Boston Scientific Vercise octopolar	2-	10-/11-
#40	69/f	6	akin.-rigid	6	-15	0	2	22.2	23.5	St Jude Directional	3-	11-, 12-
#41	71/m	8	akin.-rigid	6	78.6	25	-3	-75	25.7	St Jude Directional	2-	11-
#42	51/m	17	akin.-rigid	6	89.5	0	8	57.1	-10.5	St Jude Directional	2-	10-
#43	73/m	10	trem.-dominant	6	53.3	25	-2	-18.2	-129.6	St Jude Directional	3-	11-
#44	52/m	9	trem.-dominant	6	63.4	0	2	33.3	-125	St Jude Directional	1-	10-
#45	51/f	7	trem.-dominant	6	18.3	0	3	14.3	14.8	St Jude Directional	3-	11-
#46	77/m	7	trem.-dominant	6	100	0	0	0	-61	St Jude Directional	2-	10-
#47	76/f	11	akin.-rigid	6	96.2	0	5	71.4	-45.8	Boston Scientific Vercise octopolar	3-/4-	12-
#48	70/m	8	mixed	6	54.6	-20	4	57.1	28	Boston Scientific Vercise octopolar	2-	9+/10-

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III. Cologne

PATIENT	AGE/ GENDER	DISEASE DURATION (yrs.)	TYPE OF IPS	MONTHS BETWEEN ASSESSMENTS	LEDD REDUCTION (%)	DOPAMIN AGONIST REDUCTION (%)	ΔBDI-II (abs.)	ΔBDI-II (%)	ΔUPDRS III (% DBS ON VS. OFF – ON MEDICATION)	ELECTRODE TYPE	CONTACTS USED FOR STN DBS	
											L	R
#1	53/f	11	equivalent	11	44	54,72	3	100	-	Medtronic Activa 3389	P1: 0-; P2: 1-	P1: 8-; P2: 9-
#2	50/m	10	akin.-rigid	6	27.5	0	7	100	38.5	Boston Scientific Vercise Directed	5-	13-
#3	61/f	6	akin.-rigid	12	83.3	50	3	30	80	Boston Scientific Vercise Directed	2- (34%), 3- (33%), 4- (33%)	10- (33%), 11- (34%), 12- (33%)
#4	51/f	15	akin.-rigid	5	88.5	66,67	3	50	-100	Boston Scientific Vercise Directed	5- (33%), 6- (33%), 7- (34%)	10- (50%), 11- (50%)
#5	63/f	4	akin.-rigid	6	55	25	-1	-8.3	36.4	Boston Scientific Vercise Directed	5- (33%), 6-(33%), 7- (34%)	10- (33%), 11-(33%), 12-(34%)
#6	54/m	8	akin.-rigid	2	36.9	-33,33	-2	-50	-	Boston Scientific Vercise Directed	1-	15-
#7	71/m	14	akin.-rigid	6	18.8	0	0	0	-155.6	Boston Scientific Vercise Directed	2- (14%), 3-(13%), 4- (13%), 5- (20%), 6- (20%), 7- (20%)	10- (14%), 11- (13%), 12-(13%), 13-(20%), 14-(20%), 15-(20%)
#8	53/f	4	equivalent	5	50.6	0	3	100	-50	Boston Scientific Vercise Directed	8-	16-
#9	61/m	13	equivalent	6	36.8	0	5	45.5	-166.7	Boston Scientific Vercise Directed	1-	9-
#10	64/f	14	akin.-rigid	5	39.8	27,27	-11	-220	63.6	Boston Scientific Vercise Directed	5- (33%), 6- (34%),7- (33%	13- (27%), 14- (45%), 15- (28%)
#11	56/m	4	trem.-dominant	5	43.3	90,19	0	0	-60	Boston Scientific Vercise Directed	5- (40%), 6- (20%), 7- (40%)	13- (26%), 14- (49%), 15- (25%)
#12	68/f	13	akin.-rigid	6	51	0	-1	-16.7	7.4	Boston Scientific Vercise Directed	5- (34%), 6-(33%),7- (33%	10- (30%), 11- (10%), 13- (40%), 14- (20%)
#13	49/f	8	akin.-rigid	5	44	45,81	-9	-450	10	Boston Scientific Vercise Directed	7-	10- (25%), 11- (25%), 12- (5%), 13- (20%), 14- (25%)
#14	57/m	10	trem.-dominant	5	66	37,5	3	50	-34.5	Boston Scientific Vercise Directed	P1: 8-; P2: 4-(20%), 7- (80%)	13-(20%), 14-(40%), 15-(20%), 16-(20%)
#15	72/m	11	akin.-rigid	5	42.2	53,33	-2	-33.3	-58.8	Boston Scientific Vercise Directed	2- (18%), 3- (16%), 4- (16%), 5- (18%), 6- (16%), 7- (16%)	13- (33%), 14- (33%), 15- (34%)
#16	71/f	13	akin.-rigid	6	61	75	0	0	-76.5	Boston Scientific Vercise Directed	13- (27%), 14- (27%), 15- (46%)	2- (25%), 3- (15%), 4- (40%), 5- (10%), 7- (10%)
#17	62/f	12	equivalent	5	47.5	42,86	1	9.1	21	Boston Scientific Vercise Directed	5- (34%), 6-(33%), 7- (33%)	13- (10%), 14-(65%), 15- (25%)

#18	67/m	9	akin.-rigid	5	57.1	50	0	0	55.6	Boston Scientific Vercise Directed	2- (34%), 3- (33%), 4- (33%)	10- (34%), 11- (33%), 12- (33%)
#19	70/m	10	akin.-rigid	5	65.3	75	6	75	57.1	Boston Scientific Vercise Directed	2- (34%), 3- (33%), 4- (33%)	13- (34%), 14- (33%), 15- (33%)
#20	76/f	18	equivalent	6	38.7	-33,76	-13	-325	41.2	Boston Scientific Vercise Directed	2- (34%), 3- (33%), 4- (33%)	10- (34%), 11-(33%), 12- (33%)
#21	59/m	8	akin.-rigid	5	56.3	25	-1	0	-314.3	Boston Scientific Vercise Directed	5- (34%), 6-(33%), 7- (33%)	13- (34%), 14- (33%), 15- (33%)
#22	62/m	9	akin.-rigid	6	59.2	13,33	1	9.1	-52.9	Boston Scientific Vercise Directed	5- (34%), 6-(33%), 7- (33%)	13- (34%), 14- (33%), 15- (33%)
#23	52/m	6	equivalent	6	8.6	0	1	50	-88.9	Boston Scientific Vercise Directed	2- (34%), 3- (33%), 4- (33%)	13- (34%), 14- (33%), 15- (33%)
#24	74/m	21	akin.-rigid	5	48	100	4	40	-13	Boston Scientific Vercise Directed	2- (34%), 3- (33%), 4- (33%)	10- (34%), 11-(33%), 12- (33%)
#25	73/m	11	akin.-rigid	6	61.1	83,33	-4	-28.6	45.5	Boston Scientific Vercise Directed	5- (34%), 6-(33%), 7- (33%)	13- (34%), 14- (33%), 15- (33%)
#26	NaN/m	17	akin.-rigid	6	66	-24,76	1	8,3	-300	Boston Scientific Vercise Directed	2-(10%), 3-(10%), 4-(10%), 5-(24%), 6-(23%), 7-(23%)	10-(10%), 11-(10%), 12-(10%), 13-(24%), 14-(23%),15-(23%)
#27	75/f	10	akin.-rigid	6	26.5	0	-3	-60	31.3	Boston Scientific Vercise Directed	2- (34%), 3- (33%), 4- (33%)	10-(34%), 11-(33%), 12-(33%)
#28	71/f	7	equivalent	6	73.4	66,67	2	33.3	0	Boston Scientific Vercise Directed	2- (10%), 3- (10%), 4- (10%), 5- (24%), 6- (23%), 7- (23%)	10- (10%), 11-(10%), 12- (10%), 13- (24%), 14- (23%), 15- (23%)
#29	63/f	8	equivalent	6	49.4	50	4	25	-17.6	Boston Scientific Vercise Directed	1-	10- (34%), 11-(33%), 12- (33%)
#30	58/f	8	equivalent	5	72.7	0	3	42.9	8	Boston Scientific Vercise octopolar	5-	R: 9-(19%), 10- (39%), 11- (45%)
#31	47/f	8	akin.-rigid	5	22	75	0	0	80	Boston Scientific Vercise octopolar	3-/4-	11- (40%), 12- (30%), 13- (30%)
#32	63/f	13	equivalent	6	63.4	42,86	3	37.5	-54.5	Boston Scientific Vercise octopolar	3-/4-	P1: 11- (25%), 13- (75%); P2: 13-(50%), 14-(50%)
#33	61/m	8	trem.-dominant	5	39.2	0	2	15.4	54.3	Boston Scientific Vercise Directed	5-/6-/7+	13- (50%), 14- (50%), 15+ (100%)
#34	69/f	13	akin.-rigid	5	3.9	43,93	-1	-50	19.2	Boston Scientific Vercise Directed	1-	9-
#35	54/m	9	equivalent	5	41.2	33,33	-5	-38.5	-6,7	Boston Scientific Vercise Directed	2-(10%), 3-(10%), 4-(10%), 5-(24%), 6-(23%), 7-(23%)	10-(10%), 11-(10%), 12-(10%), 13-(24%), 14-(23%), 15-(23%)
#36	61/m	13	akin.-rigid	5	50	100	-14	-200	17.4	Boston Scientific Vercise octopolar	3- (40%), 4- (45%), 5- (15%)	11- (20%), 10- (20%), 12- (20%), 13- (20%), 14- (20%)

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Appendix D. Curriculum Vitae

Der Lebenslauf ist in der Online-Version aus Gründen des Datenschutzes nicht enthalten.

Appendix E. Eigenanteilserklärung

I hereby give a statement on my contribution in the publications included in this dissertation as it is required by the Promotionsordnung, Freie Universität, Fakultät für Erziehungswissenschaft und Psychologie § 7 Abs. 3 Satz 4.

Dies ist eine Erklärung gemäß § 7 Abs. 3 Satz 4 der Promotionsordnung über den Eigenanteil an den veröffentlichten oder zur Veröffentlichung vorgesehenen eingereichten wissenschaftlichen Schriften im Rahmen meiner publikationsbasierten Arbeit.

I. Eigene Angaben

Name, Vorname: Irmen, Friederike

Institut: Fachbereich Erziehungswissenschaft und Psychologie, Freie Universität Berlin

Promotionsfach: Psychologie

Titel: Understanding the impact of subthalamic deep brain stimulation on cognitive and affective processing

II. Nummerierte Aufstellung der eingereichten Schriften:

1. Subthalamic nucleus stimulation impairs emotional conflict adaptation in Parkinson's disease. Friederike Irmen, Julius Huebl, Henning Schroll, Christof Brücke, Gerd-Helge Schneider, Fred H Hamker, Andrea A Kühn. Soc Cogn Affect Neurosci 2017 10;12(10):1594-1604.

2. Sensorimotor subthalamic stimulation restores risk-reward trade-off in Parkinson's disease. Friederike Irmen, Andreas Horn, David Meder, Wolf-Julian Neumann, Philip Plettig, Gerd-Helge Schneider, Hartwig Roman Siebner, Andrea A Kühn. Mov Disord., 34: 366-376. doi:10.1002/mds.27576

3. Left prefrontal connectivity links subthalamic stimulation with depressive symptoms. Friederike Irmen*,Andreas Horn*, Philip Mosely, Alistair Perry, Jan Niklas Petry-Schmelzer, Haidar S. Dafsari, Michael Barbe, Veerle Visser-Vandewalle, Gerd-Helge Schneider, Dorothee Kübler, Gregor Wenzel, Andrea Kühn. bioRxiv 665976; doi: https://doi.org/10.1101/665976 (in review at Brain)

4. Functional segregation of basal ganglia pathways in Parkinson's disease. Wolf-Julian Neumann, Henning Schroll, Ana Luisa De Almeida Marcelino, Andreas Horn, Siobhan Ewert, Friederike Irmen, Patricia Krause, Gerd-Helge Schneider, Fred Hamker, Andrea A Kühn. Brain 2018 Sep;141(9):2655-2669

5. Deep Brain Stimulation induced normalization of the human functional connectome in Parkinson's Disease. Andreas Horn, Gregor Wenzel, Friederike Irmen, Julius Hübl, Ningfei Li, Wolf-Julian Neumann, Patricia Krause, Georg Bohner, Michael Scheel, Andrea A. Kühn. bioRxiv 537712; doi: https://doi.org/10.1101/537712

III. Statements of contribution to this work (Darlegung des eigenen Anteils an diesen Schriften):

For II. 1.: The task was set up and the PD patients were recruited at Charité - Universitätsmedizin Berlin by a team of neurologists at the Neuromodulation Unit, Julius Hübl and Christopf Brücke. I recruited the cohort of age-matched healthy controls, conducted the data analysis, and was responsible for data interpretation and writing of the paper. For the application of the computational model, I was supported by a Postdoc of the Neuromodulation Unit, Henning Schroll.
Contribution: Conceptualization – in parts; Literature research – entirely; Methodological development – in parts; Design – in parts; Data acquisition – in parts; Data analysis – predominantly; Discussion of results – predominantly; Writing the manuscript – predominantly; Programming – predominantly; Argumentation – predominantly.

For II. 2.: Data acquisition and analysis was conducted by me at Charité - Universitätsklinikum Berlin. The task was designed by David Meder and used in a previous publication during an fMRI experiment at the Danish Research Centre of Magnetic Resonance (Meder et al., 2016. Tuning the Brake While Raising the Stake: Network Dynamics during Sequential Decision-Making. The Journal of Neuroscience, 36(19), 5417–5426). The adaptation of the task for the use in our PD sample was done with help of Wolf-Julian Neumann. I wrote the paper and got feedback by my coauthors.
Contribution: Conceptualization – predominantly; Literature research – entirely; Methodological development – in parts; Design – in parts; Data acquisition – entirely; Data analysis – predominantly; Discussion of results – predominantly; Writing the manuscript – predominantly; Programming – predominantly; Argumentation – predominantly.

For II. 3.: Data of the Berlin dataset was gathered, and electrodes were localized by me. I also reran localization for the dataset from Cologne. The Queensland dataset was localized by the team of Phil Mosley. BDI scores in Berlin were assessed by Gregor Wenzel and Dorothee Kübler as representatives of the team of neurologists in the Neuromodulation Unit of the Clinic of Neurology. Analysis was conducted by me with essential help of Andreas Horn who also supported me in writing the manuscript.
Contribution: Conceptualization – entirely; Literature research – entirely; Methodological development – predominantly; Design – predominantly; Data acquisition – in parts; Data analysis – predominantly; Discussion of results – predominantly; Writing the manuscript – predominantly; Programming – predominantly; Argumentation – predominantly.

For II. 4.: For this project, I collected data of 10 subjects with PD but without STN-DBS, that conducted the task while ON and OFF their usual antiparkinsonian medication. Furthermore, I gave input to the manuscript.
Contribution: Data acquisition – in parts; Data analysis – predominantly; Discussion of results – in parts; Contribution to the manuscript – in parts.

For II. 5.: In this project, I conducted a literature review, where I summarized all studies that conducted resting-state fMRI ON and OFF DBS. With this, I could contribute to the manuscript in form of a table and furthermore gave input and feedback to the rest of the manuscript.
Contribution: Literature research – in parts; Contribution to the manuscript – in parts.

IV. Names and addresses as well as email adresses of coauthors (Die Namen und Anschriften nebst E-Mail oder Fax der jeweiligen Mitautorinnen oder Mitautoren):

[Excluded from published version]

Unterschrift der Doktorandin/des Doktoranden

Appendix F. Publications/Manuscripts

DOI links to published articles without permission to archive publisher's version

Friederike Irmen, Julius Hübl, Henning Schroll, Christof Brücke, Gerd-Helge Schneider, Fred H. Hamker, Andrea A. Kühn (2017). Subthalamic nucleus stimulation impairs emotional conflict adaptation in Parkinson's disease. Social Cognitive Affective Neuroscience, 12(10):1594-1604. https://doi.org/10.1093/scan/nsx090

Friederike Irmen, Andreas Horn, David Meder, Wolf-Julian Neumann, Philip Plettig, Gerd-Helge Schneider, Hartwig Roman Siebner, Andrea A. Kühn (2018). Sensorimotor subthalamic stimulation restores risk-reward trade-off in Parkinson's disease. Movement Disorders, 34: 366-376. https://doi.org/10.1002/mds.27576

Andreas Horn, Gregor Wenzel, Friederike Irmen, Julius Hübl, Ningfei Li, Wolf-Julian Neumann, Patricia Krause, Georg Bohner, Michael Scheel, Andrea A. Kühn. Deep brain stimulation induced normalization of the human functional connectome in Parkinson's disease (2019). Brain, awz239. https://doi.org/10.1093/brain/awz239

Wolf-Julian Neumann, Henning Schroll, Ana Luisa De Almeida Marcelino, Andreas Horn, Siobhan Ewert, Friederike Irmen, Patricia Krause, Gerd-Helge Schneider, Fred H. Hamker, Andrea A. Kühn. Functional segregation of basal ganglia pathways in Parkinson's disease (2018). Brain, 141(9):2655-2669. https://doi.org/10.1093/brain/awy206

Friederike Irmen*, Andreas Horn*, Philip Mosely, Alistair Perry, Jan Niklas Petry-Schmelzer, Haidar S. Dafsari, Michael Barbe, Veerle Visser-Vandewalle, Gerd-Helge Schneider, Dorothee Kübler, Gregor Wenzel, Andrea A. Kühn (2019). Left prefrontal connectivity links subthalamic stimulation with depressive symptoms. bioRxiv, 665976. (*These authors contributed equally to this work) https://doi.org/10.1101/665976

OXFORD

Social Cognitive and Affective Neuroscience, 2017, 1594–1604

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Advance Access Publication Date: 11 July 2017
Original article

Subthalamic nucleus stimulation impairs emotional conflict adaptation in Parkinson's disease

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Abstract

The subthalamic nucleus (STN) occupies a strategic position in the motor network, slowing down responses in situations with conflicting perceptual input. Recent evidence suggests a role of the STN in emotion processing through strong connections with emotion recognition structures. As deep brain stimulation (DBS) of the STN in patients with Parkinson's disease (PD) inhibits monitoring of perceptual and value-based conflict, STN DBS may also interfere with emotional conflict processing. To assess a possible interference of STN DBS with emotional conflict processing, we used an emotional Stroop paradigm. Subjects categorized face stimuli according to their emotional expression while ignoring emotionally congruent or incongruent superimposed word labels. Eleven PD patients ON and OFF STN DBS and eleven age-matched healthy subjects conducted the task. We found conflict-induced response slowing in healthy controls and PD patients OFF DBS, but not ON DBS, suggesting STN DBS to decrease adaptation to within-trial conflict. OFF DBS, patients showed more conflict-induced slowing for negative conflict stimuli, which was diminished by STN DBS. Computational modelling of STN influence on conflict adaptation disclosed DBS to interfere via increased baseline activity.

Key words: subthalamic nucleus; deep brain stimulation; emotional conflict; stroop model; Parkinson's disease

Introduction

The subthalamic nucleus (STN) is a key node in information processing during action selection receiving input via the hyperdirect and indirect pathway (Alexander and Crutcher, 1990; Nambu *et al.*, 2002). Its functional role has been related to centre surround inhibition and supression of motor output of the basal ganglia during movement selection (Mink, 2003). More recently, evidence for a role of the STN in response slowing related to conflicting input has emerged (Brittain *et al.*,). It is presumed that the STN pauses basal ganglia motor output in response to conflict until the appropriate motor plan is set

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(Frank et al., 2007). However, the STN's conflict processing capacity goes beyond the motor domain. In fact, cumulative evidence points towards its role being a more general one, coordinating and weighing input from motor and non-motor brain regions to regulate behaviour (Aron and Poldrack, 2006; Frank and Claus, 2006; Baunez and Lardeux, 2011; Péron et al., 2013).

Subthalamic deep brain stimulation (DBS) has become a guideline therapy for advanced Parkinson's disease (PD) due to its high effectiveness in the control of motor symptoms and improvement in quality of life (Schüpbach et al., 2014). Despite its great therapeutic effect, clinical studies have revealed selective undesirable effects of STN DBS on cognition, behaviour and emotion (Mallet et al., 2007; Voon et al., 2008; Witt et al., 2008; Le Jeune et al., 2010; Maillet et al., 2016; Péron et al., 2013). In particular, STN DBS has been found to increase impulsive behaviour (Hälbig et al., 2009; Florin et al., 2013; Brandt et al., 2015), with conflict-induced slowing turning into conflict-induced speeding with DBS (Frank et al., 2007). This process has been formalized using computational models such as the drift diffusion model of decision making predicting impulsive behaviour in the face of conflict if STN inhibitory activity is disrupted (Cavanagh et al., 2011; Green et al., 2013; Obeso et al., 2014). In line with this, patients with STN DBS make more erroneous choices when their stimulator is turned on, for instance, in the Stroop task, where they have to suppress reading a word while naming its colour (Jahanshahi et al., 2000; Witt et al., 2004). Lower accuracy in such action selection tasks involving conflict provides evidence for impaired response inhibition during STN DBS suggesting a role of the STN in inhibitory executive control (Jahanshahi et al., 2015; Zavala et al., 2015). Further support derives from neuroimaging studies presenting a close functional link of the STN and frontal areas of higher cognitive function via the hyperdirect pathway (Nambu et al., 2002). Yet, the STN has recently been found to also receive input from areas processing affective stimulus contents such as the basolateral amygdala (Lambert et al., 2012) or the orbitofrontal cortex (Le Jeune et al., 2008). In fact, new evidence extends the role of the STN to presenting a central hub for multi-level integration of motor, cognitive and affective information (Accolla et al., 2016). In the affective domain, the STN may play a crucial role in the temporal coordination of cortical and subcortical co-activation that is the foundation to affective sensation (Péron et al., 2013). Behavioural data supporting this notion includes studies showing DBS-induced impairments of emotion recognition and expression, especially in the domain of unpleasant emotions (Le Jeune et al., 2008; Péron et al., 2010).

A crucial question yet unanswered is whether the STN modulates the integration of affective information in the motor output relative to a conflict signal. If the processing of conflicting affective input is impaired through STN DBS, the STN could be assumed to apply the braking signal during processing of emotional input, holding back motor output until the relevance of affective information could be checked.

We employed an emotional Stroop paradigm previously established by Etkin et al. (2006), using positive and negative facial expressions and superimposed congruent (non-conflicting) or incongruent (conflicting) emotion words. In healthy individuals, conflict monitoring, i.e. the recognition that perceptual input is conflicting, induces automatic slowing of reaction times (Stroop effect) due to the recruitment of cognitive control applied to inhibit the influence of irrelevant information on performance (Botvinick et al., 2001). Etkin et al. (2006) found such conflict-related slowing to be present for conflicting emotional face stimuli with emotion word stimuli superimposed, irrespective of valence. Further, conflict-related slowing in one trial primed conflict adaptation, i.e. faster responses, in a following conflict trial. This paradigm thus allows assessing reaction time slowing in conflict trials as compared to no-conflict trials (reactive or within-trial conflict adaptation), and furthermore, reaction time adjustments from one conflict trial to the next (proactive or across-trial conflict adaptation).

A unique tool to directly modulate STN activity comes in patients with severe PD treated with STN DBS, in whom the stimulator can be switched ON and OFF. We used this approach to differentially test our hypothesis that STN DBS would interfere with emotional conflict adaptation. We predicted the Stroop effect to be equally strong in healthy controls and PD patients OFF DBS and to drop ON DBS due to the interference of DBS with physiological STN activity during conflict monitoring. Moreover, we simulated potential mechanisms by which DBS may interrupt emotional conflict processing in the STN using an adapted version of the renown Stroop model introduced by Cohen et al. (1990) and Botvinick et al. (2001).

Materials and methods

Patients

We included 11 patients (two females; mean age 62 ± 6.4 years) with idiopathic PD (disease duration 11.5 ± 4.2 years) who have undergone functional neurosurgery for subthalamic DBS. Details of surgery and electrode placement have been described previously (Huebl et al., 2011). Post-operative electrode placement within the STN was corroborated via T2-weighted magnetic resonance imaging. Furthermore, effective stimulation was indexed by a significant decrease in postoperative United PD Rating Scale-III motor score (% reduction 57.55 ± 17.58, ON vs. OFF paired t-test $P < 0.01$) and a significant reduction of levodopa daily dose (LEDD) (% reduction 61.42 ± 26.80, ON *vs* OFF paired t-test $P < 0.01$). All patients and healthy controls gave written informed consent for participating in the study. The local ethics committee approved all parts of the study in accordance with the declaration of Helsinki. Table 1 provides an overview of the patient demographics and clinical data. Major cognitive or affective disorders were ruled out prior to surgery by neuropsychological and neuropsychiatric assessment (as in Huebl et al., 2011). Depression scores [Beck Depression Inventory (BDI)] were assessed only in the ON DBS state. Patients had none or mild clinically relevant depressive symptoms (BDI scores <19 indicate minimal or moderate depressive symptoms). At the time of the study in comparison to the preoperative state, BDI scores were decreased (cases 1, 2, 7, 9 and 10) or unchanged (cases 5, 6 and 8) in all but in one (case 4) patient. Furthermore, none of the patients had difficulties recognizing facial expressions on an early processing level as indexed by a normal score in the Benton Facial Recognition Test (Benton, 1990).

Healthy controls

We included an age- and gender-matched control group of 11 subjects (two females; mean age 63.5 ± SD 7.4 years). The healthy controls denied any history of neurological or psychiatric disease and were not under influence of any medication that would affect their cognitive or affective state. Subjects had a mean BDI of 3.0 ± SD 3.9 indicating minimal depressivity and all passed the Benton Facial Recognition Test without

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Table 1. Patients sample demographic and clinical characteristics

Case/sex	Age	Disease duration	BDI prior to surgery	BDI time of study	Benton FRT	UPDRS-III score : OFF DBS	UPDRS-III score: ON DBS	LEDD pre-OP	LEDD post-OP	Contacts used for continuous STN DBS
1/f	50	6	5	1	49	40	13	1175	600	L:-1;+2 R: -1;+2
2/m	69	20	15	9	45	56	16	1260	400	L:-1 R:-1
3/m	64	7	–	–	39	45	23	1250	200	L:-1 R: -2: -3
4/m	65	12	8	14	–	30	7	1450	240	L:-1;-3 R:-1;-3
5/m	60	7	0	0	49	23	19	900	800	L:-0 R:-0
6/m	69	10	4	4	–	30	8	1400	0	L:-1 R:-1
7/m	66	14	3	1	43	34	14	1400	600	L:-1 R:-1
8/f	63	14	17	17	39	28	18	1080	140	L:-1 R:-1
9/m	56	15	13	6	39	44	11	750	300	L:-2;-3 R: -1
10/m	70	14	14	7	43	30	14	600	500	L:-0;-1 R:-1;-2
11/m	53	7	–	–	41	40	18	1100	450	L:-1;-2 R:-1;-2
M (s.d.)	62 (6.4)	11.5 (4.2)	8.7 (5.8)	6.5 (5.6)	43 (3.8)	36.4 (9.1)	14.6 (4.6)	1124.09 (263.32)	384.54 (224.23)	

M (s.d.), Mean (s.d.), disease duration in years, Benton FRT, Benton Facial Recognition Test, UPDRS-III, United PD rating scale. Part III, motor evaluation.

indication of impaired recognition of faces (mean score 46.5 ± SD 3.2). No indication of cognitive impairment was present as indicated by the Montreal Cognitive Assessment test (mean score 27.0 ± 1.4). All subjects had normal or corrected-to-normal vision acuity, were fluent in German and naïve to the hypotheses of the study.

Paradigm and conditions

PD Patients performed the behavioural task in two experimental sessions, ON and OFF DBS, in a pseudo-randomized order. After switching off the DBS device, patients waited for 30 minutes before starting (or continuing) the task. Patients were on their usual antiparkinsonian medication that was stable during the two test sessions. Healthy controls underwent the experimental procedure only once. One experimental session took about 20 minutes.

We adapted the emotional Stroop task used by Etkin *et al.* (2006). The stimulus set consisted of black and white photographs of happy and sad faces taken from the 2D Facial Emotional Stimuli dataset (Erwin *et al.*, 1992). The faces were superimposed with the German words for 'joy' [Freude] or 'grief' [Trauer] in prominent red letters (Figure 1). Stimuli could thus be non-conflicting (congruent) if the valence of facial expression and the word would match (e.g. 'joy' and a happy face) or conflicting (incongruent) if the valence would differ (e.g. 'joy' and sad face). During the analysis, similar to Gyurak *et al.* (2011), we referred to a conflict trial that was primed by a previous conflict trial as 'high across-trial conflict adaptation trial' (Figure 1). Conversely, we referred to a conflict trial that was preceded by a no-conflict trial as 'low across-trial conflict adaptation trial'.

The face stimuli were organized in two sets of 36 face stimuli, with an equal number in each condition: happy congruent, happy incongruent, sad congruent and sad incongruent. Stimuli occurred in a pseudo-randomized order, with the maximum repetition for a category being set to three. The stimulus duration was 1 second and the inter-stimulus interval was jittered between 3 and 4 seconds, during which a black screen with a white fixation cross in the centre was shown. Subjects were seated in a chair facing a 15″ laptop screen at approximately 60 cm distance. They were instructed to react to sad or happy facial expressions with a left or right button press. The assignment of button valence was pseudo-randomized across patients (7 out of 11 patients and controls pressed right for joy and left for grief). After task completion, subjects were presented the emotional task stimuli for a classification of sad and happy faces without superimposed emotion words. All patients and controls correctly classified all emotional face expressions.

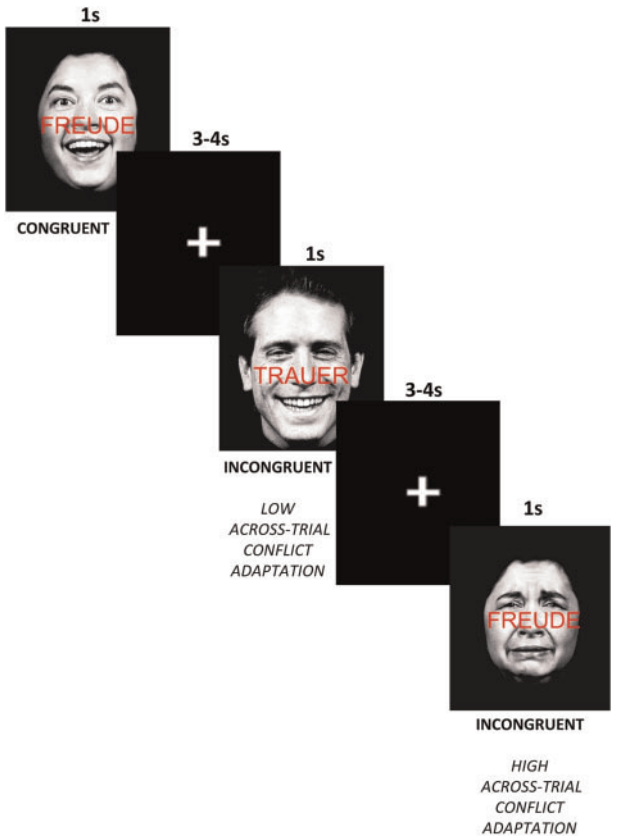

Fig. 1. Emotional Stroop paradigm. Stimuli were presented for 1 second, followed by a black screen with a white fixation cross presented for a jittered interval of 3–4 seconds.

Statistical analyses

Trials with reaction time outliers were excluded using the Thompson Tau test (rejection limit at 0.05) taking into account

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the standard deviation and average of the data (Anbarasi, 2011). Thompson Tau provides a statistically determined rejection zone that labels outliers beyond the limit. For the reaction time analysis, error trials, i.e. trials in which the response button did not match the facial expression, were excluded. Normal distribution of the reaction time data was checked with Kolmogorov Smirnov test to ensure validity of parametric testing. Intra-group reaction times changes between ON and OFF DBS test sessions were analysed using a multifactorial repeated measures analysis of variance (ANOVA) using MATLAB (The Mathworks, Natwick, MA, USA) and SPSS (IBM SPSS Statistics; IBM Corporation, Chicago, IL, USA).

To compare the patient group ON and OFF DBS with the control group, reaction times of each patient (RT_X) were standardized subtracting the mean reaction times of the control group ($RT_{controls}$) and dividing by the control group's standard deviation. The standardized mean reaction times (RTx.*std*) for each subject of the patient group thus described how far the subject's mean laid from the mean of the control group.

$$RTx.std = (RT_X – mean(RT_{controls}))/SD(RT_{controls})$$

For ANOVA I (Stroop effect), we computed the difference (delta) of conflict and no-conflict trials to describe the Stroop effect for trials with negative and positive valence. The standardized mean Stroop effect ON *vs* OFF DBS in trials with negative *vs* positive valence was compared using a repeated-measures ANOVA with the factors group (ON *vs* OFF DBS) and valence (positive *vs* negative). We tested for significance of the intercept, to see if the mean of both groups differed from the mean of the control group. Using post hoc tests we tested the mean Stroop effect of patients ON DBS, OFF DBS against zero to establish which groups differed from the control group.

To compare the effect of across-trial conflict adaptation (ANOVA II) between PD patients ON and OFF DBS and healthy controls, we standardized patients' reaction times in high *vs* low conflict adaptation trials to the control group. We then computed the delta of low and high across-trial conflict adaptation trials of positive and negative valence and compared them in a repeated-measures ANOVA in the same was as in ANOVA I.

Planned comparisons were adjusted with Bonferroni correction. In the reported comparisons of mean reaction times, *P* values regarding reaction times are results of paired two-sided t-tests for ON and OFF DBS group comparisons. Corrected *P*-values are classified significant on a 5% level. Cohen's d (*d*) and eta-squared (η^2) were used for calculation and report of effect sizes.

Computational simulations

To investigate the computational mechanisms behind patients' altered Stroop effects, we implemented a well-established computational model that consists of five modules, each containing one to three processing units (Figure 2; Botvinick *et al.*, 2001). Processing units are interconnected via connection weights that allow for the spread of activity between units. Two sensory modules, related to the processing of face and word stimuli, respectively, are activated by input stimuli according to trial types. Each sensory module contains three processing units related to the processing of negative, positive and neutral stimuli, respectively, in line with the original model (Botvinick *et al.*, 2001). These sensory modules compete for controlling the activities of a response module that selects the model's response in each given trial (i.e. negative *vs* positive).

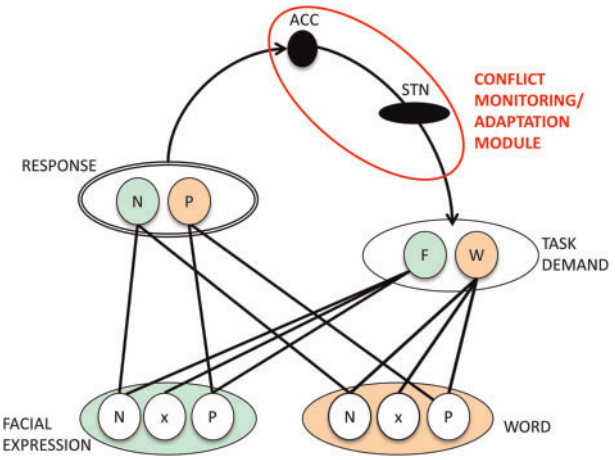

Fig. 2. Computational model of STN involvement in emotional conflict monitoring and adaptation. Small circles represent units, large ovals represent modules. Arrows represent unidirectional connections while lines represent bidirectional connections. P represents positive stimulus features, N represents negative features. x represents the assumed representation of features of neutral valence. F: Facial expression naming; W: Word naming.

The task demand module represents the task set according to which the response is to be selected (containing the units word naming and face identification). The task-relevant face identification unit of this module receives direct external input in each trial representing the explicit instruction that subjects should respond to faces, not to word stimuli. In addition, the word naming and the face identification units are bi-directionally connected with the sensory face module and the sensory word module, respectively. This means that they both receive bottom-up inputs from these sensory modules and modulate the activities of these modules in a top-down manner. Finally, the units of the task demand module receive top-down inputs from a conflict-processing module, consisting of the anterior cingulate cortex (ACC) and the STN. The ACC receives a conflict signal from the response module (representing the amount of conflict between the two response units) and forwards it to the STN, which then modulates the activities in the task demand module.

Botvinick *et al.* (2001) assumed the conflict module to be closely related to the ACC, which is known to project to the STN (Botvinick *et al.*, 2004; Lambert *et al.*, 2012). We propose that as conflict monitoring and adaptation module it contains both, the ACC and the STN (Figure 2). This assumption does not alter the model's dynamics, but allowed us to investigate a potential role of STN DBS in Stroop dynamics.

We reproduced all model equations for the healthy-state model exactly as implemented in the original publication by Botvinick *et al.* (2001). This was done to ensure comparability of our results with previous publications and to avoid overfitting of the model to our findings. All model equations are reported in Supplementary Methods. Botvinick *et al.* (2001), however, did not define a Parkinsonian version of the model so that we had to specify, in which respects such a Parkinsonian model would differ from the healthy state. Based on our empirical results, PD was implemented by changing the connection weights between the task demand module and the sensory word module. These connections specify the amount of interference that incongruent words produce (i.e. the extent of the Stroop effect). Specifically, we increased the bidirectional weight between the

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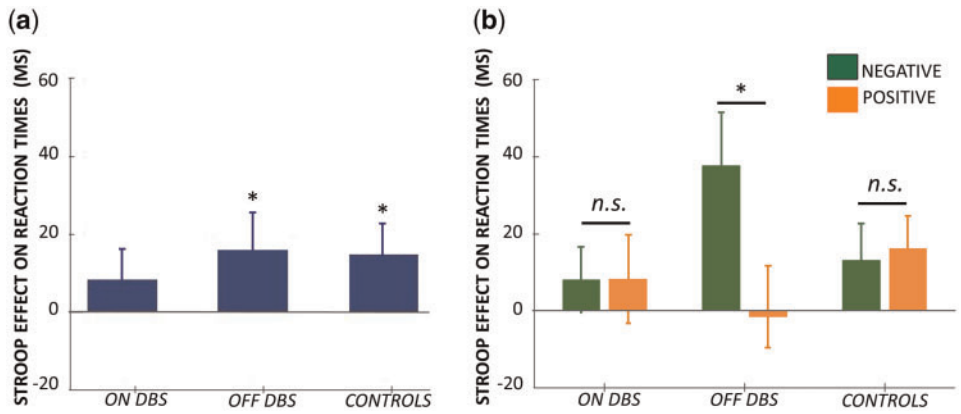

Fig. 3. Emotional Stroop effect on reaction times. (a) Over both valences, the Stroop effect of reaction times (delta of conflict – no conflict trials) is significantly different from zero in PD patients OFF DBS and healthy controls. No such difference is present ON DBS. (b) PD patients OFF DBS show a strong Stroop effect only for conflicting negative stimuli whereas no valence difference is found ON DBS and in healthy controls. Mean reaction times and standard error of the mean (SEM) are displayed (*$P < 0.05$).

sensory positive word unit and the word processing unit from 4.0 to 4.15 and reduced the bidirectional weight between the sensory negative word unit and the word processing unit from 4.0 to 3.85. Thereby, the model would reproduce increased Stroop effects in PD for negative faces and decreased Stroop effects of positive faces. The magnitude of changes was determined via manual fitting.

While it has been shown empirically that STN DBS reduces the activation of STN somata, presumably via activation of neighbouring inhibitory neurons, and at the same time directly excites STN neurons' axons (Agnesi *et al.*, 2013; Dorval *et al.*, 2008, 2010), the physiological relevance of these two effects is yet unknown. We here used the computational model by Botvinick *et al.* (2001) to investigate, whether each of these effects alone or in combination could reproduce the empirically observed effects of STN DBS on Stroop dynamics. To this end, we simulated the DBS ON condition in three versions, testing the following sets of assumptions:

i. STN inputs from the ACC were divided in magnitude by 2.0 to simulate DBS induced inhibition of STN neurons' somata. Additionally, the STN's baseline activity was increased from 0.0 to 3.0 to simulate DBS induced activation of STN neurons' axons.
ii. Again, STN inputs from the ACC were divided by 2.0. However, the baseline was not increased (i.e. axons were not assumed to be activated).
iii. The STN's baseline activity was increased to 3.0, while inputs from the ACC were not reduced (i.e. somata were not assumed to be inhibited).

We ran our simulations for a total of 72 trials per simulated subject (18 trials for each condition in random order, but precluding more than three identical trials in a row), in line with the original paradigm. Eleven subjects were simulated for each subject group. The model's Stroop effects on reaction time were fitted to empirical results by linear regression (as previously done by Botvinick *et al.*, 2001), estimating a single increment and offset parameter across four conditions. These conditions comprised the two face emotion conditions times two subject groups (i.e. healthy control subjects and patients OFF stimulation). The stimulation ON group was left out from the fitting procedure, since our goal was to compare the effects of different stimulation settings for this condition (precluding the possibility to arrive at a single set of fitted parameters). Thus, we fit the model for the other two conditions and then used the resulting parameters for all conditions.

Results

Emotional Stroop effect (within-trial conflict adaptation)

ANOVA I revealed a significant main effect of group, $F_{1,10} = 5.022$, $P = 0.049$, $\eta^2 = 0.201$, suggesting that the Stroop effect on reaction times ON DBS differed from the Stroop effect OFF DBS. Comparing the unstandardized Stroop effect in either group irrespective of valence, against zero revealed that conflict-induced slowing was significant in PD patients OFF DBS (mean Stroop effect of 17.96 ms), $t(10) = 2.006$, $P = 0.05$, $d = 0.605$, and in healthy controls (mean Stroop effect of 15.75 ms), $t(10) = 2.245$, $P = 0.045$, $d = 0.677$, but not in PD patients ON DBS (mean Stroop effect of 8.19 ms), $t(10) = 1.01$, $P = 0.35$, $d = 0.304$ (Figure 3A). Furthermore we found a significant interaction of valence and group, $F_{1,10} = 10.025$, $P = 0.01$, $\eta^2 = 0.334$, indicating that the group difference between ON and OFF was influenced by trial valence. In post hoc paired *t*-tests, trials with positive *vs* negative valence differed significantly from one another OFF DBS, $t(10) = 3.52$, $P = 0.005$, $d = 1.123$, but not ON DBS, $t(10) = 0.02$, $P = 0.97$, $d = 0.007$, or in healthy controls $t(10) = 0.34$, $P = 0.74$, $d = 0.108$. Specifically, there was a larger Stroop effect for negative than positive trials OFF DBS leading to significantly longer reaction times if the target stimulus (face) was negative and the superimposed word was positive or faster if the target stimulus (face) was positive and the superimposed word was negative, respectively (Figure 3B). Since the intercept test was non-significant, the mean patients response ON and OFF DBS did not differ from the mean of the control group, $F_{1,10} = 0.099$, $P = 0.759$, $\eta^2 = 0.005$. There were no significant correlations of the Stroop effect in either valence with disease duration, age, United PD Rating Scale III motor scale or medication intake (LEDD at time of study).

Across-trial conflict adaptation

Reaction time slowing in conflict trials has previously been described as being dependent on trial-to-trial adaptation of cognitive control, irrespective of valence. In ANOVA II, we found neither a main effect of group, $F_{1,10} = 2.61$, $P = 0.13$, $\eta^2 = 0.115$, or valence, $F_{1,10} = 0.149$, $P = 0.708$, $\eta^2 = 0.007$ nor the interaction of the two, $F_{1,10} = 1.634$, $P = 0.23$, $\eta^2 = 0.076$, to be significant. These results indicate that neither group nor valence influenced reaction time differences between high and low across-trial conflict adaptation trials. The intercept test was non-significant, $F_{1,10} = 3.374$, $P = 0.1$, $\eta^2 = 0.144$, indicating the mean of ON and OFF

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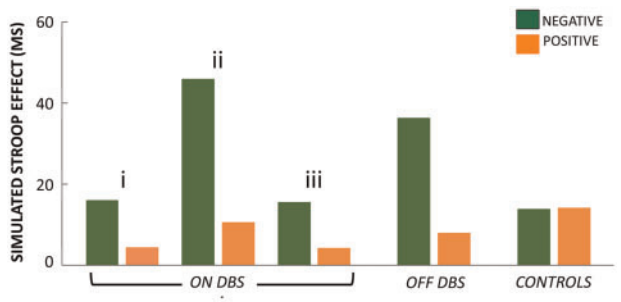

Fig. 4. Results of computational modelling of STN DBS interference with the Stroop effect. STN DBS is modelled with (i) a reduction in inputs from the ACC to the STN and increased STN baseline outputs, (ii) a reduction in STN inputs, and (iii) a reduction in STN outputs.

DBS data did not differ from the mean of the control group. Across-trial conflict adaptation was present in PD patients OFF and ON DBS and healthy controls to a similar extend, however, bearing in mind a limited number of subjects in our study.

Accuracy

Similar to Etkin *et al.* (2006), we found overall error rates to be relatively low in our sample with >99% mean accuracy in all conditions. Due to the low percentage of errors, we refrained from further analysis and discussion.

Computational results

We fitted the model by Botvinick *et al.* (2001) to the results of the healthy control group and of the stimulation OFF group as detailed in Materials and methods. Resulting Stroop effects for these two subject groups well reproduced empirically observed Stroop effects (Figure 4). For the healthy control condition, our simulations reproduced equally sized Stroop effects for negative and positive faces. For the Parkinsonian stimulation OFF condition, moreover, simulation results reproduced the observation that Stroop effects were stronger for negative than for positive faces.

As previously detailed by Botvinick *et al.* (2001), Stroop effects in this model result from increased competition between negative and positive response units (causing longer reaction times) when comparing incongruent to congruent trials. In the healthy condition, Stroop effects are of equal size for negative and positive faces as there is no bias in the original model. For simulating the results of PD patients, based on our experimental results, we expected positive words to interfere more strongly with negative faces in the PD conditions than in the healthy condition and negative words to interfere less strongly. As a consequence, our simulations reproduced a stronger Stroop effect for negative faces than for positive faces.

To investigate how STN DBS affects Stroop dynamics, we tested three different sets of assumptions with different modulation of STN input/output dynamics. In our simulations, we found that an increased baseline activity of the STN well reproduced the empirical results of PD patients ON stimulation irrespective of any reduction in inputs (Figure 4). In contrast, we found that a reduction in inputs to the STN did not reproduce findings.

Discussion

In this study, we assessed the influence of STN DBS on emotional conflict processing in patients with PD using an emotional Stroop paradigm introduced by Etkin *et al.* (2006). In this task, subjects needed to label face stimuli according to their emotional expression (negative or positive) while ignoring a superimposed emotion word congruent or incongruent to the facial expression. Because reading is automatized (Stroop, 1935), labelling a facial expression that is incongruent to the superimposed word should elicit cognitive control to suppress response to the word stimulus which in turn would slow down reaction times (Etkin *et al.*, 2006). Such conflict-related reaction time slowing is classified as being implicit, thus it requires no conscious awareness (Gyurak *et al.*, 2011). Our main result shows that ON DBS, PD patients did not slow down their reactions in trials where a conflict signal should have been detected. This implicates a defect in within-trial conflict adaptation induced through STN DBS. This finding is in line with growing evidence indicating interference of STN DBS with conflict processing and respective slowing of motor responses (Frank *et al.*, 2007; Brittain *et al.*, 2012; Green *et al.*, 2013; Zavala *et al.*, 2015, 2016; Herz *et al.*, 2016).

Previous studies had found no or even contrary effects of DBS on the traditional Stroop effect in PD patients (Jahanshahi *et al.*, 2000; Schroeder *et al.*, 2002; Witt *et al.*, 2004). However, this conflicting evidence likely relates to methodological differences in the applied paradigm: The above-mentioned studies assessed differences in total completion time of a colour-word Stroop versus a control task. In this study, we were interested in the direct reaction time differences between congruent and incongruent trials that are likely modulated by STN activity; defining the Stroop effect as trial-by-trial reaction time slowing due to recruitment of cognitive control (Botvinick *et al.*, 2001; Etkin *et al.*, 2006). Our study furthermore differs by design, as we controlled for confounding continuous stimulation effectiveness by waiting 30 minutes after switching off the DBS device before starting the task, which Schroeder *et al.* (2002) did not. Moreover, one may argue that the emotional Stroop paradigm inherently differs from the traditional colour-word Stroop task as facial expressions may, at least subtly, also be processed automatically. The evidence on processing hierarchy of faces and words is however inconsistent (Dolan and Vuilleumier, 2003; Beall and Herbert, 2008; Ovaysikia *et al.*, 2011). Yet, it cannot be ruled out that the emotional Stroop task manifests through neural resources beyond the network engaged in the traditional colour-word Stroop task.

Interestingly, we found stimulus valence to affect emotional conflict processing in PD patients OFF DBS. In particular, we found conflict-induced reaction time slowing to be much more prominent for negative conflict stimuli. That is, in PD patients OFF DBS, if a negative facial expression was superimposed with a positive word, the interference was significantly stronger than if a positive facial expression was superimposed with a negative word. This finding is evidence for a valence bias affecting conflict-induced reaction time slowing in PD patients OFF DBS. In PD patients ON DBS and healthy controls, such difference was absent resembling the findings by Etkin *et al.* (2006).

Previous research has indicated that STN DBS surgery may cause alterations in the ability to recognize emotions, especially regarding negative emotions such as fear, sadness, anger and disgust (Biseul *et al.*, 2005; Drapier *et al.*, 2008; Péron *et al.*, 2010). Our data suggest that active stimulation in the STN area

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modulates the affective bias that is present OFF DBS and reduces the interference of positive words with negative facial expressions leading to a reduced slowing of reaction times during negative emotional conflict trials.

It is worthwhile considering this DBS-induced change to occur along with the clinical improvement of the affective mood state. Psychiatric signs of PD often include emotional blunting, apathy and depression (Maillet *et al.*, 2016), possibly relating to a higher degree of modulation of alpha oscillatory activity in the STN (Huebl *et al.*, 2011). STN DBS has been found to elevate the current subjective mood, facilitating emotional experience and improving emotional memory similar to the effect of dopaminergic replacement medication (Schneider *et al.*, 2003). By altering the current affective state, STN DBS may interact with affective biases on attention and memory in PD (Gray and Tickle-Degnen, 2010), which have been described to be present in negative affective states (Gotlib *et al.* 2004; Beck *et al.*, 2012). Continuous STN DBS may thus adjust a selective attention or working-memory bias towards negative and away from positive information that is present in PD patients OFF DBS. This could occur independent of the presence of moderate or severe depressive symptoms as it was the case in our cohort although one limitation is that we did not obtain the BDI score separately ON and OFF DBS.

We were also interested in whether STN DBS would alter across-trial conflict adaptation. Conflict adaptation is adjusted based on contextual information: conflict detected in one trial triggers up-regulation of selective attention in anticipation of the next trial (Botvinick *et al.*, 2001). This trial-to-trial regulation of top-down control determines that response times are faster in a conflict trial that was cued by a previous conflict trial (high across-trial conflict adaptation) than in a conflict trial where the previous trial elicited no conflict (low across-trial conflict adaptation) (Etkin *et al.*, 2006). We found across-trial adaptation of top-down control to be present in all three groups equally, suggesting that STN DBS does not interfere with context-based adjustment of cognitive control in this task. However, we cannot rule out that STN DBS may inhibit the regulatory interplay of cognitive control regions in response to conflict. Our restricted sample size and the comparatively long inter-stimulus interval that we had to use for patients to be able to complete the task in an OFF DBS often severe bradykinetic state may have limited the observability of the effect. Future studies should use a different design focussing specifically on across-trial conflict adaptation to rule out potential disturbances induced through STN DBS.

Taken together, our findings indicate an interference of STN DBS with reaction time slowing in response to emotional conflict (within-trial conflict adaptation), but not with across-trial conflict adaptation. These results will be discussed further with regard to the dissociation of anatomical substrates guiding conflict monitoring and adaptation processes.

Neural networks of emotional conflict adaptation

Electrophysiological and neuroimaging studies suggest a partial dissociation of within-trial and across-trial conflict adaptation networks in the brain (MacDonald *et al.*, 2000; Carter and van Veen, 2007). Conflict-related slowing (within-trial conflict adaptation) has largely been attributed to follow activity of the dorsal-caudal ACC (Botvinick *et al.*, 2001, 2004; Botvinick and Cohen, 2014). In other words, during response preparation, conflicting environmental demands are automatically detected in the dorsal-caudal ACC engaging cognitive control to direct attention towards the relevant and away from irrelevant stimulus features (Egner and Hirsch, 2005). Evidence for this notion derives from studies using the classic colour-word Stroop paradigm (Botvinick *et al.*, 2004) as well as the emotional Stroop paradigm (Etkin *et al.*, 2006). The ACC seems thus to engage in monitoring of both non-emotional and emotional conflicting input (Egner *et al.*, 2008) specifying adaptive adjustments to be implemented by regulative structures such as the STN (Shenhav *et al.*, 2013).

For effective across-trial emotional conflict adaptation, it is the interplay of the ACC, PFC and amygdala that seems to be particularly important for the regulation of cognitive control (Etkin *et al.*, 2011). To minimize resource costs, cognitive control needs to adapt to contextual affective information, so that, once engaged, resolving subsequent conflicting emotional input requires less attention and less cognitive control (Kerns *et al.*, 2004; Egner and Hirsch, 2005; Walsh *et al.*, 2011). There is evidence for a pathway through which the rostral-ventral ACC exhibits inhibitory control over the amygdala to constrain the amygdalar response triggered by emotional distracters (Bush *et al.*, 2000; Egner *et al.*, 2008). On the other hand, strong associative white matter tracts link the rostral-ventral ACC with the PFC (Heilbronner and Haber, 2014) allowing for conflict-related information transfer to elicit adjustment of control resources (Keedwell *et al.*, 2016). Effective adaptation to emotional conflict seem thus to be dependent on a successful link between the ACC, prefrontal and amygdalar regions. In order to understand the role of the STN in emotional conflict processing, it is thus vital to focus on its connection with the abovementioned structures.

Out of its previously demarcated functional divisions (limbic-anterior, associative-mid, sensorimotor-posterior) (Joel and Weiner, 1997; Karachi *et al.*, 2005; Lambert *et al.*, 2012; Accolla *et al.*, 2016), it is the anterior STN that holds direct connections to emotion networks. The confirmed presence of associative tracts to and from the ACC, the basolateral amygdala, the internal globus pallidus and anterior hippocampi (Lambert *et al.*, 2012; Péron *et al.*, 2015) highlight the putative involvement of the STN in emotion processing, albeit direct evidence for emotional conflict processing in the STN is to date still sparse. However, there is evidence for the STN to be involved in processing of both affective content and conflicting perceptual input.

Direct recordings of neuronal activity from the STN during an emotional picture-viewing task have confirmed its role in processing affective content (Kühn *et al.*, 2005; Brücke *et al.*, 2007; Huebl *et al.*, 2011). Clinical studies with PD patients using STN DBS have reported occasional emotional disturbances such as hypomania, mirthful laughter or crying (Krack *et al.*, 2001; Mallet *et al.*, 2007; Wojtecki *et al.*, 2007). It could be assumed that DBS interferes with information integration from emotional processing structures such as the ACC, PFC and amygdala in the STN (Péron *et al.*, 2013); however, a clear deduction of STN contribution requires more research evidence.

Regarding the processing of conflicting perceptual input, plenty of evidence suggests that the STN modulates the integration of prefrontal conflict signals into the motor response (see Zavala *et al.*, 2015 for review). Holding a gateway position, the STN responds to mPFC conflict signals by slowing down action initiation until action tendencies are weighted based on accumulating evidence (Frank *et al.*, 2007). This capacity to slow down responses is crucial to avoid errors and premature responses and the underlying mPFC-STN interplay has been suggested to be modulated by a temporary increase of low-frequency oscillation

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synchrony between the two regions (Cavanagh *et al.*, 2011; Brittain *et al.*, 2013; Zavala *et al.*, 2014; Herz *et al.*, 2016; Zénon *et al.*, 2016). During DBS, this interplay is disturbed resulting in more erroneous and impulsive choices (Frank *et al.*, 2007; Herz *et al.*, 2016). Extending these assumptions to emotional conflict processing, it is likely that DBS would interfere with synchronization of STN and mPFC activity, on the one hand, and the integration of emotion-related signals of ACC and amygdala in the STN gateway signal, on the other hand. We aimed to provide a computational approach to verify the involvement of the STN in emotional conflict processing by applying the distinguished Stroop model (Botvinick *et al.*, 2001) on emotional content.

An adapted Stroop model of emotional conflict processing

The model by Botvinick *et al.* (2001) explains the emergence of Stroop effects by increased competition between response units for incongruent as compared to congruent trials. Applied to the emotional Stroop task, responses are fast and correct in congruent trials, where congruent face and word information adds up, while in incongruent trials, incongruent face and word information competes for access to the model's response units, requiring more time to select the correct response. Stroop effects (i.e. differences in reaction times between congruent and incongruent trials) are thus directly related to the 'strength' (i.e. saliency) of word stimulus in incongruent trials. The model thus explains stronger Stroop effects for negative faces and weaker Stroop effects for positive faces in PD patients OFF stimulation by an increased saliency of positive words and a decreased saliency of negative words in these patients. These results suggest that, other than might have been expected, non-stimulated PD patients' attention is more strongly captured by positive words than by negative words.

DBS is empirically known to directly alter pathological as well as task-related physiological activity (Garcia *et al.*, 2003; Chen *et al.*, 2006). During the colour-word Stroop task, automatized responses in incongruent trials are held back by momentary increases in STN beta activity (Brittain *et al.*, 2012). Taken together with its interference with conflict-related oscillations detailed above, such suppression of spontaneous STN activity well explains the disruptive impact of DBS on performance in tasks comparing high *vs* low conflict scenarios such as our paradigm.

On a mechanistic level, DBS has been shown to both increase the outputs of targeted brain structures (i.e. to directly activate axons) and to reduce the influence of inputs to these structures (i.e. to de-activate somata; Dorval *et al.*, 2008; 2010; Agnesi et al, 2013). With our simulations, we showed that the former of these effects, but not the latter, explains how STN DBS affects Stroop dynamics in PD patients: Our model suggests that the DBS-induced activation of STN axons is more important for explaining DBS effects on Stroop dynamics than the reduction of STN inputs from the ACC. However, the two effects might not be fully independent due to boundary effects. Frank *et al.* (2007) stressed this via computational simulations in a different model. They showed that changes in STN baseline activity can disrupt task-related cortical inputs to the STN to such an extent that PD patients become impaired in their ability to slow down with conflicting decisions.

The original model by Botvinick *et al.* (2001) has been subject to criticism mainly directed towards its primary focus on the ACC. The neural network guiding conflict monitoring and adaptation is likely more extensive including along ACC also the pre-supplementary motor area (pre-SMA) (Nachev *et al.*, 2007; Kouneiher *et al.*, 2009; Roberts and Husain, 2015) and other cortical and subcortical regions supplying information leveraged by dorsal ACC (dACC) to maximise the expected value of control (Shenhav *et al.*, 2013). In this context, the STN is counted to the regulatory structures effecting the control adjustments estimated by dACC (Cavanagh *et al.*, 2011; Shenhav *et al.*, 2013). Our model does not make this distinction between dACC as estimating and STN as implementing control structure and future development of computational models should aim to disentangle the hierarchical interplay of dACC and STN conflict signals in emotional conflict processing.

Overall, our findings suggest that STN DBS does not re-establish normal Stroop functioning in PD patients, but induces a different physiological state that results from increased output of the STN conflict unit.

Limitations

This study has a few limitations. First of all, we cannot exclude the influence of secondary confounding variables on performance. Between-patients variations in electrode placement could have influenced the results. However, post-operative imaging and a good clinical effect verified correct electrode placement (Huebl *et al.*, 2011). Moreover, between-patients variations in disease progress and degree of dopaminergic denervation could have influenced cognitive abilities. Yet, we found no correlation of the Stroop effect with clinical parameters such as disease duration or LEDD indicating their potential influence to be insignificant. Furthermore, within-patient variations in dopamine blood level could have impacted performance unnoticed, as we did not test subjects OFF their medication. However, in the tested patients, dopaminergic medication remained unchanged during each 20-minute test session and the applied randomized order of ON and OFF DBS test sessions controlled for this confound. Further, subjects performed the task with a mean accuracy of >99%, which precluded further analysis of error processing. It is likely that due to (i) the stimulus material which only included 100% correct emotional faces of joy and fear (not morphed faces that would have had a higher threshold of recognition) and (ii) the comparatively long stimulus display times used variations in accuracy could not be recorded as effectively. Finally, we did not find an effect of STN DBS on across-trial conflict adaptation, which may also be influenced by the long stimulus interval and limited number of subjects.

Conclusion

This study provides evidence for an interference of STN DBS with emotional conflict adaptation. Hereby, STN DBS regulates an emotional performance bias in PD patients that is present OFF stimulation. Specifically, STN DBS may reduce the impact of emotional conflict on the motor response leading to a respective lack of reaction time slowing ON DBS in conflicting trials. The results of our computational simulations suggest that it is the elevation of baseline activity induced by DBS and not the reduction of task-related activity within the STN caused by reduced inputs from the ACC that alter conflict processing.

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Supplementary data

Supplementary data are available at *SCAN* online.

Conflict of interest. None declared.

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