Electrophysiological Studies of Non-Motor Functions of the Subthalamic Nucleus in Patients with Parkinson's Disease

Inaugural-Dissertation

zur Erlangung des Doktorgrades
der Mathematisch-Naturwissenschaftlichen Fakultät
der Heinrich-Heine-Universität Düsseldorf

vorgelegt von

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Düsseldorf, Mai 2018

Aus dem Institut für Klinische Neurowissenschaften und Medizinische Psychologie

der Heinrich-Heine-Universität Düsseldorf

Gedruckt mit der Genehmigung der

Mathematisch-Naturwissenschaftlichen Fakultät der

Heinrich-Heine-Universität Düsseldorf

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Tag der mündlichen Prüfung: 18.12.2018

At the present time it is clear that the concept that the basal ganglia community has of the STN has dramatically evolved since its discovery by Jules Bernard Luys. Starting from a purely motor role, albeit not clearly understood, which would consist of avoiding an explosive over liberation of the motor activity, the so-called hemiballism, the "motor corpus Luysii" has now reached the status of a "subthalamic nucleus" being the central node of the basal ganglia (may be of the entire central nervous system?), a nexus that would play a crucial role in the cognitive and emotional control of behavior.

-C. Baunez (2011)

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Glossary

ACC	Anterior cingulate cortex
BG	Basal ganglia
CT	Computed tomography
DBS	Deep brain stimulation
DLPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalography
ERD	Event related desynchronization
ERS	Event related synchronization
GABA	Gamma-aminobutyric acid
GLU	Glutamate
GP	Globus pallidus
GPe	Globus pallidus pars externa
GPi	Globus pallidus pars interna
HFS	High-frequency stimulation
LFS	Low-frequency stimulation
LFP	Local field potential
LOFC	Lateral orbitofrontal cortex
MEG	Magnetoencephalography
MRI	Magnetic resonance imaging
PD	Parkinson's disease
SNc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
STN	Subthalamic nucleus
VF	Verbal fluency
5-HT	5-hydroxytryptamine

1 Abstract

Once regarded as a predominant motor structure the notion of the subthalamic nucleus (STN) has changed dramatically and is now regarded as a potent nexus for the integration of associative, limbic and sensorimotor pathways. Especially reports on the behavioral (side-) effects of STN deep brain stimulation (DBS) and recordings from the STN have supported this assumption of STN functioning. Furthermore, anatomical studies have identified subregions of the STN, corresponding to associative, limbic and sensorimotor regions. Aim of the present electrophysiological studies was to probe the different STN functions with regard to previous reports of STN DBS related (side-) effects in a population of patients with Parkinson's disease (PD).

In a first study the involvement of the STN in an associative verbal fluency mediating network was investigated. The aim was to find a possible explanation for the beneficial low-frequency DBS effects on verbal fluency performance by searching for increased low-frequency oscillatory activity. Postoperative STN local field potential (LFP) activity was recorded while PD patients performed a verbal generation task and compared to a control task. Time-frequency analysis revealed a significant low-frequency power increase during the verbal generation task and an increase of low-frequency coherence to frontal EEG channels. This study provides evidence for the involvement of the STN and its connections to frontal associative areas in a verbal generation task. Improvement in verbal generation during low-frequency DBS can possibly be explained by enhancement of this predominant frequency.

In a second study the involvement of the STN in limbic processing is discussed by reporting on the mechanism and time course of emotional side effects of STN DBS in a PD patient with affective lability under STN DBS during a follow up of over 4.5 years. In the first postoperative weeks the microlesion effect in addition to bilateral DBS considerably influenced mood, resulting in laughing behavior. In the term of various months, voltage changes lead to negative emotions. We conclude that affective lability may occur with different temporal dynamics regarding microlesion and early and chronic stimulation.

In a third study the involvement of the STN in somatosensory processing was investigated. Somatosensory stimulation by means of electrical median nerve

stimulation leads to a distinct modulation of cortical rhythmic oscillations. Responses to median nerve stimulation can also be recorded subcortically in the STN and may have a key role in the processing of somatosensory relevant information. The postoperative STN neuronal activity following median nerve stimulation in PD patients was recorded. Time-frequency analysis revealed four distinct components of rhythmic modulations: (I) a prolonged increase in alpha band power, followed by attenuation; (II) an initial suppression of power followed by a subsequent rebound in the beta band; (III) an early broad-frequency increase in gamma band power; (IV) and a sustained increase of 160 Hz frequency oscillations. These results further corroborate the involvement of the STN in somatosensory processing.

Taken together, findings of this work further support the hypothesis of the involvement of the STN in non-motor functions.

2 Zusammenfassung

Einst als prädominant motorischen Kern betrachtet hat sich die Auffassung des Nucleus subthalamicus (STN) dramatisch zu einem einflussreichen Verbindungskern für die Integration assoziativer, limbischer und sensomotorischer Information gewandelt. Insbesondere Berichte über nicht-motorische Nebenwirkungen der STN Tiefen Hirnstimulation und Ableitungen aus dem STN liefern Beweise für diese Funktionen des STN. Zudem gelang anhand von anatomischen Studien die Identifikation von Subarealen des STN, welche sensomotorischen, assoziativen und limbischen Regionen entsprechen. Ziel der vorliegenden elektrophysiologischen Studien war es, die unterschiedlichen Funktionen des STN in Bezug auf vorausgegangene Berichte über nicht-motorische Nebenwirkungen der STN Tiefen Hirnstimulation in einer Population von Patienten mit Idiopathischem Parkinson zu untersuchen.

In einer ersten Studie wurde die Beteiligung des STN in einem assoziativen wortflüssigkeits-vermittelndem Netzwerk untersucht. Ziel der Studie war die Identifikation einer möglich verstärkten niederfrequenten oszillatorischen Aktivität, welche die förderlichen Effekte der niederfrequenten STN Tiefe Hirnstimulation auf Wortflüssigkeitsleistungen begründen würden. Zu diesem Zweck wurden postoperativ lokale Feldpotentiale aus dem STN abgeleitet, während die Probanden eine Wortflüssigkeits- und eine Kontrollaufgabe ausführten. Zeit-Frequenz-Analysen offenbarten einen signifikant erhöhten Poweranstieg im Niederfrequenzbereich während der Wortgenerierungsaufgabe und einen Anstieg niederfrequenter Kohärenz zu frontalen EEG-Kanälen. Diese Studie liefert Beweise für die Beteiligung des STN und seinen Verbindungen zu frontalen assoziativen Arealen während einer Wortgenerierungsaufgabe. Die Steigerung der Wortflüssigkeitsleistung während niederfrequenter Tiefe Hirnstimulation kann durch Verstärkung dieser prädominanten physiologischen Frequenz erklärt werden.

In einer zweiten Studie wurde die Beteiligung des STN an limbischen Prozessen anhand von Mechanismen und zeitlichem Verlauf affektiver Nebenwirkungen der STN Tiefe Hirnstimulation diskutiert. Eine über viereinhalbjährige Nachbeobachtung eines Patienten mit Affektlabilität unter STN Tiefe Hirnstimulation wurde berichtet. Zusätzlich zum postoperativen Mikroläsionseffekt konnte die bilaterale Stimulation deutlich den

Affekt, im Sinne von Lachen, in den ersten postoperativen Wochen beeinflussen. Spannungsänderungen hingegen hatten einen geringen langfristigen Einfluss auf negative Emotionen. Unter Berücksichtigung des Mikroläsionseffektes und früher chronischer Stimulation kann Affektlabilität mit unterschiedlicher zeitlicher Dynamik auftreten.

Eine dritte Studie hat die Beteiligung des STN an somatosensorischer Verarbeitung überprüft. Somatosensorische elektrische Stimulation des Nervus medianus induziert eine umschriebene Modulation kortikaler rhythmischer Oszillationen. Neuronale Antworten auf Nervus medianus Stimulation können ebenfalls subkortikal im STN abgleitet werden und eine Schlüsselrolle bei der Verarbeitung somatosensorisch relevanter Information einnehmen. Zu diesem Zweck wurde postoperativ die neuronale Aktivität nach Nervus medianus Stimulation aus dem STN abgeleitet. Zeit-Frequenz-Analysen enthüllten vier markante Komponenten rhythmischer Modulationen: (I) ein ausgedehnter Poweranstieg im Alpha-Frequenzband, gefolgt von einer Abschwächung des Signals; (II) eine initiale Unterdrückung der Power, gefolgt von einem Rebound im Beta-Frequenzband; (III) ein früher breitbandiger Anstieg der Gamma-Frequenz Power; (IV) und ein anhaltender Poweranstieg von Oszillationen im 160 Hz-Frequenzbereich. Diese Ergebnisse bekräftigen weiter die Beteiligung des STN an somatosensorischer Verarbeitung.

Zusammengefasst liefern die vorliegenden Studien weitere Beweise für die Annahme nicht-motosicher Funktionen des STN.

3 Introduction

Once regarded merely as a relay station acting as a gate for ascending basal ganglia-thalamocortical circuits the concept of the functional role of the STN has changed dramatically over the past three decades to being considered as a main regulator of motor function related to the basal ganglia (BG) (Temel et al., 2005) and a nexus for the integration of associative, limbic and sensorimotor pathways (Baunez et al., 2011). Especially reports on the behavioral (side-) effects of STN DBS have led to the notion of a vital regulatory function of the STN in the processing of associative, limbic and sensorimotor information reaching cortical and subcortical areas. These findings have been further corroborated by animal and human studies. Recordings from the STN and experimental studies applying STN DBS or STN lesions to investigate involved neuronal mechanisms found significant effects on cognitive and motivational parameters (for a review please refer to (Kharazia and Weinberg, 1994; Temel et al., 2005; Baunez et al., 2011; Weintraub and Zaghloul, 2013)).

3.1 STN Structure, Connectivity and Function

The STN is a biconvex structure with a volume of about 240 mm^3 and has a high neuron density of approximately 560 000 neurons (Hamani et al., 2004). It lies ventromedial of the pallidum and is surrounded by fiber tracts of the zona incerta, substantia nigra, nucleus ruber, cerebral peduncule, internal capsule and the thalamus (Parent and Hazrati, 1995a, 1995b; Hamani et al., 2004). Histological studies from Parent and Hazrati (Parent and Hazrati, 1995b) on the primate brain have led to substantial knowledge about the STN structure and anterograde and retrograde tracer procedures revealed afferent and efferent connections from the different STN subregions. These connectivity studies led to the identification of three functionally different STN subregions: the dorsolateral sensorimotor part (two-thirds of the STN), the ventromedial associative part (one-third of the STN), and the medial (tip) limbic part (Parent and Hazrati, 1995a, 1995b; Hamani et al., 2004). It is assumed that there is a fluent junction between the functional subregions of the STN (Figure 1, (Karachi et al., 2005; Mallet et al., 2007)).

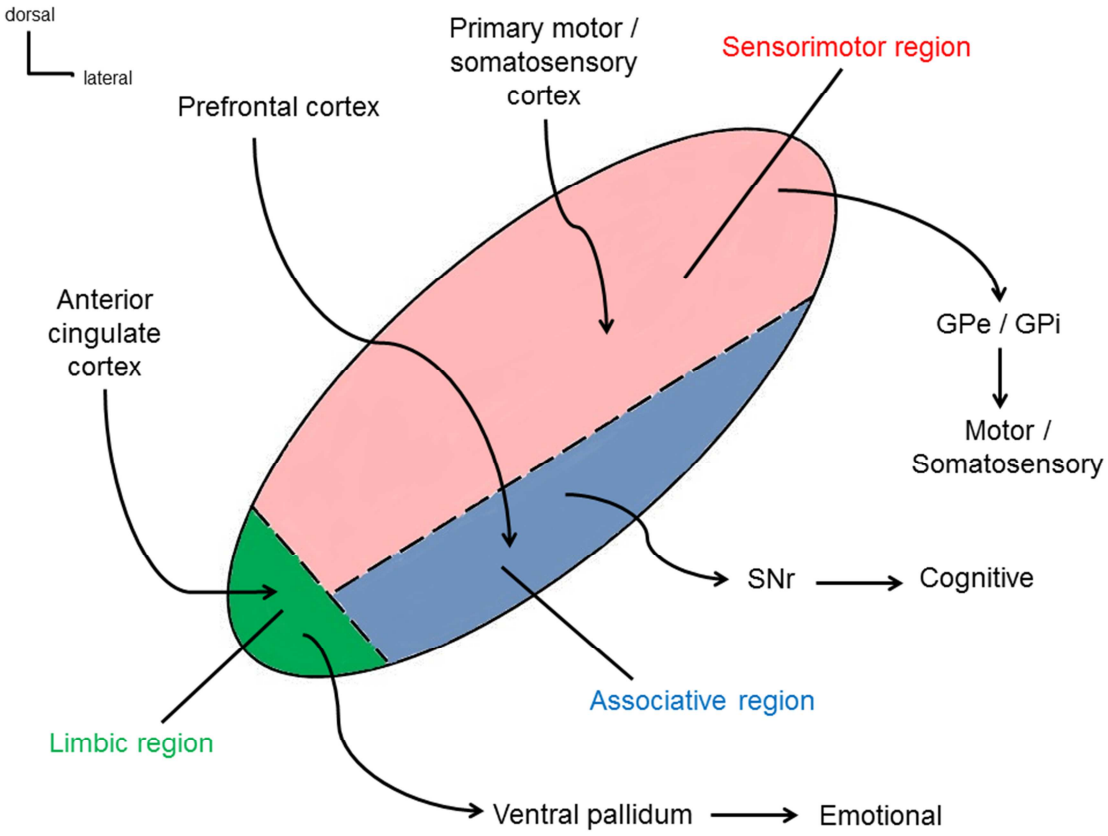

Figure 1: *Schematic illustration of the STN and its subdivision into a large dorsolateral sensorimotor territory, a ventromedial associative territory, and a medial limbic territory. Each territory receives inputs from different cortical areas and provides output to different target nuclei. Dashed borderlines between the sub-regions indicate fluent junction between these areas (adapted from* (Benarroch, 2008)*).*

3.1.1 Basal Ganglia

The STN forms part of the BG, alongside the striatum (caudate nucleus and putamen), the globus pallidus (GP) and the substantia nigra (SN). The BG are a group of nuclei that perform cohesively as a functional unit (Figure 2). The nuclei are located at the forebrain base and are thoroughly connected via neuronal loops with the cerebral cortex, thalamus and other brain areas. Importantly, they are an essential subcortical structure not only for the processing of sensorimotor information but also for the processing of cognitive and affective behaviors.

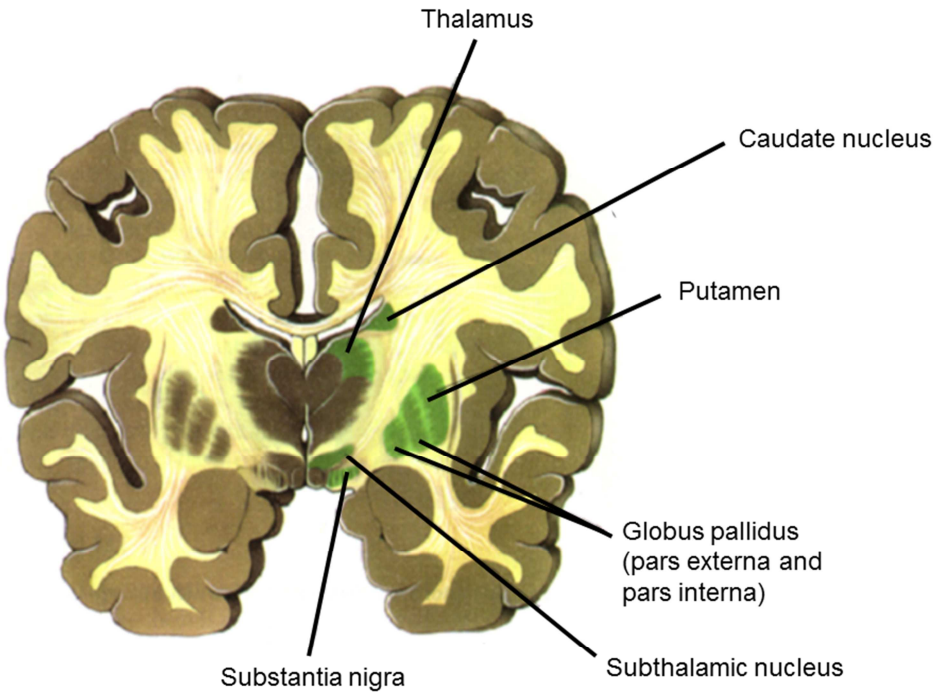

Figure 2: *Coronal view of the human brain displaying the basal ganglia nuclei (adapted from* (Bear et al., 2001)*).*

Just as the STN, the BG can be functionally subdivided into a dorsal, a medial and a ventral system. The dorsal system is prevailing for motor and somatosensory processing and the ventromedial system is substantial for cognitive and affective processing (Temel et al., 2005; Mallet et al., 2007; Benarroch, 2008). This functional subdivision remains substantially preserved throughout the individual BG nuclei. Neuronal processing in the BG takes place primarily in parallel working functional loops (sensorimotor, cognitive, and affective) which also display a certain amount of convergence between each other. This convergence or interaction seems plausible since e.g. motor actions require cognitive and/or affective influences. Five functionally different loops have been identified by Alexander et al. (Alexander et al., 1990). They have been named after their cortical association areas and can be summarized by their functions: there are two motor loops, two cognitive loops and one limbic loop. The motor loops project to 1. the (pre)-motor cortex and 2. to the frontal eye fields. The cognitive loops project to 1. the dorsolateral prefrontal cortex (DLPFC) and 2. the lateral orbitofrontal cortex (LOFC) and the limbic loop projects to the anterior cingular cortex (ACC) and the ventromedial prefrontal cortex (Parent and Hazrati, 1995b). The interaction between the cortical and

subcortical areas is mediated by their anatomical structures and their direct and indirect connections. These circuits are engaged in a variety of functions including movement, executive processes, attention and learning.

3.1.1.1 Cortical-Basal Ganglia Loops

The intrinsic connectivity in the BG is regarded as the same for all loops and branches off from the striatum onwards into a direct and an indirect pathway. This differentiation regards to a monosynaptic (direct pathway) and a polysynaptic (indirect pathway) connectivity with the BG exit points. The neurons of the direct pathway primarily carry D1 receptors and project directly from the striatum to the globus pallidus pars interna (GPi) via Gamma-aminobutyric acid (GABA). The GPi neurons themselves have GABAergic projections to the ventroanterior and ventrolateral thalamus. The thalamus has glutamatergic (GLU) projections to the respective cortical association areas and closes the loop via these. Some thalamic collaterals project back to the GPi and form a feedback-loop. The exact function of this feedback-loop in the current BG model remains unclear up to now. According to the model an excessive dopaminergic stimulation of the striatal D1-receptor neurons of the direct pathway leads to a disinhibition of thalamo-cortical signaling and thus to an elevated activity of cortical neurons. The neurons of the indirect pathway express D2-receptors and are less ramified. Beginning at the striatum GABAergic fibers spread out to the globus pallidus pars externa (GPe) and from there to the GPi and further branch out and build reciprocal connections with the STN. The projections to the STN are highly important since the STN is the only nucleus in the BG with an excitatory effect on the exit points. An activation of the indirect pathway via D2-receptors results in an excessive inhibition of thalamo-cortical signaling, explaining – at least in the motor loop- why movements are inhibited (Brown and Marsden, 1998).

It is assumed that under physiological conditions afferent information from the frontal cortex, e.g. containing movement plans, is processed via the direct pathway in the BG, while simultaneously competing movements are inhibited via the indirect pathway. The BG act as a filter of possible actions, where the motor program or the alternative is promoted after evaluation of the present context through all functional loops and the most efficient is chosen. Inadequate actions or competing motor programs are inhibited simultaneously (Mink, 1996). Importantly, within each of these circuits the STN has a central position.

3.1.1.1.1 Associative Circuit

Cognitive processes related to the BG are functionally and anatomically represented by the two basal ganglia-thalamocortical associative circuits (Figure 3, (Alexander et al., 1986, 1990; Alexander and Crutcher, 1990). These processes depend on connections between frontal, temporal and parietal association cortices and the striatum (Kunzle, 1975; Goldman and Nauta, 1977; Ragsdale Jr. and Graybiel, 1981; Parent and Hazrati, 1995a). The first associative circuit is the dorsolateral prefrontal circuit which originates anatomically from the DLPFC. The second associative circuit is the lateral orbitofrontal circuit, initiating from the LOFC (Alexander and Crutcher, 1990; Alexander et al., 1990). These cortical areas project GLUergic afferents to the caudate nucleus (Goldman and Nauta, 1977; Yeterian and Van Hoesen, 1978; Alexander et al., 1990). From here, this circuit is directed to the GPi, GPe and the SNr (Alexander et al., 1990; Parent and Hazrati, 1995a). The GPi and SNr project to the thalamus and the circuit is closed by the GLUergic thalamocortical pathway back to the DLPFC and the LOFC. This pathway is also known as the direct pathway. The indirect pathway refers to a reciprocal projection from the GPe to the STN and a one-way projection to GPi/SNr. The STN is anatomically connected with both the direct pathway, through its projection to the GPi and SNr, and the indirect pathway, through its projection to the GPe. The STN can thus regulate processing of information within the BG on the levels of an intermediate station (GPe) and of the BG output (GPi/SNr).

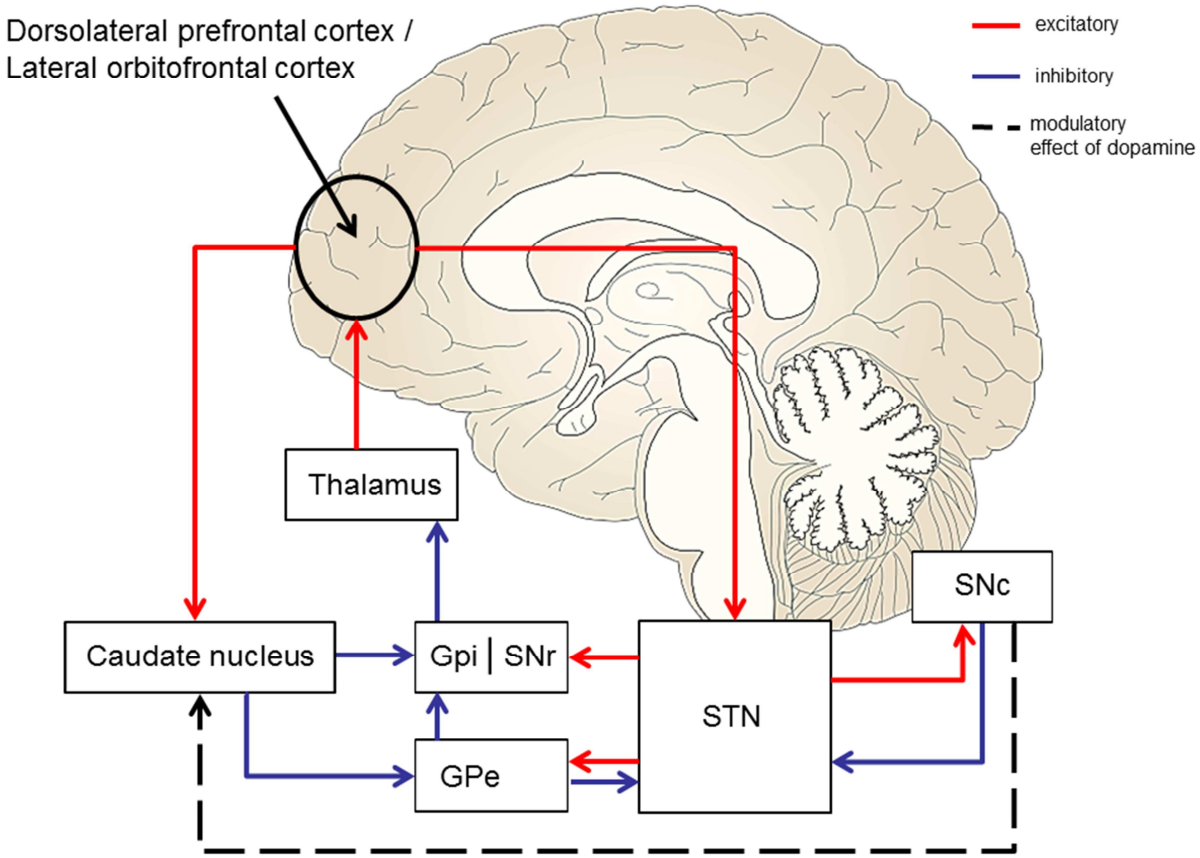

Figure 3: *Schematic illustration of the basal ganglia-thalamocortical associative circuit (adapted from* (Temel et al., 2005)*).*

3.1.1.1.2 Limbic Circuit

Affective, emotional and motivational processes related to the BG are mediated by the basal ganglia-thalamocortical limbic circuit (Figure 4, (Alexander et al., 1986, 1990; Nakano, 2000)). In the primate, afferents from the hippocampus, the amygdala, limbic and paralimbic cortices project to the ventral striatum (Alexander et al., 1990; Parent and Hazrati, 1995a). The ventral striatum is composed of the nucleus accumbens, the ventromedial part of the caudate-putamen and the mediumcelled portion of the olfactory tubercle (Parent and Hazrati, 1995a; Nakano, 2000). The ventral striatum projects to the ventral pallidum, from where the circuit is directed to the thalamus (Alexander et al., 1990). A thalamocortical pathway to the ACC and medial orbitofrontal cortex closes this circuit. The STN has a reciprocal connection with the ventral pallidum (Haber et al., 1985), which is considered to be the major limbic circuit output region.

Through this direct connection with the output region of the limbic loop the STN has an important role within this circuit.

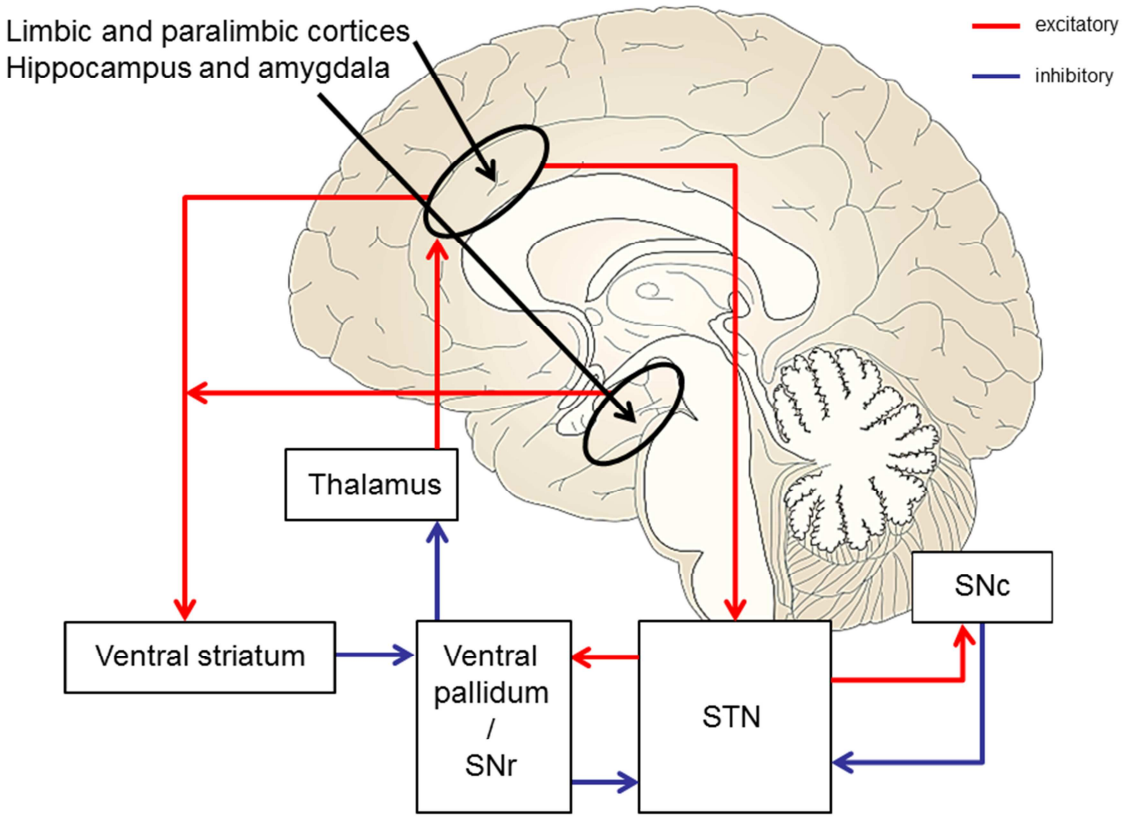

Figure 4: *Schematic illustration of the basal ganglia-thalamocortical limbic circuit (adapted from* (Temel et al., 2005)*).*

3.2.1.1.3 Sensorimotor Circuit

Sensorimotor performance is represented by the basal ganglia-thalamocortical motor circuit (Figure 5, (Alexander and Crutcher, 1990; Alexander et al., 1990)). In primates, this circuit initiates with GLUEergic projections from the primary motor cortex, premotor areas, supplementary motor area, primary somatosensory cortex and somatosensory association cortex and is mainly directed to the putamen (Kunzle, 1975, 1977; Alexander et al., 1990). The putamen projects to both the GPi and GPe and to the SNr, using GABA as neurotransmitter. From the pallidal and nigral terminals the motor circuit is further directed to the thalamus (Ilinsky et al., 1985; Francois et al., 1988;

Alexander et al., 1990), with this pathway known as the direct pathway. There is a reciprocal projection from the GPe to the STN and a one-way projection to GPi/SNr, which is known as the indirect pathway (Parent and Hazrati, 1995a, 1995b). Through its projections to the GPi and the SNr the STN is anatomically connected with the direct pathway. Furthermore, through its projections to the GPe the STN is also anatomically connected to the indirect pathway. The STN acts as the main regulator of the output of the motor circuit towards the thalamus (Plenz and Kital, 1999). The motor circuit is closed by the thalamic projection to the supplementary motor area, premotor areas, the primary motor cortex, primary somatosensory cortex and somatosensory association cortex (Kunzle, 1977; Alexander et al., 1990).

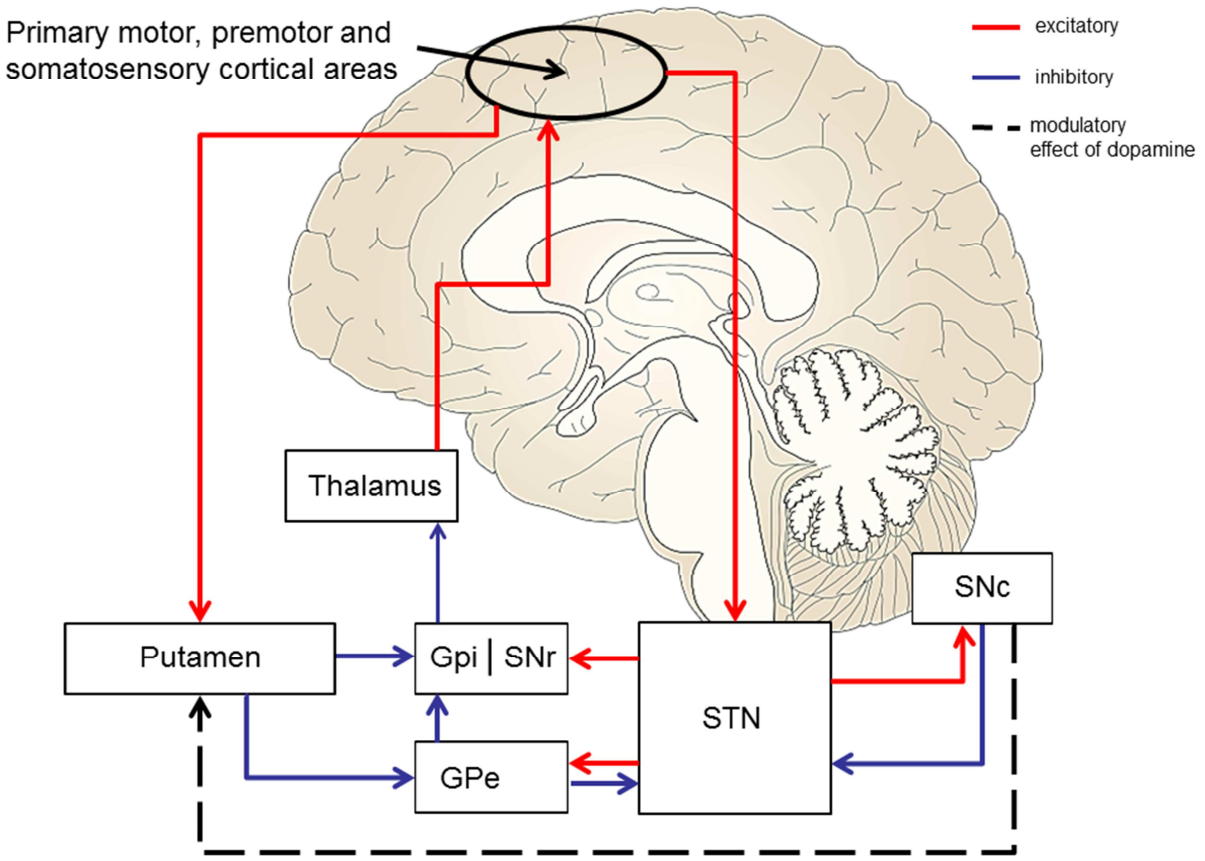

Figure 5: *Schematic illustration of the basal ganglia-thalamocortical sensorimotor circuit (adapted from* (Temel et al., 2005)*).*

In humans as well as in rats, there is evidence for a GLUEergic cortico-subthalamic projection, referred to as the hyperdirect pathway (Nambu et al., 2002; Magill et al.,

2005). It is assumed to send an early direct signal from cortical areas through the STN to GPi (Nambu et al., 2002). For the execution of voluntary movements a fast, short latency signal from the cortex is conveyed to the STN and further to the GPi, diffusely inhibiting the motor thalamus. Subsequent activation of the cortico-striatal direct pathway leads to a disinhibition of the motor thalamus for a selected motor function, while a third signal suppressing competing actions is mediated by the indirect pathway (Nambu, 2004). The functional role of this hyperdirect pathway is of exceptional importance in models including STN function in prefrontal cortex mediated decision-making processes (Frank, 2006; Bogacz and Gurney, 2007; Ratcliff and Frank, 2012). It is assumed that the STN dynamically adapts response thresholds gained from competing cortical inputs, facilitating the integration of various inputs and thus enabling an optimal decision (Frank, 2006; Frank et al., 2007).

In conclusion, the STN has an anatomically central position within the basal ganglia-thalamocortical associative, limbic and sensorimotor circuits and acts as a potent functional integrator of these pathways.

3.1.2 STN Function

Up until now there is no clear notion about the function of the STN. However, there is increasing evidence proclaiming that the STN plays a critical role in response processing and more specifically in response selection, inhibition, and execution (Baunez et al., 1995; Baunez C, 1997; Baunez and Robbins, 1999). The notion of the STN as an important inhibitory structure in the cortico-basal ganglia-thalamo-loop has received special attention. The STN has influence on the exit points of the BG (GPi, SNr) through direct excitatory connections and presumably also receives hyper-direct cortical afferents (Nambu et al., 2002). Frank and colleagues compare the STN with a curbing brake, impeding premature actions and impulsive behavior (Frank et al., 2007). Through the direct cortical excitatory influence, reaching the STN via the hyper-direct pathway earlier than via the direct or indirect pathways through the striatum, the STN can already exert inhibitory influence on the thalamo-cortical signaling, even before the processing reaches the BG exit points over the direct or indirect pathways to impede premature actions. This inhibitory STN signal could be favorable for gaining time for the selection of better evaluated actions.

3.2 Oscillatory Brain Activity

Insight into the functioning of neuronal structures has been gained from electrophysiological recordings of the electrical activity of the given structure, where voltage fluctuations resulting from ionic current flow within the neurons of the brain are measured. The spectral content of these measurements depicts the neuronal oscillations of the recorded structure. Neural oscillation is referred to repetitive or rhythmic neural central nervous activity. This neural oscillation can be generated by mechanisms within individual neurons or by interactions between neurons. Within the individual neuron, oscillations emerge either as oscillations of the membrane potential or as rhythmic patterns of action potentials, leading to oscillatory activation of post-synaptic neurons. Synchronized activity of neurons within neural ensembles can produce macroscopic oscillations. Synchronization describes the time-wise co-occurrence of certain events, thus, if two or more events occur at precisely the same time. Oscillations in neuronal groups are commonly generated by feedback connections between the neurons and result in a synchronized firing pattern. Furthermore, interactions between neurons can produce oscillations with a different frequency than the firing frequency of the individual neurons (for a review see (Schnitzler and Gross, 2005; Buzsáki, 2006)).

Oscillatory activity can be recorded throughout the central nervous system. Furthermore, it can be observed at different levels, e.g., spike trains, LFPs and large-scale oscillations, measured by electroencephalography (EEG) or magnetoencephalography (MEG). The frequency, amplitude and phase characterize the oscillatory activity. Time-frequency analysis of neural recordings may provide these signal properties. Neurons or neuronal ensembles can change their oscillation frequency in response to input, i.e. as the individual neuronal firing rate depends on the summed activity it receives. Changes in frequency are unusual in oscillatory activity involving different brain areas, as the oscillatory frequency often relates to the time delays between involved areas. Changes in synchronization within a neural ensemble generally result in amplitude changes. Increases in oscillatory activity are referred to as event-related synchronization (ERS) and decreases are referred to as event-related desynchronization (ERD), whereby the frequency specific power is calculated initially as indicator of synchrony and subsequently ERD and ERS are calculated in reference to a baseline activity and thus provide the event-related power modulations (Pfurtscheller and Lopes da Silva, 1999).

Additionally to local synchronization, distant neural structures can synchronize their oscillatory activity. Communication between distant groups of neurons has been found to be more effective when the local input is rhythmic and synchronized and the neuronal populations synchronize their activity as well (Varela et al., 2001; Fries, 2009). However, the exact functional role of neural oscillations and synchronization still remains unclear. Possible roles include feature binding, information transfer and generation of rhythmic motor output (Fries, 2005; Schnitzler and Gross, 2005).

3.2.1 Functional Role of Oscillatory Frequencies

Neural activity generated by numerous neurons has been the object of most studies and can be measured invasively by techniques such as the LFP and non-invasively by techniques such as EEG. The EEG time signals can be dismantled into their frequency components, revealing oscillatory activity in specific frequency bands: delta, 1-3 Hz; theta, 4-7 Hz; alpha, 8-12 Hz; beta, 13-30 Hz; gamma, 30-100 Hz and high frequency oscillations > 100 Hz. These functionally relevant frequency bands have been associated with specific functional roles. For example, theta-oscillations reflect working memory and enduring focused attention (Sauseng, Klimesch, Schabus, et al., 2005). Alpha-oscillations play a role in transient reactivation of long-term memory codes during short-term storage (Klimesch et al., 2005). Alpha-oscillations have also been thought to reflect idling inhibition of task irrelevant areas, but recent models hypothesize that alpha rhythmicity plays an active role in attention and consciousness (Palva and Palva, 2007). Furthermore they have been involved in motor imagination (Kuhn et al., 2006), action observation (Marceglia et al., 2009) and processing of emotional stimuli (Brucke et al., 2007; Huebl et al., 2011; Kuhn et al., 2005a). Beta-band oscillations might reflect worsening of flexible behavioral and cognitive control (Engel and Fries, 2010) and are well known for their role in sensorimotor functions (Pfurtscheller et al., 1996) and motor processing (Kühn et al., 2004). Oscillations in delta-, theta-, alpha- and beta-bands are assumed to serve long-rage communication between distant areas (Gross et al., 2004; Schnitzler and Gross, 2005). Gamma-oscillations have primarily been associated with feature binding (Tallon-Baudry and Bertrand, 1999; Engel and Singer, 2001; Buzsáki, 2006), working memory (Tallon-Baudry et al., 1998), associative learning (Miltner et al., 1999) and attention (Fries et al., 2001). Furthermore, they can also be recorded in the BG during the execution of movements (Brücke et al., 2008).

In many neurological disorders oscillatory activity also plays a pivotal role, such as excessive synchronization during seizure activity in epilepsy or tremor in PD patients. Pathological elevated beta-oscillations in the cortico-basal ganglia network probably play a major role in hypokinetic movement disorders such as PD (Kühn et al., 2004; Kühn, Trottenberg, et al., 2005; Kühn et al., 2006).

3.2.2 Local Field Potentials

Recordings of the electrical brain activity along the scalp have been performed for a long time and led to substantial insights into the functioning of the human cerebral cortex. However, knowledge about the functioning of subcortical structures is relative sparse due to the limited accessibility of these areas. Evidence regarding the functioning of subcortical areas is mostly based on imaging studies with low temporal resolution, lesion studies or on invasive recordings in animal models.

Owing to the renewed implementation of functional neurosurgery in the last decades many new insights about the functioning of subcortical structures have been gained. DBS has successfully been implemented as a therapeutic tool for the treatment of various neurological disorders such as PD, essential tremor, dystonia, epilepsy etc. (Theodore and Fisher, 2004; Kupsch et al., 2006; Benabid et al., 2009; Sixel-Döring et al., 2009). Besides targeting the symptoms of the underlying disease DBS allows for the possibility to record the neuronal activity of the deep brain structures over the stimulation leads. Besides the intraoperative recordings of single cells or small cell populations through microelectrodes LFPs can be recorded from deep brain structures. LFPs presumably reflect the input signal of the target structure and contain band-passed filtered electrical activity from a range within millimeters from an electrode, consisting of the summated synchronized postsynaptic excitatory and inhibitory potentials (Brown and Williams, 2005; Kühn, Trottenberg, et al., 2005).

The implanted DBS electrodes can be externalized for some days postoperatively before being connected to the impulse generator during a second surgical intervention. This externalization renders the unique opportunity to record from subcortical structures in awake and cooperative patients. The analysis of LFP recordings allows for statements about the dynamics of the modulation of neuronal activity with a high temporal

resolution while patients perform specific cognitive, motor or somatosensory tasks. This unique method was implemented in the present studies 1and 3.

3.3 Parkinson's Disease

PD is a degenerative disorder of the central nervous system and is one of the most notable neurological conditions of BG dysfunction. It is characterized by akinesia (poverty and slowness of movement) and one of the following cardinal symptoms: rigidity (muscle stiffness), resting tremor and postural instability. Facultative concomitant symptoms include sensory (dysaesthesia, pain, hyposmia), vegetative (dysfunctions of blood pressure, temperature regulation, bladder and bowels as well as sexual functions), psychic (depression) and cognitive dysfunctions (executive deficits, dementia in advanced stages of the disease) as well as sleep disorders. With a prevalence of 100 to 200 per 100 000 inhabitants it is one of the most frequent neurological disorders in Germany. PD is more common in the elderly and prevalence rises from 1.8% in those over 65 years of age to 2.6% of the population over 85 (De Rijk et al., 2000).

3.3.1 Pathology

The primary symptoms result from a pronounced degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), a BG nucleus. Neuronal processing in the BG primarily occurs in five parallel functional loops. These basal ganglia-thalamocortical circuits form the elementary pathways through which higher and lower regions of the brain communicate with the BG. All of these circuits originate from specific cortical areas, are processed in specific BG and thalamic nuclei and project back to at least one of the cortical input areas (Alexander and Crutcher, 1990; Alexander et al., 1990; Parent and Hazrati, 1995a). Furthermore, the communication via these circuits involves specific functions (e.g., associative, limbic functions and sensorimotor) represented by specific circuits. Due to the dopaminergic degeneration the physiological function of cortico-basal ganglia-thalamocortical circuits is altered. All of the five circuits are affected in PD leading to the described symptoms of the disease (Obeso et al., 2008).

So far, the motor circuit has been examined the most extensively. The dopaminergic depletion in the nigrostriatal system in PD leads to an imbalance in the activation of the

direct and indirect pathways in favor of the indirect pathway. A hyperactivity of the STN and GPi follows, leading to an excessive inhibition of the thamalo-cortical signaling, resulting in movement deficits such as bradykinesia and rigor in PD. It is worth noting that this pathophysiological concept can only account conclusively for the motor symptoms of PD. Some concepts have been developed to explain the non-motor symptoms in PD, giving the STN an important mediator role (Obeso et al., 2008).

3.3.2 Abnormal Synchronization in Parkinson's Disease

Past invasive and non-invasive electrophysiological studies of the normal functioning of basal ganglia-thalamocortical circuits and the pathophysiology of PD have led to insights into the functional roles of oscillations and oscillatory synchronization. It has been proposed that alterations in oscillatory discharge patterns and synchronization between BG neurons and abnormal long-range network interactions play a pivotal role in the pathophysiology of PD.

Recordings from the STN have revealed that under physiological conditions, this nucleus has a regular discharge pattern with intervals of burst activity (Magill et al., 2000). In the parkinsonian condition, the STN firing rate increases resulting in continuous burst activity, leading to an excessive inhibition of the thalamocortical drive and contributing to the motor symptoms of PD (Levy et al., 2002). In particular, pathologic synchronous beta-frequency oscillations have been recorded in the STN and GPi in primate models and patients with PD (Heimer et al., 2002; Kühn, Trottenberg, et al., 2005; Weinberger et al., 2006). Lesions or high frequency stimulation (HFS) of the GPi or STN effectively treat the symptoms of PD, possibly by a reduction or an elimination of abnormally synchronized BG output. Interestingly, the decrease of beta-oscillations correlates with levodopa administration (Levy et al., 2002), and further evidence suggests that STN DBS functions by means of disruption of these pathologic beta-oscillations (Brown et al., 2004; Meissner et al., 2005).

3.4 Deep Brain Stimulation

PD therapy consists mainly in the substitution of dopamine by the dopamine precursor levodopa and dopaminagonists. However, after a few years about 50% of all PD patients suffer from a reduction of medication efficacy and develop levodopa induced motor

fluctuations and dyskinesias, markedly reducing patient's quality of life (Encarnacion and Hauser, 2008; Chaudhuri and Schapira, 2009). These symptoms can be treated pharmacologically but in the course of the disease a therapy based purely on medications can't grant for satisfactory symptom alleviation. At this time point functional neurosurgical therapeutic measures can be applied successfully. At present the most important procedure is DBS, which has been applied since the beginning of the 1990s (Hilker et al., 2009). During a stereotactic surgical intervention stimulation electrodes are implanted in specific subcortical nuclei of the BG. The STN has advanced to the target point of choice for DBS in PD.

3.4.1 DBS Surgery

DBS surgery takes place in two stages. First, during a stereotactic intervention small holes are burred through the skullcap, through which the stimulation electrodes can be inserted into the brain. The STN location can be determined based on the Schatenbrand-Wahren-Atlas coordinates (Schaltenbrand and Wahren, 1977), stereotactic cranial computed tomography (CT) and stereotactic high resolution magnetic resonance imaging (MRI). Furthermore, the STN borders can be defined by intraoperative microelectrode recordings using the INOMED MER system (INOMED Corp., Emmendingen, Germany) with up to five electrodes concentrically configured with a distance of 2 mm from the central electrode. Final placement of the DBS electrode (electrode model 3389, Medtronic Corporation, Minneapolis, MN, USA) is then based on single cell activity, stimulation effects, and side effects. For postoperative LFP recording purposes the DBS macroelectrodes can then be connected to sterile percutaneous extension wires (model 3550-05, Medtronic), which can be lead out through the scalp and be connected to EEG amplifiers via external cable connectors (twist lock cable model 3550-03, Medtronic and custom made connector to DIN 428092 touch proof connectors) postoperatively. To ensure correct electrode placement postoperative CT scans are performed. Moreover, the anatomical location of the individual DBS electrode contacts can be obtained by fusion of the postoperative stereotactic CT and the individual preoperative stereotactic MRI scans.

Usually postoperative recording sessions take place one day after electrode implantation. To determine if the STN is involved in processing of stimuli, in a preferably

physiological state, patients should be examined after intake of their respective anti-parkinsonian medication.

During the second surgical stage, after the recordings for study purposes, the stimulation leads are connected to an impulse generator implanted subcutaneously during another surgical intervention. This impulse generator is individually programmable. By means of electrical HFS a potentially reversible modulation of the neuronal activity of the target area is achieved. The exact mechanism by which DBS exerts its function remains speculative and is subject of controversial discussion. Furthermore, the effect differs according to stimulation area and settings. Therapeutic HFS (≥100 Hz) with established pulse widths (60-210 μs) probably inhibits neuronal somata, whereas afferent and efferent connections can be activated. Proximal and distal nuclei of the stimulation region can also be influenced by stimulation. Therefore it can be assumed that besides local inhibitory effects DBS also influences the neuronal activity of the complete cortical-basal ganglia loops (Hammond et al., 2008). Besides the inhibition of disease-specific overactive regions, an induction of physiological oscillatory patterns within anomalously working cortico-basal ganglia networks is discussed (Foffani et al., 2003).

3.4.2 Postoperative Recordings and Therapeutic Stimulation Electrodes

The location and properties of the DBS electrode allow for LFP recordings directly from the implantation region. The electrode model 3389 (Medtronic Corporation, Minneapolis, MN, USA) consists of four low-ohm, platinum-iridium cylindrical contacts bundled within polyurethane insulation. The individual wires have a width of 1.5 mm and are labeled 0 to 3 beginning from the tip and are spaced 0.5 mm apart (Figure 6). The electrode delivers stimulation using either one electrode or a combination of electrodes with the same applying to the recordings.

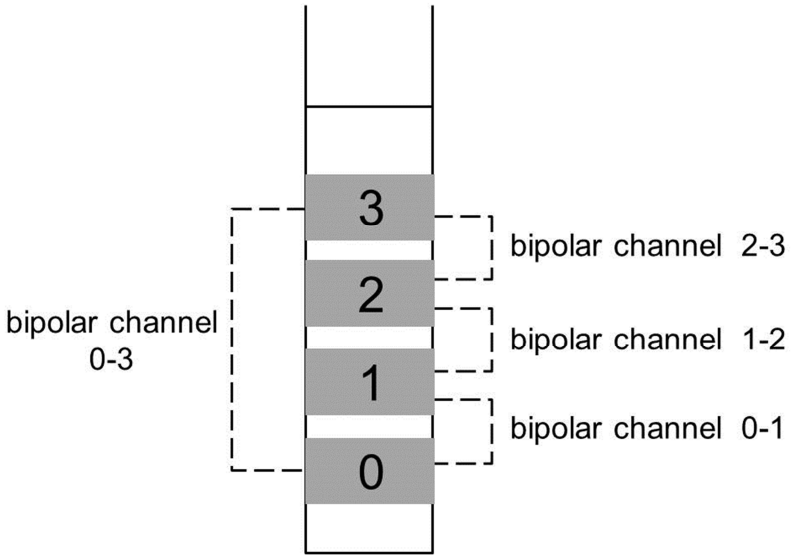

Figure 6: *Schematic Illustration of the electrode model 3389 and examples of possible bipolar contact references.*

According to basic neurophysiological principles, a cathodal (negative) stimulus applied outside a neuron may depolarize the cell and induce an action potential. Each of the contacts of the DBS lead can be programmed as a cathode and thus be considered as the "active" stimulation site. The active contact can be used in a monopolar configuration with the pulse generator referenced as the anode. Alternatively, each contact can be activated as anode or cathode in a bipolar configuration. Based on clinical stimulation and elicited side-effects, monopolar or bipolar stimulation can be applied to attain optimal therapeutic improvement. Monopolar stimulation renders a somewhat radial current diffusion, covering a spherical space around the stimulating electrode activating a relatively high volume of tissue during stimulation. In contrast, bipolar stimulation creates a narrower and more focused current field with a maximal effect near the cathode (Volkmann et al., 2002; Isaias and Tagliati, 2008).

3.5 Non-motor Aspects of STN DBS and Insights from STN Recordings

As STN DBS has become a widely applied surgical procedure motor effects and side effects have been studied extensively. Furthermore, the studies on its surgical, target and stimulation related non-motor side effects have increased over the last few years (for a review see (Temel et al., 2005; Voon et al., 2006; Volkmann et al., 2010; Péron et

al., 2013). These behavioral side effects are the *in vivo* evidence of STN's associative, limbic and somatosensory properties.

3.5.1 STN and Associative Processing

The STN forms part of the associative basal ganglia-thalamocortical circuit and functions as an input area through which the cerebral cortex controls multiple cognitive aspects (Temel et al., 2005; Benarroch, 2008). Its ventromedial part corresponds to the associative sub-region, which has connections with the DLPFC and LOFC, highly relevant structures in cognition (Alexander et al., 1990; Benarroch, 2008). Increased attention towards STN non-motor functions arose from the observed cognitive side effects following STN HFS. Approximately 40% of all patients with chronic bilateral STN DBS exhibit cognitive side effects (Temel et al., 2006). A decline in verbal fluency (VF) is the most consistent cognitive finding after STN stimulation (Temel et al., 2005; Witt et al., 2008; Weaver et al., 2009). Additional cognitive effects include premature responses and changes of response inhibition, working memory and executive function (Jahanshahi et al., 2000; Hershey et al., 2004; Temel et al., 2005; Witt et al., 2008). Other cognitive functions, such as verbal memory, digit span and delayed recall seem to be unaffected (Witt et al., 2008). Furthermore, STN DBS compared to GPi DBS leads to significantly more cognitive side effects including VF and abstract reasoning, despite improved motor efficacy (Rodriguez-Oroz et al., 2005). However, enhancement of overall cognitive function, including mental flexibility has also been observed (Jahanshahi et al., 2000). Moreover, studies on the long-term effects of STN DBS demonstrate only mild global cognitive deficits or unchanged global cognitive functioning (Contarino et al., 2007; Fasano et al., 2010).

3.5.1.1 STN DBS and Verbal Fluency

VF tests are cognitive test in which participants are instructed to say as many words as possible from a given category in a given time (usually 60 seconds). The category can either be semantic, such as animals or fruits, or phonemic, such as words that begin with letter p. (Lezak et al., 1995). VF demands a complex performance, including working memory and word retrieval, executive aspects as a retrieval strategy, selection from competing lexical alternatives, subcategory shifting and vocabulary access. In healthy subjects, VF tasks induce activation of a left sided fronto-temporal network, including

middle frontal gyrus and ACC (Schlösser et al., 1998). However, STN HFS impairs VF-associated activation in this left-sided frontotemporal network (Schroeder et al., 2003). Moreover, VF decline correlates with reduction in perfusion (Cilia et al., 2007) and metabolism (Kalbe et al., 2009) in left DLPF, inferior-frontal areas, ACC areas and right LOFC.

In contrast to HFS, low-frequency stimulation (LFS) of the STN with 10 Hz worsens motor symptoms in PD, possibly mediated by enhancement of a 10 Hz pathologic oscillatory cerebral network (Timmermann et al., 2003, 2004). However, on the other hand, LFS at 10 Hz leads to improved VF performance, possibly by activation of oscillatory connections with frontal areas (Wojtecki et al., 2006). 10 Hz oscillatory activity may represent various cognitive operations in cortico-thalamic-circuits, such as theta-oscillations reflect working memory and alpha-oscillations reflect transient reactivation of long-term memory codes during short-term storage (Klimesch et al., 2005; Sauseng, Klimesch, Schabus, et al., 2005). STN LFP recordings have suggested local involvement of theta, alpha and beta modulations during cognitive tasks (Rektor et al., 2009, 2010; Fumagalli et al., 2010). Although VF is the most often affected cognitive function during STN HFS so far it has not been investigated extensively by recordings of LFP. To this date there is only one study revealing local STN gamma activity modulation during VF (Anzak et al., 2011).

3.5.2 STN and Limbic Processing

In animals, electrophysiological studies have shown that STN neuronal activity is modified in relation to emotional information, such as reward prediction and obtainment (Darbaky et al., 2005; Teagarden and Rebec, 2007; Lardeux et al., 2009). Human electrophysiological studies have revealed modification of STN activity in relation to behaviorally relevant and emotional stimuli (Williams et al., 2003; Sauleau et al., 2009) with larger ERD for emotional compared to neutral stimuli (Kühn, Hariz, et al., 2005). Furthermore, it has been revealed that the STN is implicated in valence-related emotional processing (Brücke et al., 2007; Buot et al., 2012).

3.5.2.1 Neuropsychiatric Changes following STN DBS

A wide spectrum of abnormal behaviors has been reported after STN DBS ranging from depression to mania (Bejjani et al., 1999; Krack et al., 2001; Romito et al., 2002; Herzog et al., 2003; Mallet et al., 2007; Okun et al., 2009). In up to 15% of patients postoperative euphoria and/or hypomania have been reported and in 0.9–1.7% of patients manic episodes occur (Volkmann et al., 2010). Hypomanic or manic states usually develop with the initiation of STN DBS and typically vanish in the first 6 months postoperatively. The close association between the initiation of the STN DBS and hypomanic/manic behaviors favors the idea that mood changes can be triggered by the stimulation of the limbic part of the STN itself. It is assumed that dopaminergic and electrical stimulation of limbic circuits early in the postoperative adjustment period synergistically underlie the development of impulsivity and mania. Further studies examining mood symptoms have reported that depression develops in 20–25% of patients with PD following STN DBS. Rapid or excessive withdrawal of dopaminergic medication and a previous history of depression have been identified as risk factors for the development of postoperative depression. Therefore, depression might reflect a state of dopamine depletion (Volkmann et al., 2010). Moreover, Okun et al. reported that PD patients included in their study rated themselves as sadder, less happy, more confused and less energetic after STN DBS of the most ventral electrode contacts (Okun et al., 2009). Although the exact mechanisms by which STN DBS causes these affective side effects is not fully understood, it was shown that STN HFS inhibits midbrain 5-hydroxytryptamine (5-HT) neurons to elicit depression-related behavioral changes (Temel et al., 2007). STN DBS selectively inhibited the 5-HT neuron firing rate in the dorsal raphe nucleus of the rat, but not of the neighboring non-5-HT neurons. This effect could be induced with clinically relevant stimulation parameters, and was not evoked by DBS of neighboring or remote structures to the STN. Additionally, the depressive behavior could be reversed by a selective 5-HT-enhancing antidepressant, linking the behavioral change to decreased 5-HT neuronal activity.

Affective STN functions can also be observed regarding the effects elicited during STN DBS compared to GPi DBS. One study randomly assigning patients either STN or GPi DBS failed to detect significant changes with regard to primary motor function at 24 months (Follett et al., 2010). There were also no significant changes in quality of-life measures of

cognition or emotional well-being. However, patients with STN DBS revealed a slight but significant depression increase compared to a small decrease of depression in those patients with GPi DBS.

Interestingly, these neuropsychiatric side effects of STN DBS have not only been reported in PD but also in patients with obsessive–compulsive disorder successfully treated with STN HFS (Mallet L, Polosan M, Jaafari N, 2008). Similar behavioral modifications have also been observed following STN lesions or inactivation in healthy rats and monkeys (Baunez C, 1997; Karachi et al., 2009; Aleksandrova et al., 2013). Therefore, these side effects seem to result from STN DBS induced alterations of STN functioning, irrespective of the underlying pathology.

3.5.3 STN and Somatosensory Processing

It is an acknowledged fact that sensory information is conveyed to motor structures and exerts an essential role in the control of movements. A hypothesis proposes that the BG serve as a sensory analyzer for the motor system, processing sensory information in a way relevant for movement (Pesenti et al., 2003). A role of the STN in somatosensory processing has been suggested, since the response to peripheral somatosensory stimulation and passive movements can be recorded within this BG structure (Hammond et al., 1978; DeLong et al., 1985; Wichmann et al., 1994; Klostermann, 2003; Pesenti et al., 2003). Due to its subdivision into different territories with different connections human and primate studies have located the sensorimotor region in the dorsolateral two thirds of the STN (Wichmann et al., 1994; Rodriguez-Oroz et al., 2001). Furthermore, besides receiving topographical projections from primary motor and premotor areas to control movement, the basal ganglia-thalamocortical motor circuit also receives projections from the primary somatosensory cortex and somatosensory association cortex. As part of this network the STN receives input from these areas and functions as a main regulator for the output of this circuit (Temel et al., 2005).

3.5.3.1 PD and Somatosensory Processing

In PD subjective sensory symptoms including numbness, coldness, burning or painful limb sensations have been reported (Koller, 1984). Furthermore, various somatosensory deficits have been described during objective clinical testing. These include inadequate

kinaesthesis, tracking and targeting movements on the basis of sensory feedback, proprioception, deficits in two-point discrimination tasks, tactile localization, grating orientation and roughness (Schneider et al., 1986; Klockgether et al., 1995; Jobst et al., 1997; Sathian et al., 1997; Kaji et al., 2005). Moreover, imaging studies have revealed that sensory-evoked brain activation in PD is reduced in parietal and frontal cortical and BG areas (Boecker et al., 1999) and impaired somatosensory processing seems to be closely related to prefrontal dysfunction (Weder et al., 2000). The somatosensory dysfunction in PD is thought to be due, at least to some extent, to processing deficits at BG level, leading to a disturbed interaction within BG and the cortical sensory systems (Schwarz et al., 1992). Levodopa or apomorphine intake can restore these somatosensory abnormalities (Rossini et al., 1993; De Mari et al., 1995; Traversa et al., 1995). Furthermore, an amelioration of somatosensory deficits has also been reported after STN DBS (Maschke et al., 2005; Shivitz et al., 2006; Herzog et al., 2008). Therefore, STN DBS might modulate the processing of afferent information within somatosensory pathways and partially restore BG function.

4 Hypotheses and Aims

The aim of this thesis was to investigate the modulation of STN oscillatory activity in parkinsonian patients by means of electrophysiological LFP recordings during a cognitive and a somatosensory task. We furthermore investigated the involvement of the STN in affective behavior during DBS.

Study 1 examined the modulation of VF associated low frequency oscillatory activity in the STN. Although VF is the most often deteriorated cognitive function during STN HFS in PD so far it has not been extensively investigated by means of LFP recordings. To this end, PD patients completed a verbal generation task postoperatively, while STN oscillatory activity was measured using LFPs. It was hypothesized that VF modulates low-frequency oscillations in the STN. In response to the executive task low-frequency oscillatory activity was assumed to increase in the STN. An increase in low-frequency oscillatory activity and coherence to surface EEG would be in line with the beneficial effects on VF observed during STN LFS and provide evidence for the involvement of the STN in an executive mediating network.

Study 2 described the involvement of the STN in the limbic network by means of stimulation-induced emotional side effects. Abnormal behaviors ranging from mania to depression have been observed during STN DBS. This study reports on a parkinsonian patient with affective lability under STN DBS during a follow up of over 4.5 years. We hypothesized that the microlesion effect in addition to DBS lead to unintermediate postoperative laughing behavior, consistent with observations of mania following STN lesions during a short postoperative period. We further hypothesized that observable negative emotions during the follow up of various months could be triggered by voltage changes and possible stimulation of neighboring fiber tracts. Affective lability may thus occur with different temporal dynamics regarding the microlesion effect and early and chronic stimulation.

Study 3 investigated potential modulation of STN oscillatory activity following somatosensory stimulation. PD patients received electrical, non-painful stimulation of the median nerve. Simultaneously, subthalamic activity was recorded postoperatively by means of LFPs. In accordance with a distinct cortical oscillatory activity pattern

following median nerve stimulation, oscillations in the STN were expected to follow this same pattern. Namely, an increase in the gamma band immediately following stimulation, a decrease followed by an increase in the beta band and a prolonged increase of activity in the alpha band was assumed. Furthermore, median nerve stimulation was expected to lead to an increase of oscillations in the high frequency range. An involvement of the STN in somatosensory processing would be corroborated by modulation of oscillatory activity following electrical nerve stimulation.

Overall, this thesis aimed at extending the knowledge about the function of the STN in cognitive, emotional and somatosensory processing. Studies 1 and 3 sought to describe the dynamics of oscillatory activity recorded from this nucleus during an executive and a somatosensory task. Modulations of oscillations were expected due to the experimental paradigm and recording location. Study 2 described changes in affective behavior during stimulation of the STN. The main purpose was to broaden the understanding regarding the role of oscillatory activity in the STN, expand the knowledge of PD and identify the reasons for the (beneficial) side effects reported after STN DBS.

5 Study 1: The rhythm of the executive gate of speech: subthalamic low-frequency oscillations increase during verbal generation.

The following chapter is based on a revised form of Wojtecki and Elben 2017, please refer to Appendix 1.

5. 1 Introduction

Direct LFP recordings from the STN enable the investigation of the involvement of this nucleus in a specific task. Up to date STN LFP recordings suggest theta, alpha and beta modulations during cognitive tasks (Rektor et al., 2009, 2010; Fumagalli et al., 2010). Although VF decline is the most frequent cognitive side effect during STN HFS it has not extensively been studied by use of LFP recordings so far. There is one study reporting a local STN modulation of gamma activity during VF (Anzak et al., 2011). Moreover, STN LFS with about 10 Hz improves VF performance compared to HFS, presumably due to an activation of neuronal oscillatory connections with frontal areas (Wojtecki et al., 2006). Therefore, the aim of this study was to elaborately investigate if there is evidence for the involvement of the STN in a VF-network. We sought to find if there is increased low-frequency (theta and alpha) oscillatory LFP activity and coherence to surface EEG, and thus to find a possible explanation for the beneficial effects of STN LFS on VF.

5.2 Methods

16 PD patients with no signs of cognitive impairment or depression underwent bilateral STN implantation of DBS electrodes and were enrolled in the study. During surgery the final macroelectrodes were connected to extension wires, which could be connected postoperatively to EEG amplifiers through external cable connectors. All patients were examined under the influence of their usual anti-parkinsonian medication, as we sought to identify if the STN is involved in cognitive processing in a preferably physiological state. The anatomical location of the four DBS electrode contacts was obtained by fusion of the postoperative stereotactic CT onto the individual preoperative stereotactic planning software.

5.2.1 Paradigm

During the recordings the patients were seated about 1 meter from a personal computer screen displaying the task stimuli. The experiment comprised two tasks. The first task was a verbal generation task, including all aspects of a phonemic VF task and consisted of the presentation of the 10 most frequent initial letters of the German language, each presented 8 times successively, rendering a total of 80 trials. Subjects were instructed to think of a word beginning with that letter without speaking aloud. After a test period of 3 s, rendering speech preparation and movement artifact free segments, subjects were presented with a "go" cue indicating to speak the thought of word out loud. The control task consisted of a word retrieval task lacking the executive component of a VF task. Only the letter "P" was presented and subjects were instructed to only verbalize the word "pause" during the total of 80 trials (please also refer to Figure 1, Appendix 1).

5.2.2 Recordings

Since the operation was performed bilaterally in all patients, recordings were carried out from 32 subthalamic nuclei. LFP activity was recorded during task performance from the four contacts of the DBS-electrode against a surface midline frontopolar reference with a portable amplifier (BrainVision Recorder, BrainAmp MR plus, Brain Products GmbH, Munich, Germany, Version: 1.03). In five patients surface electrodes were placed at scalp sites to record a simultaneous scalp EEG. The LFPs were rereferenced against each other, leading to a narrow bipolar filed. The acquired neurophysiological data were then analyzed by means of time-frequency analysis with respect to the time course and strength of oscillations around 10 Hz and compared between the two different conditions.

5.3 Results

5.3.1 Task Induced Activation Changes in the Low-Frequency Band

For the verbal generation task activity increase on the STN electrodes could be detected during the task period mainly between 6-12 Hz. For the control task power decrease in the 6-12 Hz band during the task period could be observed on the same bipolar electrode contacts over the group. The activity in the 6-12 Hz band was significantly

stronger for the verbal generation task compared to the control task for the same left and right bipolar derivations during the task period (please also refer to Figure 2, Appendix 1).

5.3.2 Coherence

Coherence analysis revealed coupling of LFP activity and (inferior)-frontotemporal EEG electrodes. Significant coherence between LFPs and surface electrodes in the 6-12 Hz frequency band in STN recordings during the verbal generation condition and in recordings during the control condition could be identified. Maximum coherence to STN-LFPs was found on a (inferior)-frontotemporal location. Comparison between the largest peaks in the 6-12 Hz band of the two tasks revealed a significant difference of LFP-EEG coherence during the verbal generation task for both the left and right hemispheres (please also see Figure 4, Appendix 1). No local significant task related increase of low frequency activity could be detected on the most coherent surface EEG channels compared to the control task although modulation of activity was seen at the same mean peak frequency around 8 Hz (please also see Table 3, Appendix 1).

5.3.3 Recording Location

The mean recording coordinates concurred well with a location within the STN, depicting a recording location involving non-motor ventromedial parts of the nucleus (please also refer to Figure 5, Appendix 1).

5.4 Discussion

The results show a dynamic modulation of STN LFP low-frequency activity in response to the performance of a verbal generation task as opposed to a control task, rendering electrophysiological proof for the involvement of the STN in the processing of executive functions such as VF. The present study further supports the hypothesis of STN processing of executive functions by specific modulation of low-frequency oscillations. Cognitive sequelea during STN HFS may be accounted for by a direct modulation or interruption of this process through HFS. Improvement in VF observed during LFS (Wojtecki et al., 2006) may conclusively be justified by STN power increase in this particular frequency.

5.4.1 Frequency Range of Oscillatory Modulations

Since previous work had revealed improvement of VF during 10-Hz-STN LFS the present analysis focused on the 5-15 Hz range (Wojtecki et al., 2006). Oscillations in this frequency range have been involved in executive tasks (Rektor et al., 2009, 2010; Fumagalli et al., 2010). The main finding of the present study was a task dependent significant local activity increase between 6-12 Hz and coherence increase to surface EEG between 6-7 Hz. Alpha oscillations are involved in long term memory and transient reactivation of long term memory codes during short term storage and theta oscillations have been associated with executive functions such as working memory (Klimesch et al., 2005; Sauseng, Klimesch, Schabus, et al., 2005). Furthermore, theta oscillations can particularly be observed at frontal locations when subjects maintain focused attention during performance of an enduring task (Klimesch et al., 2005). These components are crucial to a verbal generation task and thus explain why theta-alpha activation was consistently found in our recording. Moreover, coherence to frontal surface recordings in the theta range was detected, supporting the notion of a functional role of theta oscillations for long range synchronization. Local LFP power increase was more prominent in the alpha range. Recent models of alpha oscillations propose that alpha rhythmicity is enhanced during internal tasks, such as working memory, attention and consciousness (Palva and Palva, 2007).

The “systems oscillators theory” proposed for the role of the BG in speech and language corresponds well with the notion of communication between the STN and cortical areas through theta oscillations: articulation and phoneme are represented by a higher frequency than words and sentences which are organized as packets over a slower frequency. The number of connection nodes in the basal ganglia-thalamocortical loop, represented by anatomical structures determines the frequency of oscillations. In this model the STN is part of a side loop with a specific go/no-go gaiting function of the indirect and hyperdirect pathways (Montgomery, 2008). STN microelectrode recordings have rendered evidence for this model, revealing modulation of bursting activity during the generation of meaningful speech utterances compared to meaningless syllable repetitions (Watson and Montgomery Jr., 2006).

5.4.2 Clinical Relevance of STN-Stimulation for Executive Functions

As a significant correlation of verbal generation performance with low-frequency oscillation increase in the STN was revealed, improvement in VF during LFS might be accounted for by enhancement of this predominant frequency. However, LFS can lead to deterioration of motor functions (Timmermann et al., 2004). Both findings are relevant for future stimulation patterns aiming at improvement of cognitive-motor outcome. Congruent with the present recordings modeling volume of activated tissue revealed that stimulation through ventral contacts results in greater tissue activation associated with decline of VF performance (Mikos et al., 2011). This should especially be considered for the programming of the lower electrode contacts as adjustment of stimulation parameters can already lead to improved cognitive-motor outcome (Frankemolle et al., 2010). Considering the information regarding frequency domains in executive functions derived by the present study it can be anticipated that advanced frequency programming (e.g. with special local low frequency interleaving modes on lower electrodes) might further help to improve clinical outcome.

5.4.3 Origin of Recorded Activity and the STN Associative Network

The ventromedial associative STN and its connections to cognitive circuits receive input from the DLPFC and LOFC (Temel et al., 2005). This associative circuit also involves cortical areas of the VF mediating network, including inferior frontal gyrus, ACC and superior temporal regions (Alexander and Crutcher, 1990; Benarroch, 2008). The observation, that particularly recordings of medial rather than dorsolateral parts of the STN, revealed oscillatory modulation during this executive task corresponds to neuroanatomic evidence positing that especially the ventromedial STN has connections with frontal associative areas. Interestingly, coherence analysis revealed significant coupling between the STN LFPs and the (inferior-) frontotemporal surface electrodes. This finding further supports the hypothesis of a functional relevant connection between the ventromedial STN and the frontal cortex.

6 Study 2: Long-term Time Course of Affective Lability after Subthalamic Deep Brain Stimulation Electrode Implantation

The following chapter is based on a revised form of Wojtecki 2011, please refer to Appendix 2.

6.1 Introduction

Substantial evidence for the involvement of the STN in the regulation of emotions has been obtained from reports on emotional side effects following DBS of the STN in PD, with reports ranging from depression to mania (Bejjani et al., 1999; Krack et al., 2001; Herzog et al., 2003; Okun et al., 2009). Dopaminergic and electrical stimulation of STN involving limbic circuits may lead to impulsivity and mania, whereas depression might be expressed by hypodopaminergic states (Volkmann et al., 2010). Therefore, the emotional side effects observed after STN stimulation may be influenced by medication (Funkiewiez et al., 2006) as well as stimulation parameters (Krack et al., 2001; Herzog et al., 2003) and electrode localization (Bejjani et al., 1999).

We report on a patient revealing laughing and crying behaviour a few days after STN–DBS surgery. Furthermore, we outline the change of these affective side effects over the course of 4.5 years, illustrating the temporal dynamics of microlesion effect and stimulation on emotions.

6.2 Case Report

A 69-year-old male patient with no history of cognitive impairment or psychiatric disease was selected for STN DBS of medically refractory PD. Two days following surgery the patient presented mirthful laughter when stimulated on medication on the lower contacts 0 and 1. Besides contagiously laughing at trivial things and telling jokes, mania score was increased while good suppression of tremor was obtained. After cessation of stimulation the tremor recurred after a few seconds and the patient fell into depressed mood and started crying (please also see supplementary online video, Appendix 2). One week later stimulation effects were tested extensively in the medication-OFF state at each contact up to 5 V. Only stimulation of the left electrode on the lower contacts 0 and 1 above 2.5 V lead to a slight euphoric feeling. Laughter or

strong euphoric emotions as seen during the first session could not be induced. High amplitude stimulation of the upper right electrode led to limb and face contractions as signs of stimulation of the internal capsule. The patient was discharged 10 days later with a good effect on motor symptoms and no emotional side effects. Since the emotional changes frightened the patient, lorazepame was prescribed transiently postoperatively for 2 weeks. Repeated assessment of depression and mania scores within the first 3 months revealed unobtrusive results. Over the course of 53 months the patient was followed-up several times. Stimulation of the left hemisphere was kept constant on contact 1, right-sided monopolar stimulation was changed from contact 1 to 2 and 3 in order to obtain best effects on tremor and other motor symptoms. Several programming sessions, testing all contacts with stimulation amplitudes up to 5 V failed to reinduce laughing. However, negative emotions and crying could be induced once more 9 and 37 months after surgery by swift amplitude increase up to 5.5 V or abrupt switching off and on of the right electrode stimulating upper contacts 2 and 3 (for detailed examination time points, affective behavior and stimulation parameters please refer to Table 1, Appendix 2).

6.2.1 Electrode Localization

Postoperative electrode localization revealed that left-sided active contacts were clearly positioned in the STN. Right-sided contacts activated in the beginning were located in the STN, whereas later activated contacts were located at the dorsal-anterior border and adjacent fibre tracts involving the internal capsule. The ventral plastic electrode tip of both sides was located medial-ventrally of the STN in the border zone to the substantia nigra (SN) (please also see Figure 1, Appendix 2). Electrode dislocation or structural brain alterations could not be detected on repeated cranial CT scans in the course of days to months after surgery.

6.3 Discussion

Taken together our findings revealed: (I) strong stimulation effects on emotions only found transiently after surgery; (II) induction of negative emotions up to 37 months after implantation by voltage changes of the electrode contacts located in the right STN and adjacent fibre tracts involving the internal capsule. These findings further complement knowledge on STN stimulation induced emotional side effects with

interesting aspects concerning the long-term time course of the microlesion and stimulation effect.

6.3.1 Time Course and the Role of Microlesion Effect

STN lesions may play a pivotal role for symptoms such as mania (Romito et al., 2002), generally attributed to STN input from the ACC. While lesions may have a prolonged effect on cognition, mood only seems to be affected transiently (Okun et al., 2009). Additionally, mania or hypomania can almost exclusively be observed during the first postoperative weeks (Volkmann et al., 2010). Up to date long-term follow-up of substantial affective side effects are not well described. The observation that an initially increased suicide risk seems to decrease over the course of 4 years (Voon et al., 2008) might be a correlate of diminishing emotional side effects. A decrease of affective instability is in line with our findings and may be explained in part by a regressing lesion effect.

6.3.2 DBS Effects

Compared to the lesion effect, habituation of stimulation side effects may vary from minutes to months (Kulisevsky et al., 2002; Springer et al., 2006; Tommasi et al., 2008). Thus, besides a regressing lesion effect, adaptive brain changes during stimulation have to be taken into account for the interpretation of long-term emotional side effects. In addition to the microlesion effect a strong bilateral stimulation of lower contacts was required to induce laughter in the patient. High amplitude, pulse width or bilateral stimulation can lead to affective changes either by influencing the STN itself (Wojtecki et al., 2007), the SN (Bejjani et al., 1999; Kulisevsky et al., 2002), or possibly by affection of structures nearby the STN such as the median forebrain bundle or the lateral hypothalamus (Krack et al., 2001; Coenen et al., 2009). When affecting the internal capsule, DBS can worsen mood or anxiety and cause panic and fear (Okun, 2004; Springer et al., 2006; Low et al., 2008). Long-term induction of negative emotions in the present case can possibly be attributed to stimulation of the internal capsule since sadness and crying were only evoked by stimulation of the upper right electrode. These contacts were positioned in the STN and adjacent fibre tracts involving the internal capsule. Moreover, high amplitude stimulation of these electrodes led to limb contraction as signs of capsular stimulation. Due to an overlay of the strong lesion effect,

leading to laughter, no negative emotions could be induced by right-sided stimulation at an early time point. Furthermore, transient medication with lorazepame might account for an additional neutralizing effect on negative emotions in the first weeks after surgery. This medication had been stopped at the later time point, when first negative emotions could be induced by right-sided stimulation.

Summarizing, the present report provides insights into the time course of affective lability after DBS surgery depending on microlesion effect and stimulation voltage.

7 Study 3: Human Subthalamic Oscillatory Dynamics Following Somatosensory Stimulation

The following chapter is based on a revised form of Elben 2018, please refer to Appendix 3.

7.1 Introduction

Neural oscillations in the somatosensory and motor system have extensively been investigated in the last years, revealing that specific changes in oscillatory frequency can be elicited during movements (Pfurtscheller and Aranibar, 1977; Salenius et al., 1997, (Cassim et al., 2001; Alegre et al., 2002), as well as due to somatosensory stimulation (Hari and Forss, 1999). Besides the well-known evoked response following somatosensory median nerve stimulation an induced response in the form of beta ERS in the pre-central motor cortex can be recorded. Within 1 s after stimulation this ERS can be recorded in the contralateral hand sensorimotor cortex, following a preceding short lasting ERD immediately after stimulation (Salmelin and Hari, 1994; Salenius et al., 1997). EEG and MEG studies revealed that somatosensory stimulation of the upper extremity increase beta-oscillations (Cassim et al., 2001; Neuper and Pfurtscheller, 2001; Houdayer et al., 2006) as well as decrease alpha and beta activity in the contralateral rolandic area (Pfurtscheller, 1989; Palva et al., 2005; Dockstader et al., 2008). Furthermore, median nerve somatosensory stimulation augment 100-250 Hz oscillations in the SI region within 20 ms following stimulation (Fukuda et al., 2008). Within 25 ms after stimulation these oscillations gradually slow-down in frequency to 30-100 Hz in the contralateral rolandic area and further evolve into beta and alpha augmentation (Fukuda et al., 2010, (Dockstader et al., 2010). Additionally, EEG recordings revealed oscillatory activity ranging from 30-100 Hz (Chen and Herrmann, 2001), 100-250 Hz (Buchner et al., 1995) and above (Curio et al., 1994; Hanajima et al., 2004) following median nerve stimulation.

Besides being able to record somatosensory related activity cortically, the response to passive movements and peripheral somatosensory stimulation can be recorded within the STN, suggesting a role in somatosensory processing (Hammond et al., 1978; DeLong et al., 1985; Wichmann et al., 1994; Klostermann, 2003; Pesenti et al., 2003). Owing to its

subdivision into different territories with different connections to cortical areas human and primate studies have located the sensorimotor region in the dorsolateral two thirds of the STN (Wichmann et al., 1994; Rodriguez-Oroz et al., 2001).

The current study aimed to characterize the somatosensory induced modulation of rhythmic oscillatory activity of the STN by means of postoperative LFP recordings in PD patients.

7.2 Materials and Methods

11 PD patients with postoperative externalized bilateral deep brain electrodes in the STN were enrolled in the study. LFPs were recorded thorough DBS macroelectrodes during repetitive non-painful electrical stimulation of the median nerve using the Osiris constant-current peripheral nerve stimulator (Osiris Brain Stimulator, Inomed Corp., Emmendingen Germany). Alternating cutaneous contralateral and ipsilateral median nerves stimulation with an interstimulus interval of 3000 ms was applied to both wrists with constant-current square wave pulses of 200 μs and a current intensity adjusted individually above the motor threshold. 200 sweeps per side were recorded, during which a persistent, passive twitching of the thenar muscle was documented. All patients were examined after intake of their respective anti-parkinsonian medication since we wished to determine whether the STN is involved in somatosensory processing in an as normal state as possible.

The recorded neurophysiological data was analysed offline using the BrainVision Analyser software (Brain Products GmbH, Munich, Germany, Version: 2.0) and the electrode contacts were rereferenced against the adjacent one, narrowing down the recording space. Bipolar baseline corrected trials were transformed into the time-frequency domain over the pre- and post-stimulus interval for induced activity for frequencies between 1-500 Hz and latencies between -100 and +1000 ms relative to median nerve stimulation and averaged separately for the ipsi- and contralateral stimulated wrist across all trials. Mean change in power relative to the mean power in the baseline period was analysed. To detect the possible presence of oscillatory activities in the basal condition we additionally performed the same time-frequency analysis for induced activity without the baseline correction. Inspection of the averaged time-frequency bins determined the on- and offset of somatosensory induced

oscillations and the mean activity during change in oscillatory activity in the alpha, beta, gamma and high frequency (>100 Hz) range. Furthermore, to ascertain the recording site the Schaltenbrand-Wahren-Atlas coordinates of the four contacts of the implanted DBS electrode were determined by fusion of the postoperative stereotactic CT onto the individual preoperative stereotactic planning software. The contacts used for further analysis were normalized and visualized on the stereotactic Schaltenbrand Atlas (Nowinski and Thirunavuukarasuu, 2004).

7.3 Results

In all 11 patients recorded, stimulus-related averaged signals distinctively revealed specific patterns of oscillatory activity including alpha, beta, gamma and high frequency bands. This oscillatory pattern could usually only be detected on one of the three bipolar derivations (please refer to Figure 1 of Appendix 3).

7.3.1 Somatosensory Induced Changes in Rhythmic Oscillatory Activity

For the alpha range, significantly differing from baseline activity (I) a contralateral increase in power was detected and; (II) followed by an ERD. Moreover, (III) a minimally delayed ipsilateral power increase was followed by an ERD significantly differing from baseline activity. For the beta range, significantly differing from baseline activity (I) initial contralateral power suppression was detected, followed by (II) a late contralateral power increase. Furthermore, (III) a slight delayed ipsilateral power ERD followed by (IV) an ERS was revealed. In the gamma range, significantly differing from baseline activity (I) an early contralateral broad-frequency power increase was detected and with an additional (II) slightly delayed ipsilateral power increase. In the high-frequency range, significantly differing from baseline activity (I) a prominent contralateral power increase in the 160 Hz range and (II) a slightly delayed ipsilateral 160 Hz power increase were revealed.

In addition, analysis without baseline correction also identified this same distinct pattern after median nerve stimulation, but enabled the detection of the presence of 160 Hz activity in the basal condition (please also see Figure 2, Appendix 3).

7.3.2 Recording Location

The majority of bipolar contact pairs displaying prominent somatosensory frequency modulation and therefore used for further analysis recorded a field involving dorsolateral sensorimotor subregions of the nucleus (please refer to Figure 3, Appendix 3). Comparison of bipolar contact pairs depicting somatosensory induced modulations with contacts used for therapeutic stimulation at 3 months after surgery revealed that almost 70% of contacts used for therapeutic stimulation corresponded with the contacts displaying the 160 Hz oscillations.

7.4 Discussion

Modification of neural activity in response to somatosensory stimulation in the STN revealed that (I) the STN is involved in somatosensory processing, (II) the dynamics of STN oscillatory activity resemble the cortical responses regrading frequency, amplitude and phase and (III) median nerve stimulation induces 160 Hz high-frequency augmentation.

7.4.1 Subthalamic Oscillatory Dynamics of Alpha, Beta and Gamma Ranges following Somatosensory Stimulation

The present findings of a subthalamic oscillatory pattern resembling the cortically recorded pattern (Fukuda et al., 2008, 2010; Dockstader et al., 2010) further supports the notion of somatosensory processing in the STN. The reported finding, that gamma-range oscillations peaked earlier than the known cortical N20 might suggest that the recorded gamma augmentation represents the initial subcortical processing of external somatosensory stimuli. As posited for perceptual binding, synchronous gamma-oscillations could temporarily coordinate circuits in somatosensory perception (Gray et al., 1989). Somatosensory related alpha- and beta-oscillations reflect a temporally distinct somatosensory processing stage, following the initial subcortical processing. In the somatosensory cortex post-stimulation beta ERS reflects a selective deactivation or active inhibition (Neuper and Pfurtscheller, 2001) and has been linked to alertness enhancement in thalamo-cortical systems (Steriade, 1993). Therefore, increased beta activity would signify an activation of the somatosensory or motor cortex by motor preparation or focused attention. Increased sensorimotor beta power also correlates

with attention towards a motor event (Muthukumaraswamy and Singh, 2008) and improved sensorimotor performance (Vernon et al., 2003; Egner and Gruzelier, 2004), further suggesting a role of beta-oscillations in attention. In the present study alpha synchrony preceded alpha desynchrony. Other studies have concluded that alpha ERS reflects cortical inhibition while alpha ERD represents sensory processing (Sauseng, Klimesch, Stadler, et al., 2005; Thut et al., 2006). These conclusions might also be applicable to the somatosensory induced modulations of alpha oscillations reported in the present study.

7.4.2 High Frequency (~160 Hz) Activity

Following median nerve stimulation the presence of 160 Hz oscillations could be recorded in the human STN. To this date there is only one other report of STN oscillations in this frequency range, where LFP recordings in healthy rats revealed an increase of ~150 Hz oscillations co-occurring with hyperlocomotion after administration of subanesthetic doses of ketamine (Nicolás et al., 2011). Oscillations around 140–160 Hz in the Nucleus accumbens of rats, which increased notably after a subanesthetic dose of ketamine, also accompanying hyperkinetic behavior have also been reported (Hunt et al., 2006). Ketamine is a pharmacological GLU receptor antagonist. However, subanesthetic doses of ketamine actually increase GLU outflow, enhancing GLUergic neurotransmission at these doses (Moghaddam et al., 1997). Furthermore, as revealed by a microdialysis study, electrical median nerve stimulation also activates GLU release (Chen et al., 2008). GLU mediates neurotransmission in prominent brain networks for sensory perception and sensorimotor control and is the excitatory neurotransmitter of thalamocortical inputs to the primary somatosensory cortices (Kharazia and Weinberg, 1994; Castro-Alamancos and Connors, 1997). In addition, the N20 cortical response to median nerve stimulation originates from the GLUergic excitatory postsynaptic potentials (Tecchio et al., 2011). Importantly, the STN is also GLUergic (Parent and Hazrati, 1995a, 1995b). Therefore, somatosensory related modulation of the subthalamic 160 Hz oscillations might be mediated by alterations in GLUergic transmission. As these 160 Hz oscillations were also present in the rest period before median nerve stimulation and stimulation resulted in a significant increase in amplitude a physiological origin of these activities can be assumed, positing a potential relationship between these high-frequency oscillations and somatosensory processing.

7.4.3 Clinical Relevance of 160 Hz Oscillations regarding DBS

Administration of levodopa leads to an increase of STN high-frequency oscillatory activity in the 150-200 Hz and higher frequency range, implying a physiological role of this high-frequency activity (Kane et al., 2009; López-Azcárate et al., 2010; Özkurt et al., 2011) and effective DBS frequencies are usually programmed in the 100-200 Hz range (Moro et al., 2002). The presence of such subthalamic physiological oscillations in the 100-200 Hz range suggest that the beneficial effects of STN DBS in PD patients are attained by disruption and replacement of pathological low-frequency output with high-frequency oscillations as suggested by Liu (Liu et al., 2008). Furthermore, as shown by the present data, the majority of contacts used for chronic therapeutic stimulation at 3 months after implantation coincided with the contacts displaying the 160 Hz oscillations. While the exact DBS mechanisms still remain unclear intracerebral microdialysis studies in the rat have revealed a significant increase in subthalamic extracellular GLU levels following high frequency STN DBS (Lee et al., 2007; Windels et al., 2008). Since STN DBS modulates inputs from the somatosensory cortex to the nucleus and given the fact of mostly reciprocal cerebro-basal ganglia connections, an altered STN output could influence somatosensory cortical processing, possibly facilitating somatosensory processing. Previous findings of improved sensorimotor integration during STN DBS are further corroborated by the present results, with a possibly GLUergic mediated augmentation of subthalamic 160 Hz oscillations after somatosensory stimulation (Maschke et al., 2005; Shivitz et al., 2006; Herzog et al., 2008). As proposed by Sailer, STN DBS may induce a normalization of central sensorimotor integration of peripheral sensory stimuli (Sailer et al., 2007).

7.4.4 Origin of Recorded Oscillations

In addition to receiving projections from primary motor and premotor areas, the basal ganglia-thalamocortical sensorimotor circuit also receives projections from the primary somatosensory cortex and somatosensory association cortex. Owing to its key role in this network the STN, and in particular its dorsolateral territory, receives input from these areas and serves as a main regulator and integrator of this circuits output (Wichmann et al., 1994; Rodriguez-Oroz et al., 2001; Temel et al., 2005). Postoperative imaging revealed a location inside the dorsolateral STN of contacts with strongest

stimulation induced oscillatory modulation. The anatomical identity of the pathways transmitting these responses still remains unclear, but rat studies revealed a direct projection from the primary somatosensory cortex to the dorsolateral STN (Rouzaire-Dubois and Scarnati, 1985; Canteras et al., 1988). The present findings further corroborate a functionally relevant connection between the dorsolateral STN and the somatosensory cortex.

In conclusion, the present study further substantiates the sensory function of the STN. It is the first to identify and describe oscillations in the human STN following median nerve stimulation and the first to reveal oscillations in the 160 Hz range following somatosensory stimulation. While the exact functional role of the STN oscillations remains to be scrutinized, current results suggest that they reflect processing of somatosensory information by cortico-subcortical networks.

8 General Conclusions

The present work investigated the dynamics of oscillatory activity in the STN by performing electrophysiological recordings of LFPs in the context of cognitive and somatosensory processing and PD in order to amplify the understanding of the functional role of specific oscillations in this nucleus and identify potential reasons for the (side-) effects observed during STN DBS. Results confirmed that low-frequency STN DBS might account for improvement of executive functions by enhancement of this physiological predominant low-frequency oscillatory activity in the STN during such an associative task. Additionally, STN activity revealed a specific pattern of oscillatory modulation following median nerve stimulation, similar to the established cortical pattern, corroborating a key role of the STN in somatosensory processing. The finding of physiological 160 Hz oscillations, which increased after somatosensory stimulation, might further explain the improvement of sensorimotor integration during STN HFS in this frequency range. Furthermore, and involvement of the STN in emotional processing war scrutinized and could be confirmed by observed affective behaviors during STN DBS.

8.1 Limitations

As previously stated by Weintraub et al. (Weintraub and Zaghloul, 2013) some general limitations should be discussed regarding the interpretation of the present data and previous studies and the conclusions drawn concerning STN neurophysiologic functions. First of all, all clinical studies involve patients with PD. The known pathologic STN activity in these patient populations limits any interpretation of normal STN functioning. Additionally, group effects need to be separated from effects observed in individual patients, as well as global cognitive or behavioral function must be distinguished from particular processes. Furthermore, there are only few clinical trials including control PD patients, allowing a differentiation between DBS effects and those of disease progression. Changes in medication during stimulation also need to be considered as these may also have effects on cognition or behavior. Moreover, the precise location of the stimulation electrode is not confirmed in many studies, leading to doubts whether the stimulation is in effect being applied to the STN, which STN sub-region is receiving stimulation, and whether the reported effects are not actually results of direct

stimulation or current spread to neighbouring structures. Finally, since the exact DBS mechanisms of action are not entirely understood, an assumption of normal cognitive and affective functions of the STN from clinical stimulation data is quite limited. Nevertheless, given these limitations, the present and previous studies provide exceptional insight into the non-motor functions of the STN.

8.2 Location of Recorded Physiological Activity and Stimulated Area

All patients were examined under the influence of their usual anti-parkinsonian medication. The medication ON state, eliminating or reducing the known pathologic STN activity, was chosen as we sought to understand whether the STN is involved in cognitive, limbic and somatosensory processing in a state as physiological as possible. It needs to be stated that dopaminergic medication may modulate neuronal oscillations. However, as we examined the interval after cognitive execution and somatosensory stimulation and compared this to a different cognitive task a period without somatosensory stimulation we assume that our results are generated by the task itself. In addition, in the somatosensory task results resemble those recorded on a cortical level without influence of dopaminergic medication. Thus, ruling out a sole effect of the medication state on the presented results.

Furthermore, the results from our recoding studies 1 and 3 provide evidence for the involvement of the STN in non-motor functions, since cognitive processing and somatosensory stimulation induced a LFP in this nucleus. Although it is not feasible to entirely rule out the possibility of a far field contamination, the oscillatory activity seems to reflect a local response in the STN. First, the induced activity was not present on all bipolar electrode pairs placed only a few millimetres apart from each other. In the majority of cases the oscillatory pattern could only be detected on one of the bipolar electrode pairs. The contacts used for the recordings are only 0.5 mm apart, making a far field contamination of the signal unlikely. If the recorded activity would have been a far field, two closely spaced contacts should have recorded the same activity. Second, the use of bipolar recordings, analyzing activity as focal as possible, minimizes the influence of far field potentials. The same principle applies to the stimulated area in study 2. The use of bipolar stimulation creates a focused current field with maximal effect near the cathode. This enables a stimulation of a narrow area. Furthermore, precise location of

contact position was determined postoperatively, allowing for identification of recoding and stimulation areas within the STN and its subregions.

8.3 STN Function: Integration and Inhibition

The present thesis has addressed most of the processes in which the STN has been shown to be involved, revealing a wide range of functions that are clearly further developed than the restrictive motor functions adopted until the mid-90s. Complex behavioral sequences form motor actions in humans. These are strongly influenced by the cognitive, emotional and somatosensory context in which they are conducted. However, how these processes interact with each other in the central nervous system still remains partly unknown. As proposed by Mallet et al. (Mallet et al., 2007), a key role in exactly such a function is ascribed to the STN. In this model the STN serves as a nexus for the integration of cognitive, emotional and sensorimotor behavioural components. Supporting this hypothesis they state the observations that (I) despite its small size in the BG circuitry, the STN receives convergent information from larger BG structures (GPe and striatum), which in turn themselves receive associative, limbic and sensorimotor information from the entire cerebral cortex; (II) the associative, limbic and sensorimotor STN regions are not separated by sharp boundaries but by functional gradients; and (III) the STN output to its targets is also not segregated. Since the STN does not present a clear segregation between the individual functional modalities it could merge associative, limbic and sensorimotor information into an output message; thus integrating the cognitive, emotional and sensorimotor behavioral components. This notion of STN functioning could be complemented with the model of STN function proposed by Frank et al., comparing the STN with a curbing brake, impeding premature actions and ensuing impulsive behavior (Frank et al., 2007). The STN inhibitory signal could be favourable for the allocation of time, integrating associative, limbic and sensorimotor information for the selection of optimal evaluated actions.

In conclusion, this thesis further corroborates the assumption that three functional modalities (associative, limbic and sensorimotor) can be allocated in the STN, with this nucleus thus serving as a key node for the integration of cognitive, emotional and sensorimotor components of behavior.

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11 Erklärung

Hiermit erkläre ich, dass ich die vorgelegte Dissertation eigenständig und ohne unerlaubte Hilfe angefertigt habe. Die Dissertation wurde in der vorliegenden oder in ähnlicher Form noch bei keiner anderen Institution eingereicht. Ich habe bisher keine erfolglosen Promotionsversuche unternommen.

Düsseldorf, den 28.05.2018

Saskia Elben

10 Appendix

This work is based on:

Publication 1

Lars Wojtecki*, Saskia Elben*, Jan Vesper, Alfons Schnitzler, 2017. The rhythm of the executive gate of speech: subthalamic low-frequency oscillations increase during verbal generation. European Journal of Neuroscience, May 2017, Volume 45, Issue 9, pp 1200-1211, doi:10.1111/ejn.13429 (version of record online: 31 October 2016).[1]
(Appendix 1)

* Authors contributed equally

Author contributions: Study conception and design 40%, acquisition of data 80%, analysis and interpretation of data 80%, drafting of manuscript 50%, critical revision 10%, institutional support 0%, supervision 0%.

Overall personal contribution: Approximately 50%

Publication 2

Lars Wojtecki, Lars Timmermann, Stefan J Groiss, Saskia Elben, Christiane Reck, Martin Südmeyer, Volker Sturm, Alfons Schnitzler, 2011. Long-term time course of affective lability after subthalamic deep brain stimulation electrode implantation. Neurocase 2011, Volume 17, Issue 6, pp 527-532, doi.org/10.1080/13554794.2010.547507.[2]
(Appendix 2)

Author contributions: Study conception and design 10%, acquisition of data 80%, analysis and interpretation of data 60%, drafting of manuscript 50%, critical revision 10%, institutional support 0%, supervision 0%.

Overall personal contribution: Approximately 40%

Publication 3

Saskia Elben, Carlos Trenado, Jan Vesper, Alfons Schnitzler, Lars Wojtecki. Human subthalamic oscillatory dynamics following somatosensory stimulation, 2017. Clinical Neurophysiology, January 2018, Volume 129, Issue 1, pp 79–88. doi.org/10.1016/j.clinph.2017.10.015 (version of record online: 28 October 2017).[3] (Appendix 3)

Author contributions: Study conception and design 90%, acquisition of data 90%, analysis and interpretation of data 90%, drafting of manuscript 100%, critical revision 10%, institutional support 0%, supervision 0%.

Overall personal contribution: Approximately 90%

[1] Reprinted from European Journal of Neuroscience, May 2017, Volume 45, Issue 9, pages 1200-1211, Wojtecki L, Elben S, Vesper J, Schnitzler A., The rhythm of the executive gate of speech: subthalamic low-frequency oscillations increase during verbal generation. With permission from John Wiley and Sons.

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EJN European Journal of Neuroscience

FENS Federation of European Neuroscience Societies

European Journal of Neuroscience, Vol. 45, pp. 1200–1211, 2017 doi:10.1111/ejn.13429

NEUROSYSTEMS

The rhythm of the executive gate of speech: subthalamic low-frequency oscillations increase during verbal generation

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Keywords: executive function, local field potentials, subthalamic nucleus, verbal fluency

Edited by John Foxe

Received 13 March 2012, revised 6 September 2016, accepted 5 October 2016

Abstract

We investigated neurophysiological mechanisms of subthalamic nucleus involvement in verbal fluency through a verbal generation task. The subthalamic nucleus is thought to act as a behavioural go/no-go instance by means of oscillatory communication in the theta band with the prefrontal cortex. Because subthalamic alpha-theta frequency stimulation has been shown to exert beneficial effects on verbal fluency in Parkinson's disease, we hypothesized that an alpha-theta oscillatory network involving the subthalamic nucleus underlies verbal generation task performance as a gating instance for speech execution. Postoperative subthalamic local field potential recordings were performed during a verbal generation compared to a control task. Time-frequency analysis revealed a significant alpha-theta power increase and enhanced alpha-theta coherence between the subthalamic nucleus and the frontal surface EEG during the verbal generation task. Beta and gamma oscillations were not significantly modulated by the task. Power increase significantly correlated with verbal generation performance. Our results provide experimental evidence for local alpha-theta oscillatory activity in the subthalamic nucleus and coherence to frontal associative areas as a neurophysiological mechanism underlying a verbal generation task. Thus, verbal fluency improvement during subthalamic alpha-theta stimulation in Parkinson's disease is likely due to an enhancement of alpha-theta oscillatory network activity. Alpha-theta oscillations can be interpreted as the rhythmic gating signature in a speech executing subthalamic-prefrontal network.

Introduction

The subthalamic nucleus (STN) is involved in an associative basal-ganglia-thalamocortical network (Temel *et al.*, 2005) and acts as input area through which the cerebral cortex controls motor and behavioural aspects (Benarroch, 2008). Its ventromedial part corresponds to the associative territory and has connections with the prefrontal and anterior-cingulate cortices, critical structures in cognition (Alexander *et al.*, 1990; Benarroch, 2008). The clinical relevance of this network is highlighted by cognitive side effects of high-frequency deep brain stimulation (HFS). STN-HFS is an established treatment in Parkinson's disease (PD; Deuschl *et al.*, 2006; Weaver *et al.*, 2009; Williams *et al.*, 2010). However, studies report decline in verbal fluency (VF) during HFS (Witt *et al.*, 2008; Weaver *et al.*, 2009). VF demands a complex performance, including working memory and word retrieval, executive aspects as a retrieval strategy, selection from competing lexical alternatives, subcategory shifting and vocabulary access. STN-HFS impairs VF-associated activation in a left-sided frontotemporal network (Schroeder *et al.*, 2003). Furthermore, VF decline correlates with reduction in perfusion (Cilia *et al.*, 2007) and metabolism (Kalbe *et al.*, 2009) in left dorsolateral-prefrontal, inferior-frontal and anterior-cingulate areas. Although STN stimulation below 100 Hz can be beneficial to some motor aspects (di Biase & Fasano, 2016), in contrast to HFS, low-frequency alpha-theta-stimulation (LFS) of the STN of about 10 Hz worsens limb motor symptoms in PD, possibly due to enhancement of a 10 Hz pathologic oscillatory network (Timmermann *et al.*, 2003, 2004). On the

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other hand, alpha-theta-LFS at 10 Hz improves VF (Wojtecki *et al.*, 2006), possibly by activation of oscillatory connections with frontal areas. Generally, oscillatory synchronization is a feature for information processing of neuronal networks (Singer, 1999; Varela *et al.*, 2001; Schnitzler & Gross, 2005). 10 Hz oscillatory activity may represent various cognitive operations in cortico-thalamic-circuits, such as theta-oscillations (4–7 Hz) reflect working memory and alpha-oscillations (8–12 or 13 Hz, individually variable) play a role in transient reactivation of long-term memory codes during short-term storage (Klimesch *et al.*, 2005).

A method to find evidence for the involvement of a neuronal structure in a given task is to directly record local field potentials (LFPs) from it. LFPs presumably reflect input signals of the target structure and contain electrical activity of a millimetre range from an electrode, consisting of the summated synchronized postsynaptic excitatory and inhibitory potentials (Brown & Williams, 2005; Kuhn *et al.*, 2005b). Analysis of LFP-basal-ganglia-oscillations for the cognitive domain has progressed substantially due surgery for deep brain stimulation (Munte *et al.*, 2008; Marceglia *et al.*, 2011). Up to date STN-LFP recordings suggest local involvement of theta-, alpha- and beta-modulations (13–30 Hz) during cognitive tasks (Rektor *et al.*, 2009, 2010; Fumagalli *et al.*, 2011).

Although VF is the most often affected cognitive function in STN–HFS it has not extensively been investigated with LFPs so far. There is first evidence for local gamma (30–100 Hz) STN modulation during VF (Anzak *et al.*, 2011) and beta desynchronization during speech (Hebb *et al.*, 2012). However, oscillatory activity in the theta-band seems to be crucial for communication of the subthalamic nucleus with the prefrontal cortex (Cavanagh *et al.*, 2011) to act as a behavioural go/no-go behaviour-gating instance (Frank, 2006). Thus, using a verbal generation (VG) paradigm comprising all aspects of a formal-lexical phonemic VF task we aimed to investigate more elaborately if there is evidence for the involvement of the STN in a VF-network, by means of increased low-frequency (alpha-theta) oscillatory LFP-activity and coherence to surface electroencephalography (EEG). This would provide an explanation for the beneficial effects of STN-LFS on VF and disentangle the rhythmic signature in a speech-gating network as representative example of the integrative function of the STN.

Materials and methods

Patients and surgery

Sixteen patients with Parkinson's disease (eight female, eight male; age 62 ± 6.6 years) who underwent bilateral implantation of deep brain electrodes in the STN were enrolled in the study. In all patients, cognitive impairment was excluded during routine presurgical evaluation [Mattis Dementia Rating Scale (MDRS) score 138.7 ± 5.4 points]. Mean disease duration at the time of implantation was 14.1 years (±4.9 years). All patients showed motor symptoms, consisting of akinesia, resting tremor and/or rigidity that responded positively to pharmacological treatment with levodopa, with the exception of tremors. The presurgical Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987) ON and OFF medication was assessed. Due to insufficient control of motor fluctuations and/or tremor by medication, our centre's guidelines suggested to proceed with the implantation of deep brain stimulation (DBS) electrodes to further reduce the patients' symptoms in accordance with the German recommendations for DBS in Parkinson's disease (Hilker *et al.*, 2009; Voges *et al.*, 2009).

All anti-parkinson medication was withdrawn at least 12 h before surgery (dopamine agonists 2–3 days before). The clinical details are summarized in Table 1. All patients were implanted bilaterally in the STN. The location of the STN was determined based on Schaltenbrand–Wahren-Atlas (SWA; Schaltenbrand & Wahren, 1977) coordinates, stereotactic cranial computed tomography (CT) and high-resolution magnetic resonance imaging (T1 weighted MPRAGE and T2 SPACE MRI). To determine the STN borders and the optimal implantation area, we performed intraoperative microelectrode recordings (MER), using the INOMED MER system (INOMED, Emmendingen, Germany) with up to five electrodes (central, anterior, posterior, lateral, medial) that were concentrically configured with a distance of 2 mm from the central electrode. The final placement of the DBS electrode (electrode model 3389, Medtronic Corporation, Minneapolis, MN, USA) was based on multi-unit cell activity, a profile of stimulation effects, and side effects. DBS surgery based on intraoperative multiple trajectories MER and test stimulation can be beneficial to optimal placement of DBS electrodes in the dorsolateral (motor) STN and clinical outcome

TABLE 1. Clinical characteristics of PD patients

Patient	Gender	Age (years)	Disease Duration (years)	PD Medication (LED mg/day)	Disease Type (AR: akinetic-rigid T: tremor)	Predominant Side	MDRS	Motor UPDRS	
								OFF	ON
1	Male	62	16	750	AR	Left	142	36	11
2	Female	71	24	900	AR	Right	142	25	16
3	Female	68	22	1150	AR	Left	131	72	37
4	Male	55	14	950	AR	Right	144	48	18
5	Female	62	10	200	AR	Left	141	35	13
6	Female	66	14	900	AR	Left	139	24	11
7	Male	57	8	400	T	Left	139	31	15
8	Female	74	15	400	T	Right	139	23	7
9	Female	67	14	625	AR	Right	142	38	19
10	Female	55	15	1001	AR	Left	133	45	21
11	Male	64	11	1300	AR	Right	141	35	19
12	Male	68	8	700	AR	Left	139	28	10
13	Male	60	15	300	AR	Right	143	35	4
14	Male	51	10	1480	AR	Right	138	35	26
15	Female	64	21	200	T	Left	138	32	12
16	Male	55	9	600	T	Left	140	45	38

LED, Levodopa equivalent dose of PD-medication at the day of the recording; MDRS, Mattis Dementia Rating Scale; UPDRS, Unified Parkinson´s disease-rating scale with and without medication at the preoperative screening.

(Reck *et al.*, 2012). During the operation, final macroelectrodes were connected to sterile percutaneous extension wires (model 3550-05, Medtronic), which were externalized through the scalp and could be connected postoperatively to EEG amplifiers via external cable connectors (twist lock cable model 3550-03, Medtronic and custom made connector to DIN 428092 touch proof connectors). Postoperative stereotactic computed tomography (CT) scans were performed in all patients to ensure correct electrode placement.

Paradigm

The experiment consisted of two parts (Fig. 1). The first task was a VG task, comprising all aspects of a formal-lexical (phonemic) VF task. The task consisted of the presentation of the 10 most frequent initial letters of the German language (S, A, M, K, B, G, R, H, E, D), each presented for eight times successively (total of 80 trials). Each trial began with the presentation of a letter in the centre of the screen for 1 s. Onset of the letter was time point zero. Subjects were instructed to think of a word beginning with that letter without speaking aloud. Furthermore, patients were asked to avoid repetitions, words with the same word stem and names. After a test period of 3 s, rendering speech preparation and movement artefact-free segments, an exclamation mark appeared on the screen for 1 s representing a 'go' cue and indicating to the subjects to speak the thought of word out loud during the presentation of the exclamation mark and the following second. Between trials there was a variable interstimulus interval of 1–3 s during which a fixation cross was provided at the centre of the screen. The last 1 s before time point zero was used as baseline. The principle and timing of the task was derived from electrophysiological studies examining word processing and generation (Snyder *et al.*, 1995; Rowan *et al.*, 2004; Dalal *et al.*, 2009). The control task consisted of a word retrieval task lacking only the executive component of a VF task. Instead of different initial letters only the letter 'P' was presented. Subjects were instructed to always think of and verbalize the German version of the word 'pause' during the total of 80 trials. To ensure efficient performance, patients were trained with the task 1 day before operation.

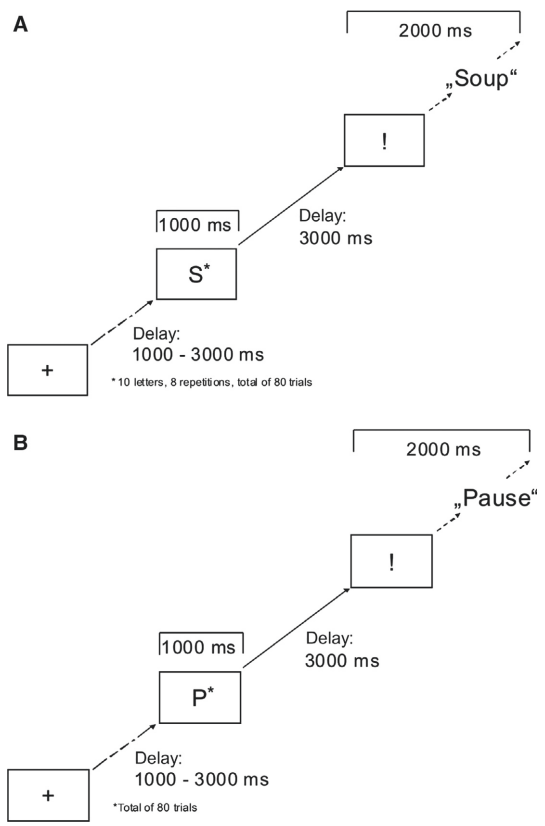

FIG. 1. Paradigm. (A) Verbal generation task. (B) Control task. After a jittered interval of 1–3 s with a fixation cross on the screen patients were presented a certain letter in the VG task or the letter 'P' in the control task for 1 s. After letter offset, the movement artefact-free test period of 3 s for LFP analysis began. After that an exclamation mark appeared on the screen for 1 s representing a 'go' cue and indicating to the subjects to verbalize the thought-of word.

Recordings

All patients gave written informed consent and the study was approved by the ethics committee of the Medical Faculty of the Heinrich-Heine-University Duesseldorf in accordance to the Declaration of Helsinki. The whole postoperative recording session took place 1 day after electrode implantation. All patients were examined with their respective anti-parkinson medication without any change to the preoperative dose. The medication ON state was chosen as we wished to determine whether the subthalamic nucleus is involved in the execution of a VG task in a state as physiological as possible. None of the patients showed tremor or levodopa-induced dyskinesia during the experimental session. During the experiment, patients were comfortably seated in their bed about 80 cm from a personal computer screen (10.6″ screen diagonal, screen refresh rate 60 Hz) displaying the task stimuli, using E-PRIME software (Psychology Software Tools, Inc., USA).

As the operation was performed bilaterally in all patients, recordings were carried out from 32 subthalamic nuclei. LFP activity was monopolarly recorded during task performance from the four platinum-iridium cylindrical contacts of the DBS-electrode numbered 0, 1, 2, 3 from the tip of the electrode (1.27 mm diameter and 1.5 mm length and a contact to contact separation of 0.5 mm) against a surface midline frontopolar reference. Signals were amplified and band-pass filtered from 0.5 to 1000 Hz, using a portable amplifier (BrainVision Recorder, BrainAmp MR plus, Brain Products GmbH, Munich, Germany, Version: 1.03). Signals were sampled at 5 kHz and monitored online. The responses to the stimuli were monitored, tagging wrong or no responses to obtain a measure for task performance for later correlation with electrophysiological findings. Additionally, in five patients, surface electrodes were placed at scalp sites Fz, F3/4, F7/8, Cz, C3/4, Pz, Oz, and O1/2 to record a simultaneous scalp electroencephalogram (EEG).

Analysis

The aim of the analysis was to compare the focal maximum-induced oscillatory activity changes from baseline – predominantly in the alpha-theta band – during the test interval in a correct performed VG task with the respective maximum activity changes during the test interval in the control task. An additional aim was to compare maximal STN-to-surface-EEG-coherence in the respective time period and frequency band and at the same recording location between the tasks. Thus, the first analysis step was to select only data with correct behavioural performance in the test interval. Furthermore, bipolar STN references for each hemisphere with the

strongest averaged power changes during the test interval of the considered task were selected for the alpha-theta band. For the power analysis, the maximum activity was derived from 1-s during the strongest activation in each task for each STN and an additional *t*-test was applied. For coherence analysis, the EEG channel with the strongest coherence in the alpha-theta band to the selected STN reference was chosen and this coherence was compared between tasks. In a further step, individual data were averaged for group statistics between tasks. Details for each analysis step are provided below.

All data were analysed offline, using the BRAINVISION ANALYSER software (Brain Products GmbH, Munich, Germany, Version: 1.05). Individual traces were visually inspected and trials containing noise, movement or eye blink artefacts and trials with wrong or no behavioural responses were discarded from further analysis. The four DBS-electrode contacts were re-referenced against each other, resulting in six bipolar derivations for each STN (0–1, 0–2, 0–3, 1–2, 1–3, 2–3). The bipolar activity was filtered with a low pass filter of 160 Hz and down-sampled to 512 Hz. Trials were segmented starting 1 s prior to stimulus onset to 2 s after exclamation mark onset, resulting in segments of 7 s duration.

Definition of frequency bands

We focused our analysis on the theta, alpha, beta and gamma frequency bands known from literature and stated in the introduction. However, to exclude low frequency noise common in LFP recordings, we only included activity in the high theta range and defined theta as 5–7 Hz. Regarding alpha activity, it should be mentioned that individual alpha frequency (IAF) varies to a large extent as a function of age, neurological diseases, memory performance, brain volume and task demands from 8 to 13 Hz and 'upper alpha' can be defined as 2 Hz above IAF and thus up to 15 Hz (Klimesch *et al.*, 2005). Therefore, we defined for our analysis alpha as 8–15 Hz and alpha-theta as 5–15 Hz, Beta was defined as 13–30 Hz and gamma as 30–100 Hz.

Local field potential activity analysis

LFP segments further underwent normalized baseline corrected time-frequency analysis for induced activity with a continuous Morlet Complex Wavelet transformation with Morlet c = 8 and 10 linear frequency steps (layers) from 5 to 15 Hz for the alpha-theta band and 10 linear steps from 13 to 30 Hz for the beta band. For the gamma band Morlet c = 15 was used with 10 linear steps from 30 to 100 Hz. Time-frequency plots were averaged across trials and power modulations were defined as power change over the trials during the 3 s test interval compared to individual baseline, consisting of 1 s before stimulus presentation. The contact pair used for further analysis was chosen according to the strongest activation during the test interval in the VG tasks. For statistical comparison, the mean activity of the 1-s and the respective frequency layer displaying the strongest activation during the test interval was exported for both tasks from each STN recording (for layer definition please refer to the first sentence of this paragraph). As beta and gamma bands represent a wide frequency range, a wide-band layer (13–30 Hz for beta and 30–100 Hz for gamma) was exported for statistical analysis of higher frequencies. Mean activation over the group was then compared between both conditions, using a Wilcoxon Test (SPSS 18, Chicago, IL, USA). Differences were considered significant at $P < 0.05$.

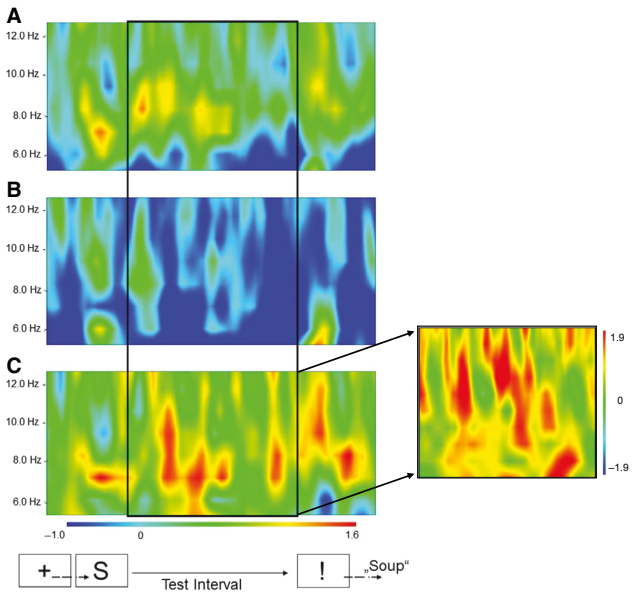

FIG. 2. Time frequency plot of temporal activation changes from baseline during the course of the task period. (A) Verbal generation. (B) Control tasks. (C) Difference between both tasks. The temporal changes depict the modulation of activation during the course of the task as indicated by the paradigm schema at the bottom, starting from letter onset until exclamation mark offset. The black frame highlights the task interval used for analysis. Strongest activation relative to baseline in the difference plot between both tasks takes place around 6–12 Hz. Mean relative wavelet power (Unit Scale) changes are shown color coded (grand average of left bipolar contact pairs, $n = 16$ subjects, 16 subthalamic nuclei of the left hemisphere). Arrows furthermore highlight color coded *t*-values of *t*-test of the task interval.

Furthermore, grand averages for left and right STN-LFP time frequency plots were visualized for the lower frequency band and an additional *t*-test between conditions was applied.

For surface EEG recordings, activation changes were calculated and statistically analysed in the same way as for deep brain recordings. For this analysis, the bipolar surface EEG channels of both hemispheres were chosen that showed the strongest coherence to the ipsilateral bipolar STN recording with maximum activity increase.

Coherence analysis

Coherence analysis between the bipolar derivations of the left and the right macroelectrode and respective ipsilateral and frontal scalp electrodes (F3/7, F4/8 to Fz) was calculated for 10 STN recordings to determine whether there was coupled activity between the recorded low frequency LFPs and cortical activity changes during VG and control tasks. Coherence is calculated in the range of 0–1, with 1 representing an ideal linear correlation and 0 an independence of the two signals (Halliday *et al.*, 1995). After bipolar referencing of the respective ipsilateral scalp electrodes against Fz and bipolar re-referencing of the DBS-electrode contacts, raw data was processed as mentioned above. From the 7 s epoch, the period of 3 s only including the test interval, starting at stimulus offset to exclamation mark onset was selected. This segment was further divided into equal sized segments of 1 s, with an overlap of 0.5 s. Using the fast-Fourier transformation (FFT) power spectra of this time window was obtained. To calculate the coherence, FFT transformed data was analysed using the formula (abbreviations: c: channel, f: frequency, CS: cross spectrum, i: index number of segment):

$$\mathrm{Coh}(c1,c2)(f) = \frac{|\mathrm{CS}(c1,c2)(f)|^2}{(|\mathrm{CS}(c1,c1)(f)||\mathrm{CS}(c2,c2)(f)|)}$$

with

$$\mathrm{CS}(c1,c2)(f) = \sum c1,i\,(f)\,c2,i\,(f).$$

To analyse the confidence level for the coherence, the methodology implemented by Halliday *et al.* (1995) was used. Only peaks of LFP-EEG coherence were accepted as significant if they reached a 95% confidence level in the main frequency band of interest (alpha-theta). The ipsilateral bipolar frontal electrode with strongest significant coherence to the bipolar STN-LFPs during the VG task was chosen for further analysis for each STN. The largest peak in the alpha-theta band was determined for both conditions and statistically compared over the group for the right and the left STNs separately with using a Wilcoxon-Test (SPSS 18, Chicago, IL, USA), considering differences as significant at $P < 0.05$. As an additional step, we analysed the coherence between the STN and frontal regions during the overt speech. We used the same procedure as stated above but only included the active speech component of the trial (5000–6000 ms).

Recording location

For the inspection of the anatomical location of the contacts used for analysis, the location of the electrodes was derived by fusion of the postoperative stereotactic CT onto the individual preoperative stereotactic planning software. This was available for 28 STNs (Table 2). Contact coordinates with reference to the middle of anterior-posterior-commissural line (mid-commissural point, MCP) were normalized and visualized on the stereotactic Schaltenbrand Atlas (Nowinski & Thirunavuukarasuu, 2004).

Results

Task-induced power changes

In the VG task, alpha-theta activity increase on the STN electrodes could be detected during the task period mainly between 6 and 12 Hz. On the same bipolar electrode contacts, for the control task power decrease in the alpha-theta band during the task period could be observed over the group, with some individual recordings showing a slight increase, decrease, or no change (see Table 3). Figure 2 displays the time-frequency representation during the VG and control task for all left nuclei. The activity in the alpha-theta band (mean peak frequency around 8 Hz, see Table 3) was significantly stronger for the VG task compared to the control task for the same left and right bipolar derivations during the task period, as revealed by the Wilcoxon test [relative modulation from baseline: during VG task for all left nuclei = 1.4 (standard error of mean (SEM) 0.2), during control task for all left nuclei = −0.6 (SEM 0.3), $P < 0.001$; mean during VG task for all right nuclei = 1.4 (SEM 0.4), during control task for all right nuclei = −0.8 (SEM 0.4), $P < 0.001$; Fig. 3]. Even when comparing the bipolar contact derivations with the maximum activity during the VG task with the bipolar derivation that showed maximum activity increase in the control task [mean (SEM): left −0.1 (0.2), right 0.1 (0.2)], the difference between both tasks remained highly significant for both hemispheres ($P < 0.01$). Peak activity change latencies were around 2000 ms.

On the most coherent surface EEG channels no local significant (compared to the control task) VG-task related increase in low frequency activity could be detected over the group altough modulation of activity was seen at the same mean peak frequency around 8 Hz with increased activity in some patients (see Table 3C).

Beta activity showed no task-induced modulation from baseline that differed significantly between the two tasks [STN activity change (SEM) left VG 0.07 (0.07), control −0.08 (0.1) right VG −0.19 (0.1) control −0.29 (0.17), $P > 0.05$, n.s.].

Gamma activity showed minimal task-induced modulation, and the comparison between the two tasks failed to reach significance level [STN activity change in (SEM) left VG 0.00 (0.04), control −0.04 (0.03), right VG −0.06 (0.06) control −0.1 (0.5), $P > 0.05$, n.s.].

As a further control beta and gamma activity during baseline (−1000–0 ms) was compared with the active speech component (5000–6000 ms) of the trial. For beta a minimal desynchronization during the active speech component could be observed, but as revealed by the Wilcoxon test failed to reach significance ($P > 0.05$). Gamma activity was also minimally modulated during the active speech component, but not in a significant manner ($P > 0.05$).

Coherence

Coherence analysis showed coupling of LFP- and (inferior)-frontotemporal EEG-electrodes. We identified significant coherence between LFPs and surface electrodes in the alpha-theta frequency band (mean peak frequency around 7 Hz) in all 10 STN recordings in the VG condition and in six recordings in the control condition. Maximum coherence to STN-LFPs found for (inferior)-frontotemporal location was: four times F3/F4 respectively, six times F7/F8 respectively. Comparison between the largest peaks in the alpha-theta band of the two tasks revealed a significant difference of LFP-EEG coherence during the VG task for both hemispheres (coherence left hemisphere $P = 0.036$, coherence right hemisphere $P = 0.016$, Fig. 4).

During overt speech, coherence analysis between the STN and (inferior)-frontotemporal EEG electrodes failed to reveal significant coupling of activity in the alpha-theta frequency band.

TABLE 2. Bipolar contact combinations used for final analysis and their coordinates

Patient	Contact left	*x*	*y*	*z*	Contact right	*x*	*y*	*z*
1	1–2	−11.3	−2.1	−4.3	0–1	11.8	−3.5	−4.3
2	1–2	−12	−1	−0.9	2–3	11	−1.9	−1.6
3	0–2	–	–	–	0–2	–	–	–
4	0–2	−12.2	−2.8	−1.2	0–2	11.3	−2.8	−5.2
5	0–3	−12.3	−2.2	−2.7	0–3	12.6	−1.4	−1.9
6	1–2	−14.1	−1.1	−0.4	0–1	11.3	−3.6	−1.8
7	0–1	−12.3	3.4	−3.4	0–2	12	−1.8	−2.2
8	0–1	−12.7	−2.8	−5.4	0–2	11.6	−1.9	−4.8
9	1–2	−15.1	4.1	1.1	0–2	13.8	5.7	0.3
10	1–3	–	–	–	0–2	–	–	–
11	0–3	−11.2	−4.4	−3.9	0–2	11.4	−4.8	−6.9
12	1–2	−12.4	−0.1	−1.9	0–2	11.7	−4	−3.8
13	0–2	−12	−1.2	−4.6	1–2	8.8	−2.4	−2.4
14	0–2	−11.9	−1.8	−5.1	1–3	10.2	−1	−3.7
15	0–3	−13.5	1.2	−0.7	1–3	11.4	−1.8	−0.1
16	1–2	−13.1	−2	−5.2	1–2	12.7	−0.7	−4.1

Coordinates in mm with reference to the mid-commissural point (MCP) derived from individual postoperative imaging.

TABLE 3. Individual task-related alpha-theta power changes and coherence. (A) STN power changes. (B) STN-Surface-EEG coherence. (C) Surface-EEG power changes

A

	Power left STN				Power right STN			
Patient	VG	Control	Peak Frequency (Hz)	Peak Latency (ms)	VG	Control	Peak Frequency (Hz)	Peak Latency (ms)
1	1.9	0.3	8	2400	0.4	−0.8	9	2300
2	1.8	−1.1	8	1600	0.1	−2.1	8	1900
3	1.1	0.8	6	2500	2.9	2.3	9	2000
4	1.6	−1.6	8	1600	3.2	−2.6	6	1700
5	0.5	−2.1	10	2000	3.3	−0.2	8	2200
6	0.8	0.5	11	1700	0.9	0.4	10	2000
7	0.9	0.6	8	1900	0.9	−0.1	8	2500
8	2.3	−0.4	8	3200	3.1	0.3	7	1300
9	0.2	−1.3	10	2500	0.4	−2.2	10	1100
10	1.6	−0.9	7	1500	3.2	−4.5	8	1500
11	1.5	0.6	9	1200	2.5	−0.9	9	1700
12	1.0	0.6	8	2600	0.5	0.1	8	3100
13	2.0	−2.1	9	1600	1.1	−1.5	11	1500
14	2.3	−0.9	8	2500	1.5	−1.5	8	2700
15	0.6	−1.4	9	2800	0.3	0.3	9	3000
16	1.5	−0.3	8	2200	1.1	0.3	10	1300
Mean	1.4***	−0.6***	8.4	2113	1.4***	−0.8***	8.6	1988
SEM	0.2	0.3	0.3	139	0.4	0.4	0.3	152
SD	0.6	0.9	1.2	540	1.4	1.5	1.2	589

B

	Coherence left STN to surface EEG			Coherence right STN to surface EEG		
Patient	VG	Control	Peak Frequency (Hz)	VG	Control	Peak Frequency (Hz)
1	0.04	0.03	8	0.04	0.00	6
5	0.06	0.01	6	0.08	0.00	8
11	0.03	0.00	7	0.01	0.00	7
14	0.03	0.03	6	0.05	0.01	6
16	0.05	0.02	7	0.06	0.02	6
Mean	0.04*	0.02*	6.8	0.05*	0.01*	6.6
SEM	0.01	0.01	0.4	0.01	0.01	0.4

C

	Power left surface EEG			Power right surface EEG		
Patient	VG	Control	Peak Frequency (Hz)	VG	Control	Peak Frequency (Hz)
1	−4.6	−3.4	7	−3.4	−0.3	6
5	−0.6	−1.9	9	−1.3	−3.5	12
11	0.4	−0.2	9	0.4	−0.2	9
14	1.5	0.6	7	1.0	0.8	6
16	1.3	−0.1	8	1.1	−0.2	8
Mean	−0.4†	−1.0†	8	−0.4†	−0.7†	8.2
SEM	1.1	0.7	0.4	0.8	0.7	1.1

(A) Rounded numbers for relative power changes from baseline at peak frequency and peak latency for the left and right STN in the VG and control task for contact combination with strongest VG activation changes. ***$P < 0.001$ significant differences for the comparison between tasks. (B) Rounded numbers for STN-surface-EEG coherence at peak frequency for the individual most coherent surface-EEG contact for both conditions. 0.00 indicates no significant coherence peak. *$P < 0.05$ significant differences for the comparison between tasks. (C) Rounded numbers for power changes of surface recordings for EEG channels with highest coherence to STN channels. †No significant differences for the comparison between tasks.

Recording location

All 32 bipolar contact pairs that showed the strongest task-dependent low frequency modulation and thus were used for further analysis are listed in Table 2. The majority (28/32) of bipolar derivations were recording a field below or around contact 1 (0–1, 0–2, 0–3, 1–2), which refers to the lower part of the electrode. Accordingly, the most frequent contact combination was 0–2 ($n = 12$). Additionally, as Fig. 5 illustrates, the mean recording coordinates with reference to the mid-commissural point (MCP) of both the right and left hemispheres corresponded well with a location within the STN rather than the outer dorsolateral border to adjacent fibre tracts and thus reflect a recording location involving non-motor parts of the nucleus (coordinates in mm with standard deviation: right hemisphere $x = 11.5 \pm 1.6$, $y = -1.9 \pm 2.5$, $z = -3.0 \pm 2.0$ mm; left hemisphere $x = -12.6 \pm 1.1$ mm, $y = -0.9 \pm 2.4$ mm, $z = -2.8 \pm 2.1$ mm; Fig. 5).

Correlation of task-dependent activity changes with performance

As a measure of performance in the VG task and the control task the number of correctly performed words was counted. Discarding

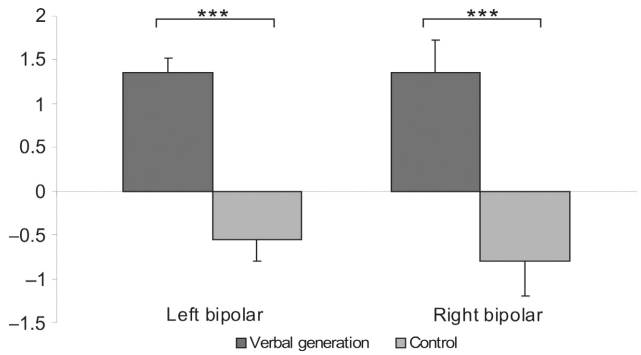

FIG. 3. Mean wavelet power (Unit Scale) relative to baseline during the VG and control tasks. VG task is shown in dark grey and control task in light grey from the left (left plot, $n = 16$) and the right (right plot, $n = 16$) bipolar macroelectrode pairs in the alpha-theta band. ***$P < 0.001$. Errors bars showing standard error of mean.

trials with no responses (in the control and VG task) or with wrong responses (repetitions, words with the same word stem and proper names for the VG task) resulted in a mean performance of 71.3 (SEM 1.0) words in the VG task and 72.2 (SEM 0.8) words in the control task. Furthermore, discarding trials containing noise, movement or eye blink artefacts from further electrophysiological analysis left on average 65.8 (SEM 1.6) trials for the VG task and 70.4 (SEM 0.8) for the control task. Pearson r was used to determine correlation between performance and activity changes. Correct performance of words correlated significantly with activity increase in the left ($r = 0.58$, $P < 0.05$) and right ($r = 0.82$, $P < 0.001$) STN in the VG task. This correlation was not significant in the control task, additionally as Fig. 6 illustrates performance and activation showed a restricted range in this task.

Discussion

We investigated the role of the STN in a VG task by means of postoperative recordings of oscillatory activity. We show a dynamic modulation of STN-LFP alpha-theta activity in response to and correlated with the performance of a VG task as opposed to a control task. This finding renders electrophysiological proof for the involvement of the STN in the processing of executive functions such as VF and further supports the hypothesis that the STN processes these functions by specifically modulating low-frequency oscillations. Alpha-theta oscillations can be interpreted as the rhythmic gating signature in a speech executing subthalamic-prefrontal network. A direct modulation or interruption of this process through high frequency stimulation may explain behavioural sequelea seen in patients with STN-HFS. Furthermore, the improvement in VF during LFS (Wojtecki *et al.*, 2006) may thus be due to power increase in this particular frequency. In the following, some particular aspects of the work will be discussed.

Origin of recorded activation and the STN – cortical cognitive network

The STN is part of the cortico-basalganglia-thalamo-cortical network and is subdivided into different territories. Its ventromedial part corresponds to the associative territory with connections to pallidal and nigral behavioural-cognitive circuits and input from the dorsolateral-prefrontal and lateral-orbitofrontal cortex. This associative circuit also involves cortical areas of the VF-mediating network, including inferior frontal gyrus, anterior cingulate cortex and superior temporal regions (Alexander *et al.*, 1990; Benarroch, 2008).

In our analysis, contacts showing the strongest task-dependent activation were located within the STN according to postoperative imaging. Furthermore, placement of the electrode in the STN was supported by intraoperative microelectrode recordings and test stimulation. Finally, the use of bipolar re-referencing, analysing activity as focal as possible, makes volume conduction from another neuronal source unlikely. Our finding that the oscillatory activity was modulated during an executive task therefore most likely represents neuronal oscillatory activity of the STN or from the cortex projecting into the STN. The observation, that particularly recordings of the lower contacts, with locations involving central rather than

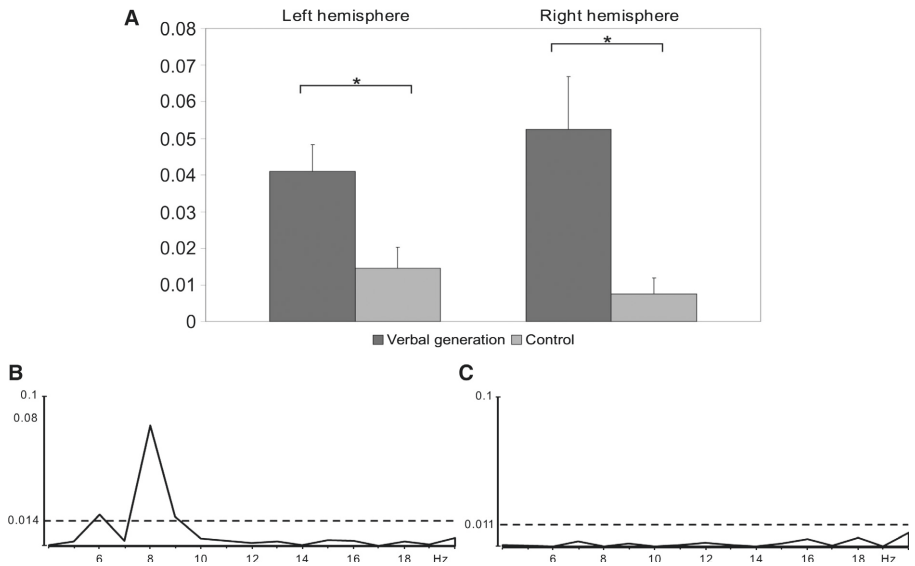

FIG. 4. Coherence at peak frequency. Mean over the group coherence (A) and example of coherence spectra during the VG (B) and the control task (C). Mean coherence (with errors bars showing standard error of mean) between STN contacts and respective ipsilateral frontal surface electrodes for the VG (dark grey) and control (light grey) tasks from the left hemisphere (left plot, $n = 5$) and the right hemisphere (right plot, $n = 5$). *$P < 0.05$. Example for coherence between contact pair 1–2 of one right macroelectrode and the respective bipolar surface electrodes (F8 against Fz). Dotted line indicates the 95% confidence level. Coherence is normalized between 0 and 1. Main peak in alpha but also small significant peak in theta frequency during the VG task.

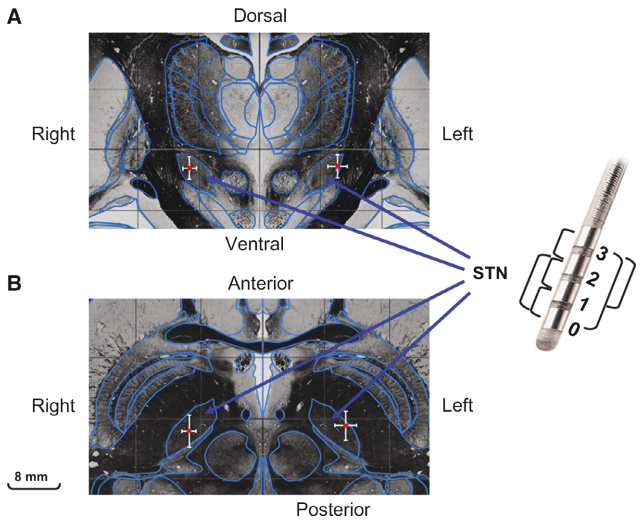

FIG. 5. Recording location visualized on anatomical atlas. (A) Coronary slice, (B) Axial slice. Mean recording sites with standard deviation of analysed bipolar referenced contacts of (0–1, 0–2, 0–3, 1–2, 1–3 or 2–3) for both the right and left STN visualized on the Schaltenbrand atlas. Coronary slice 3 mm postmid-commissural point (MCP), axial slice 3.5 mm below anterior-posterior commissure line (AC-PC line). STN, subthalamic nucleus.

dorsolateral parts of the STN, displayed activation during this cognitive task corresponds to neuroanatomic evidence that especially the ventromedial STN has connections with inferior-frontal associative areas. Additionally, coherence analysis revealed significant coupling between the STN LFPs and the (inferior-)frontotemporal surface electrodes. This finding further supports a functional relevant connection between the ventromedial STN and the frontal cortex. No significant coherence was found for overt speech production. Failing to do so might be due to the fact that the exact time point of overt speech production for the analysis was not available to us. Due to technical reasons, measured speech onset with EMG and a microphone did not provide an exact time point for overt speech production and we discarded this recording. Furthermore, the limited number of available patients with surface EEGs has to be taken into account pertaining to interpretation of the chorence statistics.

Verbal generation paradigm

VF has been shown to be affected by STN DBS on a behavioural basis (Wojtecki *et al.*, 2006) as well in functional imaging (Schroeder *et al.*, 2003). For methodological reasons, we used a verb*al generation* task rather a verbal fluency task, however, still comprising all aspects of a formal-lexical phonemic VF task. We chose a phonemic task as it mainly involves frontal and subcortical regions, compared to an involvement of temporal and parietal regions during a semantic fluency task (Troyer *et al.*, 1998; Baldo *et al.*, 2006). In order to be able to analyse averaged time-locked-induced activity changes from baseline, we developed a paradigm in which a single word was produced in each trial. Thus, we also had the possibility to delineate the time point when the subthalamic nucleus was engaged in the task (around 2000 ms). It has to be noted that this might differ from a verbal fluency paradigm in which the production of as many words as possible in 1 min is demanded. Therefore, we termed the used paradigm as verbal generation. However, the usefulness of a VG paradigm to assess frontal networks involved in

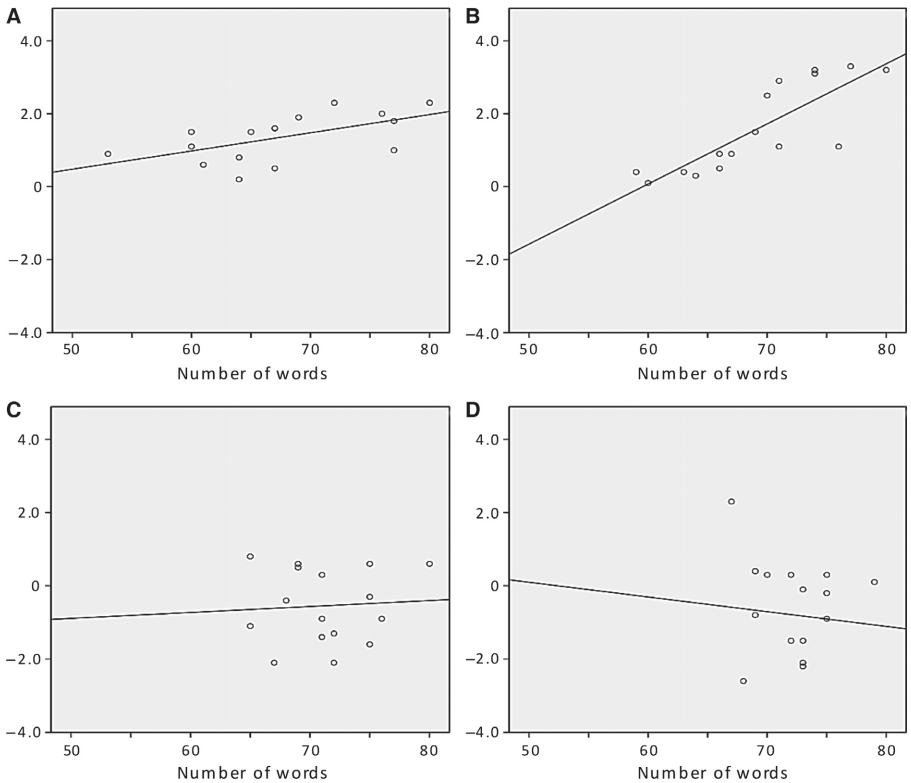

FIG. 6. Correlation of task-dependent relative wavelet power changes with number of correctly performed words. (A) Verbal generation task left STN, (B) Verbal generation right STN. (C) Control task left STN, (D) control task right STN. Coefficients: VG task: left: $r = 0.58$, $P < 0.05$/right $r = 0.82$, $P < 0.001$. Control task: left: $r = 0.07$, n.s./right $r = -0.08$, n.s.

executive function was derived from several publications outlined in the following.

Invasive and non-invasive electrophysiological recording showed processing of written words within the first second (Snyder *et al.*, 1995; Dalal *et al.*, 2009). For VG event-related potential (ERP) changes in surface EEG starting about 1 s after a cue and lasting 3-s until a 'speak'-cue can be found on frontocentral and inferior-frontal electrodes in contrast to passive listening, non-word repetition and word repetition. Furthermore, frontal EEG modulation is in agreement with functional MRI data showing left inferior-frontal activation during this VG paradigm (Rowan *et al.*, 2004). In terms of timing, other imaging studies assessing a VF network ranged from real fluency task with covert production of several words over a period up to a minute, to overt production of a few words in a short block or overt production of a single word during a 2–4 s period (Yetkin *et al.*, 1995; Pujol *et al.*, 1996; Phelps *et al.*, 1997; Schlosser *et al.*, 1998; Abrahams *et al.*, 2003; Schroeder *et al.*, 2003; Weiss *et al.*, 2003, 2004; Amunts *et al.*, 2004; Schaufelberger *et al.*, 2005). Whatever paradigm was chosen, the results revealed activation of a fronto-temporal network including the middle frontal, anterior-cingulate, inferior-frontal gyrus and superior temporal regions. We aimed to investigate oscillatory communication of the STN with this proposed network. In the light of functional imaging and EEG studies it is plausible to use the paradigm with the timing as presented. In order to have control over the performance and to exclude movement artefacts, we chose an overt speech paradigm and short trials with analysis of the signals before the onset of speech of a single word. However, one should be aware of limitations of the task, such as that in the seconds after the letter presentation there is no clear evidence as to what the patients are doing (e.g. maintain a word repeating it continuously vs. searching for a new word). Furthermore, a similar limitation should be noted for the control condition. Patients were carefully instructed to covertly think of the word 'pause' during the covert phase of the task. However, there is no absolute control over the adherence of the patients to the instructions.

Frequency range of oscillatory activity changes

We focused the analysis on alpha-theta range between 5 and 15 Hz as our previous work revealed improvement of VF with 10-Hz-STN-LFS (Wojtecki *et al.*, 2006). Our main finding was a significant task-related modulation of local alpha-theta activity increase focused between 6 and 12 Hz with a peak around 8 Hz. Our definitions of the theta (5–7 Hz) and alpha bands (8–15 Hz) thus included the relevant oscillations, regardless of defined boarders. There is further evidence that oscillations in this frequency might be involved in non-motor tasks such as motor imagination (Kuhn *et al.*, 2006), action observation (Marceglia *et al.*, 2009) and emotional processing (Kuhn *et al.*, 2005a; Brucke *et al.*, 2007; Huebl *et al.*, 2011). A modified oddball paradigm with increased demand on executive function revealed an evoked potential in the STN which was modulated by repetitive transcranial magnetic stimulation (TMS) of the inferior-frontal cortex (Balaz *et al.*, 2008). Respective STN oscillatory activity showed alpha-beta desynchronization (8–20 Hz) in the oddball tasks with increased demand on executive function (Rektor *et al.*, 2010). In a complex visuomotor-cognitive task including planning, inhibition of automatic responses and mental inversion 7–14 and 16–30 Hz modulation of alpha-beta was observed in the STN (Rektor *et al.*, 2009). During conflict decision, low frequency alpha-theta (5–13 Hz) STN-modulation was reported (Fumagalli *et al.*, 2011). When it comes to language processing, recordings from the thalamus showed ERP changes, reflecting the processing of syntactic and semantic language violations (Wahl *et al.*, 2008) and first STN-LFP recordings suggest gamma changes associated with verbal fluency (Anzak *et al.*, 2011). However, there is lack of evidence for the lower frequency range and its presumed network. In this study, our main finding was a task-dependent significant local alpha-theta activity increase between 6 and 12 Hz (peak around 8 Hz) and coherence increase to surface EEG between 6 and 7 Hz. We also found activity in higher frequencies up to the gamma range, but it has to be noted that this activity revealed no significant time locked task-specific modulation, as it was the case for alpha-theta. Irrespective of the used task gamma activity was expected, especially due to the used dopaminergic ON-state (Alegre *et al.*, 2010; Lopez-Azcarate *et al.*, 2010). Minimal gamma and beta-modulation during active speech phase was also not significant in our data although this was reported before (Anzak *et al.*,2011; Hebb *et al.*, 2012). It should be taken into consideration that a lack of power changes in the beta frequency may be due to a selection of bipolar pairs that are representative of alpha-theta modulation and not beta modulation. Our results reveal mild changes in beta activity that did not differ significantly between both tasks. It should be noted, that our main analysis focused on the test interval, during the cognitive epoch of the task. As cited in our introduction and found in previous studies, mainly theta and alpha oscillations are revealed during such cognitive processes. Additionally, as a further control, beta activity during baseline was compared to the active speech component of the trial. For beta, a minimal desynchronization during the active speech component could be observed, but failed to reach significance. This might be due to an analysis not timed precisely to the time epoch of speech onset and termination. It should also be noted, that for beta modulation, the window for the analysis of beta changes for a single word might have been too wide.

Previous studies focusing on limb motor control have manly revealed basal ganglia oscillations in the beta and gamma range (Brittain & Brown, 2014). Theta and alpha oscillations have been associated with ongoing cognitive processes such as verbal generation, as cited in our introduction.

As we aimed at studying a cognitive process underlying a verbal generation task, we specifically employed a paradigm rendering LFP recordings free from speech and movement artifacts. This paradigm has already been used in previous electrophysiological studies examining word processing and generation (Snyder *et al.*, 1995; Rowan *et al.*, 2004; Dalal *et al.*, 2009). The analysis of the test interval free of movement revealed results in line with previous studies, depicting a role of theta and alpha oscillations during verbal control. Additionally, analysis of the overt speech production epoch revealed beta desynchronization, as expected by previous findings in literature.

Generally, theta oscillations found dominantly in our data reflect working memory functions and alpha oscillations play a role in long-term memory and transient reactivation of long-term memory codes during short-term storage (Klimesch *et al.*, 2005). Additionally, theta oscillations can particularly be observed at frontal sites when subjects maintain focussed attention by concentrating on a task during an extended period of time (Klimesch *et al.*, 2005).

All these components are crucial in our VG task and thus alpha-theta activation is consistently found in our recording. Furthermore, we found mean coherence to surface recording in the theta range, which reflects the idea, that long-range synchronization is a functional role of theta oscillations. On the other hand, local LFP power increase was more prominent in the alpha range. Alpha oscillations have been thought to reflect idling inhibition of task irrelevant areas, but recent models propose that alpha rhythmicity plays an active role in attention and consciousness (Palva & Palva, 2007). In

contrast, beta-band oscillations might reflect a deterioration of flexible behavioural and cognitive control (Engel & Fries, 2010). The idea of theta communication of the STN with cortical areas would correspond well with the 'systems oscillators theory' proposed for the role of the basal ganglia for speech and language: articulation and phoneme are represented by a higher frequency than words and sentences which are organized as packets over a slower frequency. The frequency of oscillations in the basal-ganglia-thalamo-cortical loop is given by the number of connection nodes, represented in anatomical structures. In this model the STN is in a side loop with a specific go/no-go gating function of the indirect and hyperdirect pathway (Montgomery, 2008). As an experimental base for that model STN microelectrode recording showed a modulation of bursting activity during the generation of meaningful speech utterances in sentence repetition compared to meaningless syllable repetitions (Watson & Montgomery, 2006). Current findings further support this model of a go/no-go gating instance of the STN by revealing oscillatory theta activity in decision processes (Cavanagh *et al.*, 2011). These findings correspond well with our recordings suggesting that the STN has oscillatory alpha-theta signature in gating speech execution.

Clinical relevance of STN-stimulation for speech

This study provides evidence for regions in the STN relevant for executive speech functions. We found a significant correlation of VG performance with low-frequency oscillation increase in the STN, thus improvement in VF during LFS might be explained by enhancement of this predominant frequency. However, LFS can lead to detoriation of motor functions (Timmermann *et al.*, 2004). The findings can be relevant for future stimulation patterns to improve cognitive-motor outcome. New approaches of modelling volume of tissue activated showed – congruent with our recordings – that ventral contacts result in more tissue activation associated with affection on VF performance (Mikos *et al.*, 2011). This should be regarded especially for the programming of the lower contacts. Modelling stimulation parameters can lead to improved cognitive-motor outcome (Frankemolle *et al.*, 2010). Taking into account information about frequency domains in executive functions derived by the current study, one can anticipate that advanced frequency programming (e.g. with special local low frequency interleaving modes on lower electrodes) might further help to improve clinical outcome.

Disclosure

LW, JV and AS have received – unrelated to the current project – honoraria in the past from Medtronic and St. Jude Medical and Boston Scientific, companies that manufacture DBS hardware. The authors thank the patients for their excellent cooperation.

Acknowledgements

This work was supported by the Research Commission (′Forschungskommission′) of the Medical Faculty of the Heinrich-Heine University Duesseldorf and by BMBF/ERANET Neuron Grant 'TYMON' (01EW1411) to LW.

Abbreviations

c, channel; CS, cross spectrum; CT, computed tomography; DBS, deep brain stimulation; EEG, electroencephalography; ERP, event-related potential; f, frequency; FFT, Fast-Fourier Transformation; HFS, high-frequency deep brain stimulation; Hz, Hertz; i, index number of segment; LFP, local field potentials; LFS, low-frequency alpha-theta-stimulation; MCP, mid-commissural point; MDRS, Mattis Dementia Rating Scale; MER, microelectrode recordings; mm, millimetre; MRI, magnetic resonance imaging; PD, Parkinson's disease; STN, subthalamic nucleus; SWA, Schaltenbrand-Wahren-Atlas; TMS, transcranial magnetic stimulation; UPDRS, Unified Parkinson's Disease Rating Scale; VF, verbal fluency; VG, verbal generation.

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NEUROCASE
2011, 17 (6), 527–532

Psychology Press
Taylor & Francis Group

Long-term time course of affective lability after subthalamic deep brain stimulation electrode implantation

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The mechanism and time course of emotional side effects of subthalamic deep brain stimulation in Parkinson's disease are a matter for discussion. We report a 53-month follow-up of a patient with affective lability. Postoperative lesion plus bilateral stimulation strongly influenced mood in the first week in terms of laughing behavior, while voltage changes had only minor long-term impact up to 37 months on negative emotion, possibly caused by the right electrode stimulating the subthalamic nucleus and adjacent fiber tracts involving the internal capsule. Thus we conclude that affective lability can occur with different temporal dynamics of microlesion, and early and chronic stimulation.

Keywords: Deep brain stimulation; Parkinson's disease; Subthalamic nucleus; Affective lability; Voltage; Lesion; Long-term; Emotion.

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) improves quality of life in Parkinson's disease (PD) and does not reduce overall cognition and emotional function (Smeding et al., 2006; Witt et al., 2008). However, there are reports of side effects ranging from mania to depression (Bejjani et al., 1999; Herzog et al., 2003; Krack et al., 2001). STN–DBS might lead to emotional lability (Smeding et al., 2006) and in the first year risk of suicide seems to increase (Voon et al., 2008). The STN is known to be a central modulatory station of basal ganglia-thalamocortical loops that regulate movements, behavior, and emotions. It is thought that dopaminergic and electrical stimulation of limbic circuits underlie synergistically the development of impulsivity and mania, whereas depression might reflect hypodopaminergic states (Volkmann, Daniels, & Witt, 2010). Thus, medication (Funkiewiez et al., 2006) as well as stimulation parameters (Herzog et al., 2003; Krack et al., 2001) and electrode localization (Bejjani et al., 1999) can have an impact on emotional side effects of STN stimulation. We report a case showing amplitude-dependent laughing and crying

The authors thank the patient for his excellent cooperation.
Funding: Lars Wojtecki was supported by a grant of the 'Forschungskommission' of the Medical Faculty HHU Düsseldorf.
Supplementary data (MP4 video) published online alongside this article at www.psypress.com/neurocase
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http://www.psypress.com/neurocase http://dx.doi.org/10.1080/13554794.2010.547507

a few days after STN–DBS surgery that changed over the course of 5 years illustrating the temporal dynamics of micro-lesion and stimulation on mood.

CASE REPORT

Operative procedure and clinical data

A 69-year-old patient was selected for STN–DBS of medically refractory tremor-dominant PD. He had no former history of cognitive impairment or psychiatric disease. In the recent history before DBS he revealed slight dopaminergic-induced visual hallucinations. Thus, 400 mg L-Dopa and 12 mg Ropinirol were supplemented by 25–100 mg Clozapine preoperatively resulting in a stable clinical psychiatric condition. In a preoperative baseline screening for cognitive and emotional function he scored normal in the Mattis Dementia Rating Scale (MDRS, 139 points), Becks Depression Inventory (BDI, 3 points), Hamilton Depression Scale (HAMD, 2 points), Mania Self Rating Scale (MSS, 0 points) and Bech Rafaelsen Mania Scale (BRMAS, 0 points.) Electrode localization was planned on stereotactic CT and MR image fusion and placement was determined by macrostimulation effects. Two days postoperatively the patient presented mirthful laughter when stimulated on medication bilaterally with 3.5 Volts (V), 60 microseconds (μs), 130 Hertz (Hz), contacts 0/1 negative, impulse generator (IPG) positive (see Table 1). He laughed at trivial things, told jokes and laughter was contagious while good suppression of tremor was obtained. In this period the BRMAS was transiently increased to 12 points. When the generator was deactivated the tremor recurred after a few seconds and the patient fell into depressed mood and started crying (see Supplementary online video). One week later stimulation effects were tested in more detail in a medical-OFF state at each contact up to 5 V. Only when stimulating the left electrode above 2.5 V on contacts 0 and 1 the patient reported a slight euphoric feeling. However, laughing or strong emotions as in the first session were not induced. When stimulating the upper right electrode above 4.5 or 5.0 V, limb and face contractions as signs of stimulation of the internal capsule were observed. The patient was discharged 10 days later with 2.0 V for the left and 2.1 V for the right hemisphere (both 60 μs, 130 Hz, contact 1 negative, IPG positive) with a good effect on motor symptoms and no emotional side effects. Medication was reduced to 200 mg L-Dopa and 25 mg Clozapine. Because the patient stated that the emotional changes had scared him, lorazepame had been prescribed transiently (1 mg/day) beginning at the fourth day postoperatively for 2 weeks. Scores for depression and mania were repeated five times within the first 3 months and were normal. Over the course of 53 months the patient was seen several times for follow-up. Stimulation of the left hemisphere was kept constant on contact 1, right-sided monopolar stimulation was changed from contact 1 to 2 and 3 in order to obtain best effects on tremor and other motor symptoms. Laughing could not be induced again during various programming sessions testing all contacts with stimulation amplitudes up to 5 V. However, sad emotions and crying could be induced again 9 and 37 months after implantation by rapid amplitude increase up to 5.5 V or abrupt turning off and switching on and vice versa of the right-sided electrode using contacts 2 and 3.

Postoperative electrode localization

Stereotactic postoperative X-rays were re-imported into stereotactic planning system. Coordinates of all contacts were normalized and visualized on corresponding axial slices of the Schaltenbrand and Wahren brain atlas (SWA). Coordinates of the plastic electrode tip were calculated to determine the most ventral localization of the microlesion effect (Figure 1). Coordinates of the electrodes were the following (x, y, z): left: contact 0: −13.1, −2.9, −3.6, contact 1: −13.8, −1.2, −2.0, contact 2: −14.6, 0.5, −0.4, contact 3: −15.3, 2.2, 1.2, right: contact 0: 13.2, −2.4, −5.3, contact 1: 13.9, −1.0, −3.5, contact 2: 14.5, 0.5, −1.6, contact 3: 15.2, 2.0, 0.2. Left-sided activated contacts were clearly positioned in the STN. Right-sided contacts that were activated in the beginning were located in the STN, whereas later activated contacts were located at the dorsal-anterior border and adjacent fiber tracts involving the internal capsule. The right electrode was located more ventral but the ventral plastic electrode tip of both sides was located medial-ventrally of the STN in the border zone to the substantia nigra (SN). Repeated cranial CT scans 4 days, 12 days, and 9 months after surgery showed no dislocation of the electrodes or any other structural brain alterations.

TABLE 1
Mood changes induced by deep brain stimulation settings

Time point	*Event*	*Induced emotion*	*Contact left*	*Amplitude threshold (V) left*	*Pulse width (μs) left*	*Frequency (Hz) left*	*Contact right*	*Amplitude threshold (V) right*	*Pulse width (μs) right*	*Frequency (Hz) right*
2 days postop	Admission to Neurology Med On/Stim On	Affective lability with laughing in Stim On and crying in Stim Off (see Supplementary online video)	0−1−C+	3.5	60	130	0−1−C+	3.5	60	130
7 days postop	Detailed contact test Med Off	Euphoric feeling	0−C+	2.5–3.5	60	130				
		Euphoric feeling	1−C+	2.5–3.5	60	130				
		No emotional change but pseudodystonic contraction left face/hand					1−C+/2−C+/3−C+	4.5–5	60	130
19 days postop	Discharge from hospital		1−C+	2.0	60	130	1−C+	2.1	60	130
3 months postop	Routine control, no adverse events		1−C+	3.0	60	180	1−C+	3.6	60	180
9 months postop	Routine control, no adverse events		1−C+	2.8	60	180	2−3−C+	3.5	60	180
	Stim ON/OFF test for boths hemispheres separately	Crying after turning On and OFF the right hemisphere					2−3−C+	3.5	60	180
17 months postop	Routine control, no adverse events		1−C+	2.0	60	180	2−3−C+	3.0	60	180
37 months postop	Detailed contact test	Affective lability when activiting or deactivating contact 2 or 3					2−(3−)C+	<5.5	60	130
53 months postop	Routine control, no adverse events		1−C+	4.0	60	180	2−C+	4.0	60	180

Listed are inpatient events and settings that led to affective changes. Various outpatient programming sessions to optimize tremor effects and settings without any emotional side effects are not listed. Amplitude thresholds: stimulation with this or above this value induced affective changes. Amplitude in V, Volts; Pulse with in μs, microseconds; Frequency in Hz, Hertz; C, Case/Impulse Generator.

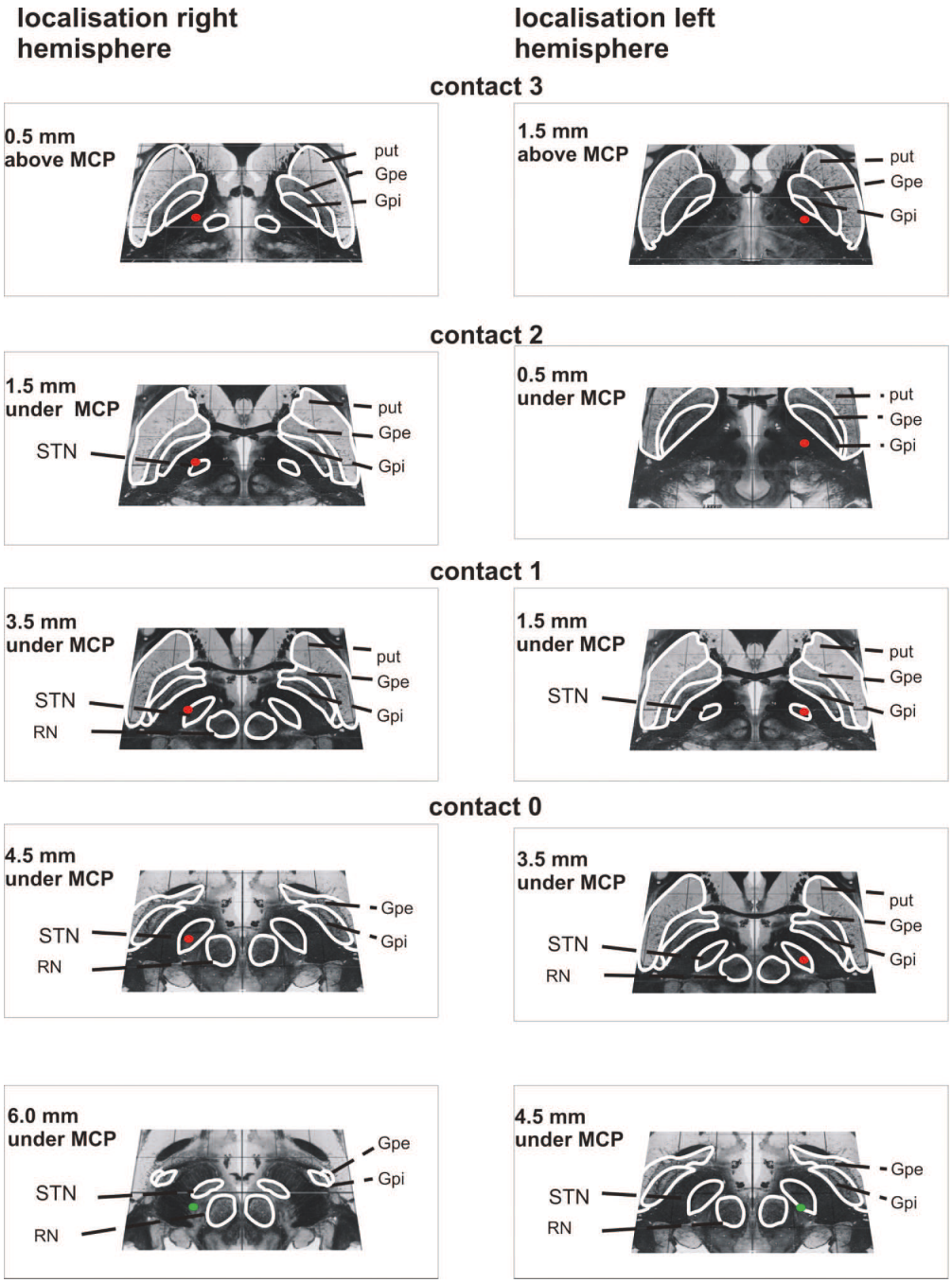

Figure 1. Contacts (red dots in online colour figure) and ventral plastic end (green dots in online colour figure, bottom line) on axial SWA slices corresponding to the determined coordinates. Abbreviations: STN, Subthalamic nucleus; RN, Red Nucleus; Gpe, Globus pallidus externus; Gpi, Globus pallidus internus; put, Putamen. [To view this figure in colour. Please visit the online version of this Journal.]

DISCUSSION

We present long-term follow-up of a PD patient with affective lability after subthalamic electrode implantation for DBS. Our findings in this case were the following: (1) strong emotional effects by stimulation were only found transiently after the operation and (2) only slight negative emotions could be induced up to 37 months after surgery by voltage variations of the right electrode contacts located in the STN and nearby adjacent fiber tracts involving the internal capsule. This case supplements knowledge from literature with interesting aspects concerning the long-term time course of the microlesion and stimulation effect on emotional side effects.

Time course and the role of the lesion effect

It is known that STN lesions can have a major impact on symptoms as mania (Romito et al., 2002). These mood changes are generally attributed to the fact that the STN receives input from the anterior cingulate cortex. While lesions can show a prolonged effect on cognition it seems to affect mood only transiently (Okun et al., 2009). It is known that mania or hypomania is almost exclusively observed during the first postoperative weeks (Volkmann, Daniels, & Witt, 2010). Up to date long-term follow-up of strong affective side effects are not well described, but the fact that initially increased risk of suicide seems to decrease over 4 years (Voon et al., 2008) might be one correlate of diminishing emotional side effects. The decrease of affective lability is in line with our findings and we think that it can be explained in part by the decreasing lesions effect. However, when it comes to the interpretation of long-term emotional adaption it is known that the time course of habituation of stimulation side effects can vary from minutes to months (Kulisevsky et al., 2002; Springer et al., 2006; Tommasi et al., 2008). Thus, besides a decreasing lesion effect adaptive changes in the brain during stimulation have to be taken into account. Furthermore, medication changes and disease progression have to be discussed. However, postoperative dopaminergic decrease and lack of changes in psychiatric scores over the course of months do not support these underlying causes for transient mania in our patient.

Stimulation effects

Additionally to the microlesion effect strong bilateral stimulation of lower contacts was needed to induce laughing in our patient. It is known that especially high amplitude or pulse width or bilateral stimulation can cause affective changes either by effecting the STN itself (Wojtecki et al., 2007), the SN (Bejjani et al., 1999; Kulisevsky et al., 2002; Ulla et al., 2006), or possibly also by affection of structures nearby the STN like the median forebrain bundle or the lateral hypothalamus (Coenen et al., 2009; Krack et al., 2001). Interestingly, when affecting the internal capsule, DBS can furthermore worsen mood or anxiety and cause panic and fear (Low, Sayer, & Honey, 2008; Okun et al., 2004, 2007; Shapira et al., 2006).

We think that long-term induction of negative emotions in our case can possibly be attributed to stimulation of the internal capsule for the following reasons. In long-term observation sadness and crying were only evoked by stimulating the upper right electrode. These contacts were positioned in the STN and adjacent fiber tracts involving the internal capsule. Furthermore, in the first contact test session 1 week postoperatively, stimulation of these electrodes above 4.5–5 V led to limb contraction as signs of capsular stimulation. We propose that due to an overlay of the strong lesion effect in the opposite emotional direction no negative emotions could be induced by right-sided stimulation at this early time point. Transient medication with lorazepam might have had an additional neutralizing effect on negative emotions in the first 2 weeks after the operation. This medication had been stopped at the later time point when first negative emotions could be induced by right-sided stimulation.

Summing up, the present case gives insights into the time course of affective lability after DBS surgery depending on lesion effect and stimulation voltage. High amplitude stimulation at the time point of the microlesion effect can transiently lead to strong affective changes, whereas stimulation amplitude manipulations after diminishing of the microlesion effect and with chronic adaption to stimulation only induce minor negative emotions over the time course of about 3 years and habituate in the long-term follow-up of about 5 years. This illustrates in one single case different temporal dynamics of lesion, and early and chronic stimulation.

Supplementary data (MP4 video) published online alongside this article at www.psypress.com/neurocase

Original manuscript received 15 July 2010
Revised manuscript accepted 4 November 2010
First published online 6 July 2011

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Clinical Neurophysiology 129 (2018) 79–88

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Human subthalamic oscillatory dynamics following somatosensory stimulation

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ARTICLE INFO

Article history:
Accepted 4 October 2017
Available online 28 October 2017

Keywords:
Subthalamic nucleus
Local field potential
Oscillations
Somatosensory stimulation
160 Hz oscillations

HIGHLIGHTS

- STN oscillatory activity following somatosensory stimulation is similar to cortical oscillations.
- Recordings also revealed unique previously unknown oscillatory activity in the 160 Hz range.
- Recorded oscillatory patterns reflect the processing of somatosensory information in the STN.

ABSTRACT

Objective: Electrical median nerve somatosensory stimulation leads to a distinct modulation of cortical oscillations. Initial high frequency and gamma augmentation, as well as modulation of beta and alpha oscillations have been reported. We aimed at investigating the involvement of the subthalamic nucleus in somatosensory processing by means of local field potential recordings, since recordings during passive movements and peripheral somatosensory stimulation have suggested a prominent role.
Methods: Recordings of subthalamic neuronal activity following median nerve stimulation in 11 Parkinson's disease patients were performed. Time-frequency analysis from 1 to 500 Hz was averaged and analyzed.
Results: Several oscillatory components in response to somatosensory stimulation were revealed in the time-frequency analysis: (I) prolonged increase in alpha band power, followed by attenuation; (II) initial suppression of power followed by a subsequent rebound in the beta band; (III) early broad-frequency increase in gamma band power; (IV) and sustained increase of 160 Hz frequency oscillations throughout the trial.
Conclusions: These results further corroborate the involvement of the subthalamic nucleus in somatosensory processing.
Significance: The present results not only support the notion of somatosensory processing in the subthalamic nucleus. Moreover, an improvement of somatosensory processing during subthalamic deep brain stimulation in Parkinson's disease might be accounted for by enhancement of prevailing high frequency oscillations.

1. Introduction

The functional significance of neural oscillations in somatosensory and motor control has been of growing interest in the last years. Specific frequency changes can be elicited both during voluntary (Pfurtscheller and Aranibar, 1977; Salenius et al., 1997) and passive movements (Alegre et al., 2002; Cassim et al., 2001), as well as due to somatosensory stimulation (Hari and Forss, 1999). Besides focusing on sensorimotor mu and beta rhythms the investigation of gamma and high-frequency (>100 Hz) oscillations has gained increasing interest. Oscillatory synchronization is essential for local information processing and the transfer of information within neuronal networks (Schnitzler and Gross, 2005; Singer, 1999; Varela et al., 2001). Within sensory systems gamma band activity has a functional role in perceptual binding

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https://doi.org/10.1016/j.clinph.2017.10.015
1388-2457/

of multiple inputs (Engel et al., 2001) and of functional coupling in distributed cortical networks serving perceptual processes (Tallon-Baudry and Bertrand, 1999). Sensorimotor rhythms have been implied to serve the same role within the motor and somatosensory systems (Marsden et al., 2000; McAuley and Marsden, 2000).

As described by previous studies (Dockstader et al., 2010; Hari et al., 1984; Della Penna et al., 2004; Tiihonen et al., 1989), in the primary somatosensory cortex (SI) a phase-locked (evoked) event-related potential or field follows somatosensory stimulation. Furthermore, synchrony of endogenous oscillations can be modified by this stimulation; generating either a non-phase-locked (induced) event-related desynchronization (ERD) or event-related synchronization (ERS) of oscillations. In response to an external event, transmission of information between brain areas is believed to be represented by evoked activities. On the other hand, induced activities alter a networks sensitivity to external events and are suggested to represent top-down processes (Klimesch et al., 2007; Pineda, 2005).

Studies of median nerve stimulation evoked potentials have revealed that a complex somatosensory cortical network is engaged (Hari and Forss, 1999). The first activation peaks contralateral at about 20 ms (N20) in the area 3b of SI and continues up to 100 ms. Activation of the second somatosensory cortex (SII) usually follows at 60–70 ms up to 200 ms (contralateral SII before ipsilateral SII). Since there are bilateral receptive fields in SII neurons there is a bilateral activation after unilateral stimulation. Still, a faster and stronger response in SII can be recorded following contralateral stimulation compared to ipsilateral stimulation. Cutaneous input is transferred via SII to the motor cortex (Burton, 1986). Median nerve stimulation not only leads to an evoked response in the somatosensory cortex, but also induces a beta ERS in the motor cortex. This ERS can be recorded within 1 s after stimulation in the contralateral hand sensorimotor cortex, after a preceding short lasting ERD immediately after stimulation (Salenius et al., 1997; Salmelin and Hari, 1994). Moreover, EEG and MEG recordings revealed increased beta oscillations after somatosensory stimulation of upper extremities (Cassim et al., 2001; Houdayer et al., 2006; Neuper and Pfurtscheller, 2001) as well as a decrease in alpha- and beta oscillations (Dockstader et al., 2008; Palva et al., 2005; Pfurtscheller, 1989) in the contralateral rolandic area. Fukuda et al. (2008) showed that stimulation of the median nerve increased 100–250 Hz oscillations within 20 ms following stimulation in the contralateral SI. At 25 ms these oscillations gradually slowed down in frequency to 30–100 Hz in the contralateral rolandic area. This 30–100 Hz activity further shifted into an increase of beta and alpha activity (Fukuda et al., 2010). Similar cortical patterns were found by Dockstader et al. (2010). Due to the temporal course of amplitude changes it is assumed that this somatosensory related gamma augmentation reflects the primary cortical processing of the applied stimuli. Alpha and beta oscillations following somatosensory stimulation presumably reflect a different stage of somatosensory processing occurring after cortical processing (Fukuda et al., 2008). Furthermore, previous EEG recordings revealed that a median-nerve evoked potential trace includes oscillations from 30 to 100 Hz (Chen and Herrmann, 2001), 100–250 Hz (Buchner et al., 1995) and above (Curio et al., 1994).

The response to peripheral somatosensory stimulation on a subcortical level has not been well addressed. However, within the subthalamic nucleus (STN) a response to passive movements and peripheral stimulation can be recorded, suggesting a role in somatosensory processing (DeLong et al., 1985; Hammond et al., 1978; Klostermann, 2003; Pesenti et al., 2003; Wichmann et al., 1994). It is an acknowledged fact, that sensory information is transferred to motor networks and thus exerts an essential role in movement control. The basal ganglia have been suggested to act as a sensory analyzer for the motor system, processing sensory information in a way relevant for movement (Pesenti et al., 2003). Due to its subdivision into different territories with different connections an involvement of the STN in motor functions, associative, limbic and somatosensory networks is assumed (Benarroch, 2008). Human and primate studies have identified the dorsolateral two thirds of the STN as the sensorimotor region (Rodriguez-Oroz et al., 2001; Wichmann et al., 1994). Owing to its key role in the basal ganglia-thalamocortical motor circuit the STN also serves as the targeted nucleus for deep brain stimulation (DBS) in advanced Parkinson's disease (PD) (Deuschl et al., 2006; Weaver et al., 2009). PD patients, besides displaying the characteristic motor signs, also have numerous somatosensory deficits (Kaji et al., 2005; Klockgether et al., 1995; Sathian et al., 1997; Schneider et al., 1986). A pathological communication between the basal ganglia and the sensory systems has been held accountable for the sensory deficits in PD (Schwarz et al., 1992). These somatosensory abnormalities can be restored, at least in part, by levodopa or apomorphine intake (De Mari et al., 1995; Rossini et al., 1993) and by STN DBS (Herzog et al., 2008; Maschke et al., 2005; Shivitz et al., 2006). STN DBS could therefore alter the information processing within somatosensory networks and partially restore basal ganglia function.

The aim of the current study was to characterize the impact of somatosensory stimulation on the rhythmic oscillatory STN activity by means of postoperative local field potential (LFP) recordings in PD patients.

2. Materials and methods

2.1. Patients and surgery

11 PD patients (22 STNs; 4 female, 7 male; age 61.2 ± 4.8 years) with mean disease duration of 11.6 years (±5.0 years) at time point of surgery had deep brain electrodes implanted bilaterally in the STN and were enrolled in the present study. Only patients displaying normal early somatosensory evoked potentials to median nerve stimulation (N20) and without cognitive impairment (Mattis Dementia Rating Scale (MDRS, (Mattis, 1988)) score 139.8 ± 2.9 points) during presurgical clinical evaluation were included in the study. Table 1 displays the clinical details.

Patients were bilaterally implanted in the STN at the Department of Stereotactic and Functional Neurosurgery of the Heinrich-Heine-University Hospital Düsseldorf. The STN location was determined based on coordinates of the Schatenbrand-Wahren-Atlas (SWA) (Schaltenbrand and Wahren, 1977) and fusion of stereotactic cranial computed tomography (CT) and stereotactic high resolution magnetic resonance imaging (MRI). The STN borders and optimal implantation area were defined by multiunit microelectrode recordings (INOMED MER; INOMED Corp., Emmendingen, Germany) with up to five concentrically configured electrodes. Recordings of single cell activity, stimulation and side effects yielded the final placement of the DBS electrode (electrode model 3389, Medtronic Corporation, Minneapolis, MN, USA). The DBS macroelectrodes were connected to externalized extension wires (model 3550-05, Medtronic) and could postoperatively be connected to EEG amplifiers. To ensure correct electrode placement postoperative CT scans were performed in all patients. Fusion of postoperative stereotactic CT and individual preoperative stereotactic MRI scans rendered the anatomical location of the individual contacts on the final DBS electrode.

2.2. Postoperative median nerve stimulation paradigm

Written informed consent was provided by all patients and the local ethics committee of the medical faculty of the Heinrich-Heine

Table 1
Clinical characteristics of PD patients.

ID	Gender	Age	Disease Duration	PD Medication	Disease Type	Predominant Side	MDRS	Motor UPDRS		Right Median Nerve		Left Median Nerve	
			(years)	(LED mg/day)				OFF	ON	ms	μV	ms	μV
1	Male	62	16	750	AR	Left	142	36	11	22.1	3.2	21.4	4.6
2	Male	55	5	900	Tremor	Right	141	33	13	20.5	2.1	21.90	2.0
3	Female	62	10	200	AR	Left	141	35	13	21.1	2.1	20.7	2.4
4	Male	57	8	400	Tremor	Left	139	31	15	20.3	2.3	20.5	2.0
5	Male	62	8	625	Tremor	Left	143	49	26	19.8	3.1	19.9	2.9
6	Female	55	15	1001	AR	Left	133	45	21	19.7	4.6	19.7	4.8
7	Male	64	11	1300	AR	Right	141	35	19	21.9	3.1	22.1	3.0
8	Male	72	14	700	Tremor	Right	139	33	8	20.9	1.6	20.6	1.3
9	Male	60	15	300	AR	Right	143	35	4	21.4	2.0	20.9	1.8
10	Female	64	21	200	Tremor	Left	138	32	12	21.0	4.7	20.9	2.8
11	Female	60	5	200	Equivalent	Right	138	14	7	19.7	9.5	20.4	8.7
Mean		61.2	11.6	597.8			139.8	34.4	13.5	20.8	3.5	20.8	3.3
SEM		1.5	1.5	112.2			0.9	2.6	1.9	0.3	0.7	0.2	0.6

Clinical characteristics of PD patients, including averages and standard errors of mean (SEM). Abbreviations: LED: levodopa equivalent dose, AR: akinetic-rigid subtype, MDRS: Mattis Dementia Rating Scale, UPDRS: Unified Parkinson's Disease Rating Scale Motor Part. Right and left median nerve: presurgical clinical evaluation including latency (ms) and amplitude (μV).

University Duesseldorf approved the study in accordance to the Declaration of Helsinki (1967) (World Medical Association). Recordings were performed on the postoperative day. All patients were examined with their usual antiparkinsonian medication. The medication ON state was chosen as we aimed at examining the activity of the subthalamic nucleus during the median nerve stimulation task in an as normal state as possible. None of the patients showed tremor or levodopa-induced dyskinesias during the experimental session. During the experiment patients comfortably sat in their bed and were carefully instructed no to move to achieve complete muscle relaxation. Furthermore, to avoid movement artefacts the investigators controlled for movements visually during the sessions.

The experimental protocol consisted of repetitive non-painful electrical median nerve stimulation using the Osiris constant-current stimulator (Osiris Neurostimulator, Inomed Corp., Emmendingen Germany). Alternating contralateral and ipsilateral cutaneous median nerve stimulation at both wrists with constant-current square wave pulses of 200 μs, an interstimulus interval of 3000 ms and a current intensity adjusted individually just above the motor threshold was applied. A total of 200 stimuli per side were delivered over approximately 12 min. During stimulation a persistent, passive twitching of the thenar muscle was documented. Additionally 5 min of resting activity were recorded while the patients remained still with eyes open.

2.3. LFP post-operative recordings

LFPs were recorded during median nerve stimulation from the four micro–macroelectrode contacts labelled 0, 1, 2, 3 (1.27 mm circumference; 1.5 mm length and a distance of 0.5 mm between contacts) against a monopolar frontal surface reference. Amplified signals were sampled at 5 kHz, band-pass filtered from 0.5 to 2000 Hz and monitored online using a portable amplifier (BrainVision Recorder, BrainAmp MR plus, Brain Products GmbH, Munich, Germany, Version: 1.03), which was synchronized with the Osiris constant-current stimulator (Osiris Neurostimulator, Inomed Corp., Emmendingen Germany).

2.4. Offline analysis

Data analysis was performed with the BrainVision Analyzer software (Brain Products GmbH, Munich, Germany, Version: 2.0). The LFP signals underwent visual inspection and sections containing noise, movement or eye blink artefacts were rejected from further analysis. The four DBS-electrode contacts were rereferenced against the adjacent contact, yielding three bipolar derivations for each hemisphere (0–1, 1–2 and 2–3). Signals corresponding to each bipolar contact were divided into segments of 1100 ms duration, beginning 100 ms prior to stimulus onset (baseline period) to 1000 ms after stimulation onset. The segments were further baseline corrected.

2.4.1. Analysis of local field potential oscillatory activity

To identify LFP oscillatory activity (short lasting changes in LFP frequency spectra) at relevant frequency bands during pre- and post- median nerve stimulation onset, time-frequency representations were gained by utilizing a continuous wavelet transform. In particular, we made use of the continuous Morlet wavelet and focused on a 1–500 Hz frequency window and a −100 to + 1000 ms time window relative to stimulus onset. Next, we calculated the averaged time-frequency representation across trials for each stimulation side, as this step favours the identification of non-phase-locked (induced) activity (Tallon-Baudry et al., 1996). Furthermore, to detect the possible presence of oscillatory activities in the basal condition we performed the same time-frequency analysis for induced activity with a continuous Morlet wavelet transformation for frequencies between 1 and 500 Hz and a time window from −100 to +1000 ms relative to stimulus onset *without* the baseline correction.

The time-frequency plots were used to visualize prominent oscillatory activity and to determine frequency bands of interest in the α-, β-, γ- and high frequency (>100 Hz) range (see Fig. 1).

2.4.2. Assessment of the on- and offset of somatosensory induced change of oscillatory activity

Furthermore, the time-frequency plots were used to determine the on- and offset of somatosensory induced oscillations. The onset of induced activity was defined as the peak of sustained α -, β -, γ - and high frequency (>100 Hz) range waves exceeding the baseline range. To identify the dynamics of subthalamic somatosensory induced oscillations all time-frequency plots of all bipolar contact pairs were screened and then narrowed down to 22 (11 patients with 2 contralateral median nerve stimulation each). All 22 stimulus-related averaged signals should clearly reveal the appearance of different patterns of oscillatory activity including α-, β-, γ- and high frequency bands. The source of the most pronounced response to somatosensory stimulation as obtained from the

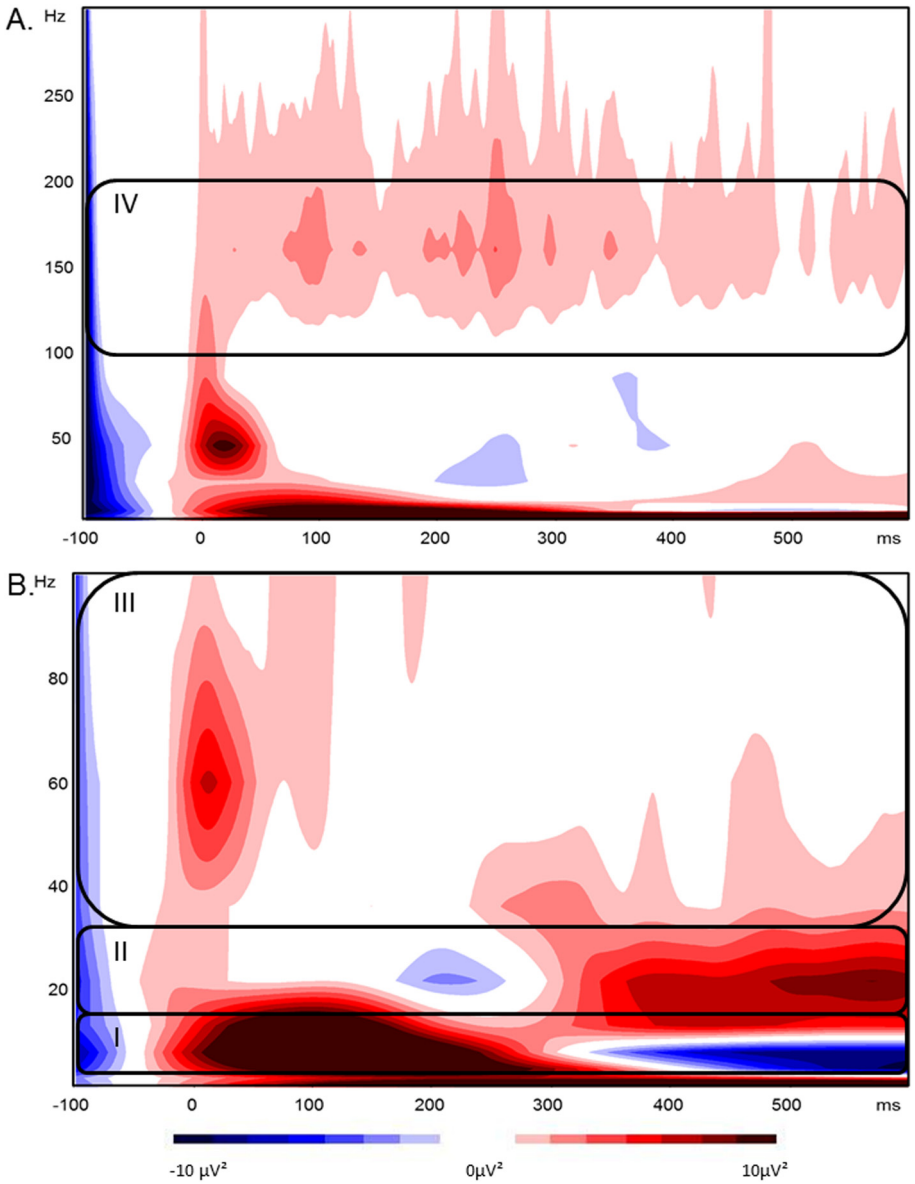

Fig. 1. Time-frequency representation of the grand average of all contralateral bipolar contacts used. Time-frequency representation of the grand average of all contralateral bipolar contacts used (n = 11 subjects, 22 subthalamic nuclei of the contralateral hemisphere). Fig. 1 A displays the power change in the frequency range 1–300 Hz, Fig. 1 B displays the power change in the frequency range 1–100 Hz. Power scale is shown in μV^2. In all figures red colour indicates a significant increase of amplitude and blue colour indicates a significant decrease of amplitude relative to the reference period. The stimulus-related averaged signals were generally characterized by following components for the specific frequency ranges: (I) a prolonged increase in alpha band power, followed by an attenuation (II) a suppression of power and subsequent rebound in the beta band in the mid and later stages of the trial and, (III) an early broad-frequency increase in gamma band power, (IV) and a sustained increase of 160 Hz frequency oscillations throughout the trial. We report the peak frequency and latency of detected power ERD and ERS derived from the wavelet based time–frequency analysis. However, it should be noted that the precise identification of onset and duration of frequency band power modulations in individual recordings is complicated due to the temporal smearing by the wavelet transform.

time-frequency plot averaged over all trials was identified for each individual and the respective contact pair displaying this response was chosen for all subsequent analysis.

2.4.3. Power analysis for high frequency oscillations

As time-frequency plots revealed a novel pattern of induced oscillations in the 160 Hz range (please refer to Results section) we sought to determine if these oscillations were physiological and present in the resting state. To check for power differences between the somatosensory induced oscillatory changes and the resting state activity in the 160 Hz range a Fast-Fourier-Transformation (FFT) was performed, transforming the LFP signal to the frequency domain. After bipolar referencing the data were segmented from 0 to 1000 ms, including only the period after median nerve stimulation. Using the FFT power spectra of this time window was obtained. The same procedure was applied to the rest activity. An average was performed over an equal number of segments (222 segments) to ensure comparability between the two conditions. For statistical comparison the power peak in the 160 Hz range was exported and then compared using a Wilcoxon test (GraphPad Software, La Jolla California, USA). At $p < .05$ differences were considered significant.

2.5. Statistical analysis

For statistical comparison of mean LFP power and the specific latency range between the reference and the post MNS onset periods in the considered frequency bands (α-band: 6–12 Hz, β-band:

13–32 Hz, γ-band: 30–100 Hz, high frequency-band: 100–220 Hz), we made use of the Wilcoxon test as the data violated assumptions of normality (Shapiro Will test). Concerning the defined frequency bands, it needs to be taken into consideration that i.e. individual α-frequency (IAF) can vary depending on age, disease, brain volume, cognition and task demands and may thus be defined as 2 Hz below or above IAF (Klimesch et al., 2005). Therefore, we widened our frequency bands and defined alpha as 6–12 Hz and beta as 13–32 Hz. All the statistical analysis was performed with GraphPadPrism 5 (GraphPad Software, La Jolla California, USA). The significance level was fixed at $p < .05$. Correction for multiple comparisons testing by means of Bonferroni correction yielded a significance level at $p < .0125$.

2.6. Recording location

To calculate the recording site the Schaltenbrand-Wahren-Atlas coordinates of the four DBS electrode contacts were determined by fusion of the individual postoperative stereotactic CT and the preoperative stereotactic planning software. Contact coordinates with reference to the midcommissural point were normalized and visualized on the stereotactic Schaltenbrand Atlas (Nowinski and Thirunavuukarasuu, 2004). Furthermore, to examine if the recorded activity was associated with the therapeutic stimulation we compared the contacts used for stimulation at 3 months after implantation with the contacts chosen for subsequent time-frequency analysis.

3. Results

3.1. Somatosensory induced changes in rhythmic oscillatory activity

Fig. 1 displays the time-frequency plot of the grand average of all contralateral bipolar contacts used for further analysis. In the 11 patients recorded, all 22 stimulus-related averaged signals clearly revealed the appearance of different patterns of oscillatory activity including α-, β-, γ- and high frequency bands. In the majority of cases this oscillatory pattern could only be detected on one of the three bipolar electrode pairs.

Somatosensory induced oscillations were generally characterized by following components for the specific frequency ranges:

For the α range (I) a contralateral increase in power (peak frequency: 10 Hz, SEM: 1 Hz, peak amplitude: 9.5 μV^2, SEM 2.1 μV^2) peaking at 137 ms (SEM 12 ms) with a latency of 35–388 ms significantly different from baseline activity ($p < .0001$) was detected and; (II) followed by an ERD (peak frequency: 10 Hz, SEM: 1 Hz, peak amplitude: −5.2 μV^2, SEM 1.6 μV^2) peaking at 552 ms (SEM 22 ms) with a latency of 312–609 ms significantly differing from baseline activity ($p < .0001$). Furthermore, (III) a slightly delayed (peak latency: 152 ms, SEM 19 ms, duration: 43–263 ms) ipsilateral increase in power (peak frequency: 9 Hz, SEM: 0.0 Hz, peak amplitude: 7.2 μV^2, SEM 1.4 μV^2) also significantly differing from baseline activity ($p < .0001$) (IV) was also followed by an ERD (peak frequency: 9 Hz, SEM: 0.0 Hz, peak amplitude: −2.5 μV^2, SEM 1.1 μV^2) peaking at 586 ms (SEM 28 ms) with a latency of 334–590 ms significantly differing from baseline activity ($p < .0001$) .

For the β range (I) an initial suppression of contralateral power (peak frequency: 20 Hz, SEM: 1.2 Hz, peak amplitude: −1.7 μV^2, SEM 0.5 μV^2) peaking at 220 ms (SEM 32 ms) differing significantly from baseline activity ($p < .0002$) was detected, followed by (II) a late contralateral increase in power (peak frequency: 20 Hz, SEM: 1 Hz, peak amplitude: 3.6 μV^2, SEM 0.5 μV^2) peaking at 556 ms (SEM 60 ms) with a latency of 309–600 ms significantly different from baseline activity ($p < .0001$). Moreover, (III) a slightly delayed ERD of ipsilateral power (peak frequency: 20 Hz, SEM: 1.2 Hz, peak amplitude: −0.6 μV^2, SEM 0.5 μV^2) peaking at 243 ms (SEM 35 ms) also significantly different from baseline power ($p < .002$) followed by (IV) an ERS (peak latency: 572 ms, SEM 43 ms, duration: 347–635 ms) ipsilateral increase in power (peak frequency: 20 Hz, SEM: 1 Hz, peak amplitude: 2.8 μV^2, SEM 0.5 μV^2) also significantly differing from baseline activity ($p < .0001$).

In the γ range (I) an early contralateral broad-frequency increase in power (peak frequency: 62 Hz, SEM: 1 Hz, peak amplitude: 7.9 μV^2, SEM 2.1 μV^2) peaking at 17 ms (SEM 4 ms) with a latency of 10–31 ms significantly different from baseline activity ($p < .0001$) was detected and (II) a slightly delayed (peak latency: 20 ms, SEM 2 ms, duration: 13–35 ms) ipsilateral increase in power (peak frequency: 62 Hz, SEM: 1 Hz, peak amplitude: 7.3 μV^2, SEM 2.1 μV^2) also significantly differing from baseline activity ($p < .0001$).

In the high-frequency range (I) a prominent contralateral increase in power (peak frequency: 157 Hz, SEM: 3 Hz, peak amplitude: 3.5 μV^2, SEM 0.5 μV^2) peaking at 219 ms (SEM 43 ms) with a duration of 48–648 ms significantly different from baseline activity ($p < .0001$) was detected and; (II) a slightly delayed (peak latency: 226 ms, SEM 27 ms, duration: 66–499 ms) ipsilateral increase in power (peak frequency: 160 Hz, SEM: 1 Hz, peak amplitude: 2.1 μV^2, SEM 0.3 μV^2) also significantly differing from baseline activity ($p < .0001$).

Table 2 displays an overview of the contralateral and ipsilateral results for the analyzed frequency bands.

Furthermore, the analysis without baseline correction also revealed this same pattern after somatosensory stimulation, but allowed the detection of high-frequency activity in the basal condition (Fig. 2). Statistical comparison between non-baseline corrected mean activity after somatosensory stimulation in the 160 Hz range and respective mean activity in the baseline period revealed a significant increase in 160 Hz activity after median nerve stimulation (contralateral $p < .0001$, ipsilateral $p < .0001$).

Power differences between the somatosensory induced oscillatory changes and the resting state activity in the 160 Hz range by means of FFT analysis were compared. The comparison between

Table 2
Contralateral and ipsilateral results for the frequency bands α, β, γ and 160 Hz.

	Contralateral recordings		Ipsilateral recordings	
α	ERS 10 Hz, 9.5 μV^2, 137 ms*	ERD 10 Hz, −5,2 μV^2, 552 ms*	ERS 9 Hz, 7.2 μV^2, 152 ms*	ERD 9 Hz, −2,5 μV^2, 586 ms*
β	ERD 20 Hz, −1.7 μV^2, 220 ms**	ERS 20 Hz, 3.6 μV^2, 556 ms*	ERD 20 Hz, −0.6 μV^2, 243 ms***	ERS 20 Hz, 2.8 μV^2, 572 ms*
γ	ERS 62 Hz, 7.9 μV^2, 17 ms*		ERS 62 Hz, 7.3 μV^2, 20 ms*	
160 Hz	ERS 157 Hz, 3.5 μV^2, 219 ms*		ERS 160 Hz, 2.1 μV^2, 226 ms*	

Time-frequency-plot results are provided as mean peak frequency (Hz), mean peak amplitude (μV^2) and mean peak latency (ms). ERS: Event-related synchronization, ERD: Event-related desynchronization.

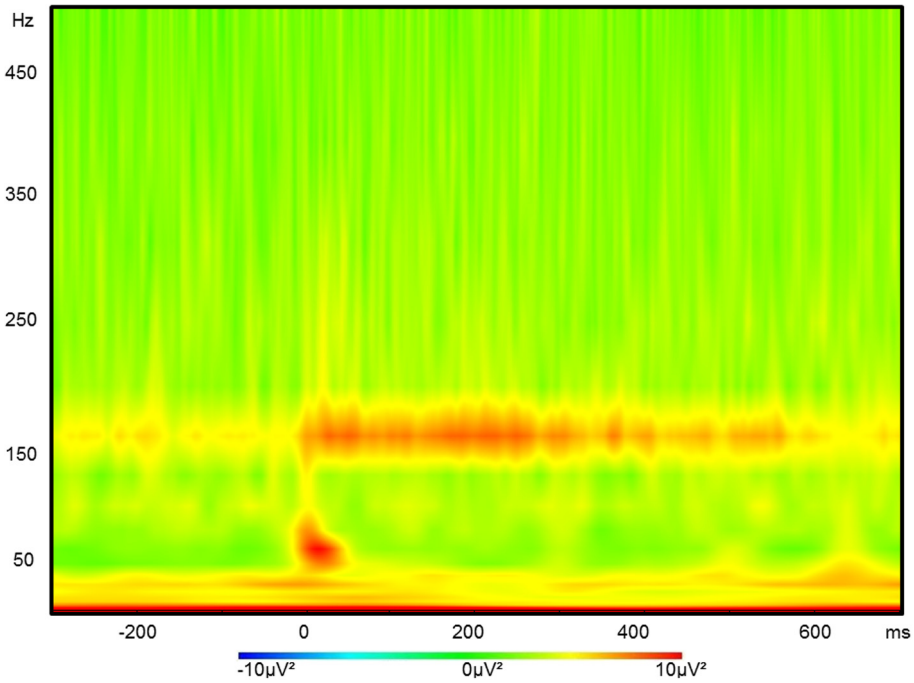

Fig. 2. Time-frequency representation of the grand average of all contralateral bipolar contacts used. Time-frequency representation of the grand average of all contralateral bipolar contacts used (n = 11 subjects, 22 subthalamic nuclei of the contralateral hemisphere) without baseline correction in the frequency range 1–500 Hz. Power scale is shown in μV^2. Red colour indicates a significant increase of amplitude and blue colour indicates a significant decrease of amplitude.

resting state activity (peak power: 0.003 μV^2, SEM 0.001 μV^2) and median nerve induced changes in oscillatory activity (peak power: 0.006 μV^2, SEM 0.001 μV^2) by means of FFT analysis also revealed a significant power increase in the 160 Hz range after median nerve stimulation ($p < .0212$).

Overall, several oscillatory components in response to somatosensory stimulation were revealed in the time-frequency analysis with pronounced contralateral compared to ipsilateral responses in the STN: (I) a prolonged alpha band augmentation, followed by an attenuation (II) an initial suppression in beta band power followed by a subsequent rebound, (III) an early gamma band augmentation, (IV) and a sustained increase of 160 Hz frequency oscillations throughout the trial.

3.2. Recording location

The majority (18) of all 22 bipolar contact pairs that showed strongest somatosensory frequency modulation and thus were used for further analysis recorded a field below or around contact 1 (0–1 or 1–2). The mean recording coordinates with reference to the midcommissural point of both hemispheres concurred with a location within the STN, involving dorsolateral sensorimotor subregions of the nucleus (coordinates in mm with standard error of mean: right hemisphere x = 11.1 ± 1.6, y = −3.9 ± 1.6, z = −2.9 ± 0.8 mm; left hemisphere x = −12.6 ± 1.1 mm, y = −1.8 ± 1.6 mm, z = −3.0 ± 1.8 mm) as depicted in Fig. 3. When comparing bipolar contact pairs displaying somatosensory induced modulations with the contacts used for stimulation at 3 months after implantation we found that 68% of contacts used for therapeutic stimulation coincided with the contacts displaying the 160 Hz oscillations.

4. Discussion

We examined the changes of subthalamic neural activity in response to somatosensory stimulation. Our major results indicate that (A) the STN is involved in somatosensory processing, (B) the dynamics of subthalamic oscillatory activity are similar to that of a cortical response in terms of frequency, amplitude and phase and (C) a unique 160 Hz high-frequency augmentation is induced by median nerve stimulation.

The main results of our study correspond well with findings of previous studies on somatosensory processing on a cortical level. Especially the work of Fukuda et al. renders comparable results (Fukuda et al., 2008, 2010). They showed that stimulation of the median nerve increased 100–250 Hz oscillations within 20 ms following stimulation in the contralateral SI. At 25 ms these

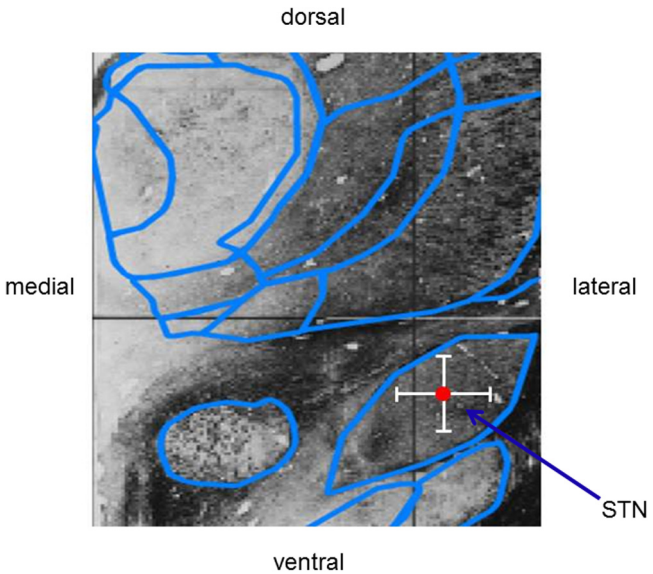

Fig. 3. Recording location of the contralateral induced oscillations. Mean recording sites for both the right and left STN mirrored onto the left STN.

oscillations gradually slowed down in frequency to 30–100 Hz. And this 30–100 Hz activity further shifted into an increase of beta and alpha activity. Similar cortical patterns were found by Dockstader et al. (2010).

4.1. Origin of recorded oscillations

The present findings provide evidence for the involvement of the STN in sensory functions, since the somatosensory stimulation induced a local field potential in this nucleus. Although it is not possible to completely rule out the possibility of a far field contamination, the oscillatory activity seems to be a local response in the STN. First, the induced components were not present on all bipolar electrode pairs placed only 2 mm apart from each other. In the majority of cases the oscillatory pattern could only be detected on one of the three bipolar electrode pairs. Second, the use of bipolar recordings, analyzing activity as focal as possible, minimizes the contribution of far field potentials. Furthermore, it should be taken into consideration that the patients were recorded after intake of their usual dopaminergic medication. Dopaminergic medication may attenuate alpha and beta oscillations and can be associated with an increase in gamma oscillations. However, as we examined the interval after somatosensory stimulation and compared this to a period without somatosensory stimulation we concur that our results are generated by the somatosensory stimulation. Additionally, the oscillatory patterns resemble those found on a cortical level in previous studies without dopaminergic stimulation. Thus, ruling out a sole effect of the medication state.

Besides receiving topographical glutamatergic projections from primary motor and premotor areas to control movement, the basal ganglia-thalamocortical motor circuit also receives information from SI and somatosensory association cortex. As part of this circuit the STN receives input from these areas and acts as a output regulator of this network (Temel et al., 2005). Due to its subdivision into different territories the dorsolateral part of the STN is regarded as the target area for somatosensory input. According to postoperative imaging the contacts displaying most prominent stimulation induced oscillatory modulation in our study were located inside the STN. In addition, the finding that particularly recordings of the second lowest contacts involving dorsolateral STN regions revealed stimulus induced oscillations corresponds to human and primate studies locating the sensorimotor subregion in the dorsolateral two thirds of the STN (Rodriguez-Oroz et al., 2001; Wichmann et al., 1994). Checking for a spatial distribution of the sensory induced oscillatory modulations failed to deliver a specific pattern on adjacent or nearby contacts. As the STN is subdivided into different territories with motor, associative, limbic and somatosensory functions and since not all of the electrode contacts were placed in the sensorimotor sub-region we did not expect to be able to record somatosensory responses from contacts possibly placed outside of this sub-region.

The anatomical identity of the exact pathways that transmit these responses has not been identified, but electrophysiological recordings prompt an involvement of transcortical circuits (Hammond et al., 1978). Furthermore, there is evidence for a direct projection from SI to the STN (Rouzaire-Dubois and Scarnati, 1985). Canteras also found a direct projection from SI to the dorsolateral area of the STN of the rat (Canteras et al., 1988). As median nerve stimulation elicited both contralateral and ipsilateral oscillations feedback projections reaching the STN from SII via the primary motor cortex, the precentral gyrus or the posterior parietal cortex can be assumed (Trenado et al., 2017). A functionally relevant connection between the dorsolateral STN and the somatosensory cortex is further supported by our findings.

4.2. Subthalamic oscillatory dynamics of alpha, beta and gamma ranges following somatosensory stimulation

The presence of an oscillatory activity pattern in the STN similar to that recorded cortically (Dockstader et al., 2010; Fukuda et al., 2010, 2008,) further corroborates the role of the STN in somatosensory processing. Just as in previous cortical recordings median nerve stimulation augmented gamma oscillations at 17 ms. Following this gamma band increase a beta and alpha band augmentation was induced. Due to surgical dressings we were not able to record a scalp EEG but it is a well-known fact that median nerve stimulation elicits evoked peaks at 20 ms and later over the primary somatosensory hand area. These evoked potentials generated a gamma frequency augmentation and might be accountable for the gamma band increase recorded following a somatosensory stimuli (Allison et al., 1989; Fukuda et al., 2010, 2008). The gamma-range oscillations observed here peaked earlier than 20 ms, namely at 17 ms. This might imply that the recorded gamma increase reflects the primary subcortical processing of somatosensory stimuli. One possible explanation could be that synchronous gamma oscillations may temporarily coordinate circuits in somatosensory perception in a way similar to that posited in perceptual binding (Gray et al., 1989). Somatosensory related alpha and beta oscillations presumably reflect a different stage of information processing occurring after the initial subcortical somatosensory processing. The post stimulation beta ERS has been suggested to serve as a selective deactivation process or "active inhibition" in the somatosensory cortex (Neuper and Pfurtscheller, 2001). Beta band activity has also been linked to enhanced alertness in thalamo-cortical systems, such that augmented beta oscillations suggest an activation of the somatosensory or motor cortex by motor preparation or focused attention (Steriade, 1993). Further evidence for attention related beta oscillations comes from the correlation of augmented sensorimotor beta power with attention focused on a motor event (Muthukumaraswamy and Singh, 2008) and an improvement in sensorimotor performance (Egner and Gruzelier, 2004; Vernon et al., 2003). In our study alpha synchrony was followed by desynchrony. Previous studies have shown that median nerve stimulation elicits a prompt and robust alpha power augmentation in SI. This increase precedes an alpha ERD when stimulated with a frequency of 0.5 Hz or below (Dockstader et al., 2009; Palva et al., 2005). Visual and auditory studies have suggested that alpha ERS reflects cortical inhibition while alpha ERD reflects sensory processing (Sauseng et al., 2005; Thut et al., 2006). This hypothesis might also apply to the somatosensory induced changes in alpha range oscillations recorded here.

Furthermore, analysis of late or slow SSEPs by our group on a subthalamic level following median nerve stimulation with an ISI of 3000 ms revealed four distinctive SSEPs (P80, N100, P140 and N200) besides reporting the expected N20 (Trenado et al., 2017). Phase reversal and/or maximum amplitude in these cases lead to the conclusion that these long-latency-SSEPs were generated within the STN. The evoked potentials reported by Trenado et al. may form oscillations in the distinct frequency ranges and account for the modulation of oscillatory activity reported in the present paper.

4.3. High frequency (~160 Hz) activity

In contrast to findings by Buchner et al. (1995); Curio et al. (1994); Hanajima et al. (2004) we did not identify prominent rhythmicities in the STN above 200 Hz. The absence of very high frequency oscillations in our recordings might be specific to the electrical stimulus applied. The previous studies mentioned above used a fast stimulation frequency (every 0.1–0.2 ms) compared to

our slow stimulation frequency (ISI of 3000 ms). In our study the absence of oscillations above 200 Hz may simply be due to the slow stimulation frequency.

However, we report the presence of 160 Hz oscillations in the human STN after median nerve stimulation. The only other report of 160 Hz oscillations in the subthalamic nucleus comes from Nicolas, where LFP recordings in healthy rats revealed an increase of ~150 Hz oscillations together with hyperlocomotion after administration of subanesthetic doses of ketamine (Nicolás et al., 2011). Hunt et al. also reported oscillations around 140–160 Hz in the Nucleus accumbens of rats, which increased notably after a subanesthetic dose of ketamine, concomitant with hyperkinetic movements (Hunt et al., 2006). Ketamine acts as a pharmacological glutamate receptor antagonist. However, a microdialysis dose-response study in conscious rats suggested that low (subanesthetic) ketamine doses actually increase glutamate outflow, indicating that at low doses ketamine can enhance glutamatergic neurotransmission (Moghaddam et al., 1997). A further microdialysis study showed that electrical median nerve stimulation activated glutamate release (Chen et al., 2008). As the most relevant excitatory neurotransmitter glutamate mediates neurotransmission in key brain networks for sensory perception and sensorimotor control. Moreover, excitatory thalamocortical inputs to SI are glutamatergic (Castro-Alamancos and Connors, 1997; Kharazia and Weinberg, 1994) and the N20 cortical response to peripheral median nerve stimulation are generated from excitatory glutamatergic postsynaptic potentials (Tecchio et al., 2011). Additionally, the STN is also glutamatergic (Parent and Hazrati, 1995). The effect of somatosensory stimulation on the STN 160 Hz oscillations might therefore be mediated by changes in glutamatergic transmission. We also detected the presence of these 160 Hz oscillations in the rest period before somatosensory stimulation. After stimulation there was a significant enhancement in the amplitude of these oscillations. This result indicates a physiological origin of these activities, which are increased by somatosensory stimulation. Thus, indicating a possible relationship between these 160 Hz oscillations and somatosensory processing.

4.4. Clinical relevance of 160 Hz oscillations regarding DBS

When examining the stimulation parameters used for postoperative chronic therapeutic stimulation we found that 68% of all contacts used for stimulation at 3 months after implantation coincided with the contacts displaying the 160 Hz oscillations. Effective DBS frequencies are predominantly adjusted between 100 and 200 Hz (Moro et al., 2002). The presence of subthalamic physiological oscillations in this range renders a probable explanation for the beneficial effects of subthalamic DBS in PD patients, by altering pathologic low-frequency oscillations to high-frequency oscillations as suggested by Liu et al. (2008). Although the exact mechanism underlying DBS induced amelioration of PD symptoms remains unclear intracerebral microdialysis studies have revealed that high frequency STN DBS induces a significant increase in subthalamic extracellular glutamate levels (Lee et al., 2007; Windels et al., 2008). Since STN DBS modifies the inputs from the somatosensory cortex that reach the nucleus and given the fact of primarily reciprocal cerebro-basal ganglia connections, a modified STN output would eventually alter processing in somatosensory areas, possibly facilitating somatosensory processing. The results of our study with a possibly glutamatergic mediated increase of subthalamic oscillations in the 160 Hz range after somatosensory stimulation can further support previous findings of enhanced sensorimotor processing during STN-DBS (Herzog et al., 2008; Maschke et al., 2005; Shivitz et al., 2006), possibly due to an STN DBS induced normalization of central sensorimotor integration of somatosensory stimulation as proposed by Sailer et al. (2007).

In conclusion, our data support the notion of a sensory function within the STN. Furthermore, to date this is the first study to identify and describe median nerve stimulation induced oscillation in the human STN. It is also the first to describe the presence of 160 Hz oscillations following this stimulation. Although the functional role of the presented subthalamic oscillations remains uncertain, our findings suggest that they represent somatosensory information processing by cortico-subcortical circuits.

Conflict of interest

JV, AS, LW have received — unrelated to the current project — honoraria and travel expenses in the past from Inomed and Medtronic: companies that manufacture hardware that has been used in this project.

Acknowledgements

L.W. is supported by the Research Commission ('Forschungskommission') of the Medical Faculty of the Heinrich-Heine University Duesseldorf and ERA-NET NEURON/BMBF Germany (TYMON; Grant No. 01EW1411).

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