Neural oscillations underlying bicycling and walking

Inaugural-Dissertation

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

vorgelegt von

Lena Storzer

aus Duisburg

Düsseldorf, November 2016

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

Referent: Prof. Dr. Alfons Schnitzler

Korreferent: Prof. Dr. Tobias Kalenscher

Tag der mündlichen Prüfung: 09.02.2017

Table of Contents

Glossary

APA	anticipatory postural adjustment
BG	basal ganglia
DBS	deep brain stimulation
EEG	electroencephalography
EMG	electromyography
fMRI	functional magnetic resonance imaging
FOG	freezing of gait
FOG-Q	freezing of gait questionnaire
GPe	external segment of the globus pallidus
GPi	internal segment of the globus pallidus
LFP	local field potential
M1	primary motor cortex
MEG	magnetoencephalography
MLR	mesencephalic locomotor region
PD	Parkinson's disease
PIGD	postural instability and gait difficulty
PMC	premotor cortex
PMRF	pontomedullary reticular formation
PPC	posterior parietal cortex
PPN	pedunculopontine nucleus
SMA	supplementary motor area
STN	subthalamic nucleus
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulate
UPDRS	Unified Parkinson’s Disease Rating Scale

Summary

Bicycling and walking are two highly automated movements based on oscillatory activity in a distributed network comprising cortical and subcortical brain regions, spinal cord, and muscles. Alterations in the communication between these regions are observed in Parkinson's disease (PD), a neurodegenerative disorder associated with pathological synchronization of oscillatory activity in the basal ganglia (BG). Consequently, gait impairments are a hallmark of PD. These are even more pronounced in PD patients suffering from freezing of gait (FOG), a puzzling phenomenon characterized by the sudden inability of forward progression. Although accumulating evidence suggests FOG to be associated with deficient movement automaticity, executive dysfunctions, and altered communication between cortical and subcortical regions, the exact underlying mechanism remains elusive so far. As bicycling ability is surprisingly retained in this patient population, comparing neural control of bicycling and walking offers a unique starting point for understanding the complex pathophysiology of FOG. Importantly, bicycling was also shown to be effective ameliorating PD symptoms, raising the question about its effect on brain activity.

This thesis contrasted modulation of neural oscillations by bicycling and walking in healthy subjects and PD patients in order to provide insight into both cortical and subcortical control of movement. Its ambition was to contribute to the understanding of the paradoxical bicycling capacity in patients with FOG, thereby revealing oscillatory signatures related to freezing susceptibility.

Two studies were performed based on the same experimental paradigm including initiation, execution, and termination of bicycling on a stationary bicycle as well as walking. Brain activity was concurrently recorded together with electromyography of the leg muscles and movement parameters including the knee angle and the pedal position.

Since not much is known about how bicycling differs from walking with respect to motor cortex activity, study 1 acquired electroencephalography in healthy participants to scrutinize modulation of alpha (8-12 Hz) and beta (13-35 Hz) rhythms that are known to be crucial for movement control. Interestingly, bicycling and walking were found to be accompanied by different oscillatory dynamics. Bicycling resulted in stronger sustained modulations of high beta band (23-35 Hz) activity but weaker alpha band activity relative to walking. At the same time, walking was characterized by stronger power modulations in the 24-40 Hz range as a function of the movement cycle. Apart from identifying frequency specific aspects of cortical motor control, these results suggest that bicycling involves stronger overall cortical activation while walking demands more cortical monitoring of ongoing movement.

Study 2 aimed at characterizing modulation of oscillatory activity in the BG of PD patients by recording local field potentials from electrodes implanted in the subthalamic nucleus (STN) for deep brain stimulation (DBS). Especially synchronization in the beta band was scrutinized as this is closely associated with the pathophysiology of PD. Study 2 revealed stronger STN beta power suppression during bicycling relative to walking. Crucially, patients with FOG showed an abnormal ~18 Hz oscillation during walking that was alleviated in bicycling. This suggests synchronization at ~18 Hz as an oscillatory signature for freezing susceptibility with freezing episodes being the consequence of a movement-inhibiting signal in a subcortical network.

The presented studies elucidate functional differences in the motor network subserving bicycling and walking, providing a key piece of the mechanism explaining how bicycling ability can remain preserved in patients with FOG. Results highlight the pivotal role of different specific beta rhythms in this context. Bicycling was accompanied by stronger beta power suppression in the striato-thalamo-cortical network, likely arising from its more continuous nature entailing low computational load on the motor system. Walking, on the other hand, is computationally more demanding and thus susceptible to excessive synchronization in the BG. This might finally result in 'overloading' the network involved in locomotion. This thesis thus provides important groundwork for future research clarifying the mechanism behind FOG. It may enlarge the therapeutic options for treating PD symptoms by including new DBS stimulation strategies and cycling protocols.

Zusammenfassung

Fahrradfahren und Gehen sind zwei hoch automatisierte Bewegungsabläufe. Sie basieren auf einer feinabgestimmten Modulation neuronaler oszillatorischer Aktivität in einem motorischen Netzwerk. Dieses umfasst sowohl kortikale und subkortikale Gehirnregionen, als auch Rückenmark und Muskeln.

Die Kommunikation im motorischen Netzwerk ist bei Morbus Parkinson gestört. Bei dieser neurodegenerativen Erkrankung der Basalganglien, die mit pathologisch veränderter oszillatorischer Aktivität assoziiert wird. Damit verbunden sind erhebliche Beeinträchtigungen beim Gehen. Diese sind noch schwerwiegender bei Patienten mit dem sogenannten „Freezing-Phänomen“, was durch ein plötzliches „Einfrieren“ der Bewegung charakterisiert ist. Zahlreiche Studien lieferten Hinweise darauf, dass „Freezing“ mit einer gestörten Kontrolle automatisierter Bewegungen, exekutiven Defiziten und einer beeinträchtigten Kommunikation zwischen kortikalen und subkortikalen Gehirnregionen einhergeht. Dennoch ist der genaue Pathomechanismus bisher unerkannt. Im Rahmen dieser Studien wurde außerdem die erstaunliche Beobachtung gemacht, dass Parkinson-Patienten, die unter dem „Freezing-Phänomen“ leiden, nahezu immer ohne Probleme Fahrradfahren können. Dies bietet einen vielversprechenden Ansatzpunkt, um den komplexen Pathomechanismus des „Freezing-Phänomens“ zu erforschen. Darüber hinaus wurde eine positive Wirkung von Fahrradfahren auf die Symptome der Parkinson-Krankheit gezeigt, was die Frage nach den zugrundeliegenden neuronalen Prozessen mit sich zieht.

Diese Doktorarbeit befasste sich mit der Modulation neuronaler oszillatorischer Aktivität beim Fahrradfahren und Gehen. Es wurden sowohl die kortikale Gehirnaktivität gesunder Probanden als auch die subkortikale Gehirnaktivität von Parkinson-Patienten untersucht. Ziel war es, durch den Vergleich bewegungsspezifischer Gehirnaktivität Rückschlüsse auf neuronale Bewegungssteuerung und neuronale Korrelate des „Freezing-Phänomens“ zu ziehen.

In diesem Sinne wurden zwei Studien basierend auf einem einheitlichen Paradigma durchgeführt. Dabei wurden Gehirn- und Muskelaktivität beim Initiieren, Ausüben und Terminieren von Fahrradfahren auf einem Ergometer und Gehen gemessen. Zusätzlich wurden Bewegungsparameter wie der Kniewinkel und die Pedalposition simultan aufgezeichnet.

Studie 1 erforschte die bewegungsspezifische Modulation oszillatorischer Aktivität im sensomotorischen Kortex bei gesunden Probanden mithilfe der Elektroenzephalographie. Der Fokus lag dabei auf dem Alpha- (8-12 Hz) und Beta-Band (13-35 Hz), entscheidende Frequenzbänder im Rahmen der Bewegungskontrolle. Während Fahrradfahren zu einer anhaltenden Verminderung von

Aktivität im oberen Beta-Band (23-35 Hz) führte, war Gehen mit einer Verminderung von Aktivität im Alpha-Band assoziiert. Zudem zeigte sich eine ausgeprägte Modulation der Aktivität im 24-40 Hz Band beim Gehen, die an spezifische Phasen des Bewegungszyklus gekoppelt war. Diese Ergebnisse legen eine differenzierte, frequenzabhängige kortikale Kontrolle von komplexen Bewegungsabläufen nahe. Sie deuten auf eine stärkere allgemeine kortikale Aktivierung beim Fahrradfahren hin, die mit einem reduzierten Bedarf an kortikaler Kontrolle augenblicklicher Bewegungsabläufe einhergeht.

Studie 2 beschäftigte sich mit der Modulation von Hirnaktivität der Basalganglien von Parkinson-Patienten durch Bewegung. Dabei ermöglichte die chirurgische Implantation von Elektroden zur therapeutischen Tiefenhirnstimulation die Aufzeichnung lokaler Feldpotentiale aus dem Nucleus subthalamicus (STN). Der Fokus lag insbesondere auf Beta Oszillationen, die bekanntermaßen ein pathologisches Korrelat der Parkinson-Erkrankung darstellen. Es zeigte sich eine stärkere Unterdrückung der Aktivität im Beta-Band beim Fahrradfahren. Zudem konnte erstmalig gezeigt werden, dass Parkinson-Patienten mit dem „Freezing-Phänomen“ abweichende oszillatorische Aktivität um 18 Hz beim Gehen, nicht jedoch beim Fahrradfahren, aufweisen. Diese stellt vermutlich ein neurophysiologisches Korrelat für die Anfälligkeit für „Freezing“ dar. Das legt den Schluss nahe, dass „Freezing-Episoden“ die Konsequenz eines bewegungshemmenden Signals in subkortikalen Netzwerken sind.

Die vorliegenden Studien tragen wesentlich zum Verständnis funktionaler Unterschiede im motorischen Netzwerk beim Fahrradfahren und Gehen bei. Die Ergebnisse betonen in diesem Zusammenhang die herausragende Rolle verschiedener frequenzspezifischer Beta Oszillationen. Fahrradfahren ging mit einer Minderung von Beta Oszillationen im motorischen Netzwerk einher. Dies ist wahrscheinlich auf den kontinuierlichen Bewegungsablauf zurückzuführen, der mit einer niedrigen Belastung des motorischen Systems einhergeht. Die mit dem Gehen verbundene erhöhte Belastung des motorischen Systems ist stattdessen mit einer Anfälligkeit für erhöhte STN Aktivität um 18 Hz bei Patienten mit „Freezing-Phänomen“ assoziiert. Das kann eventuell in einer Überlastung des motorischen Systems enden, einem Einfrieren der Bewegung. Die Ergebnisse bieten somit wichtige Ansatzpunkte, um den Pathomechanismus des „Freezing-Phänomens“ genauer zu untersuchen und die bisherigen Therapieoptionen bei Parkinson durch neue Stimulationsstrategien und Radfahrprotokolle zu bereichern.

1 Introduction

Both bicycling and walking are complex coordinated movements. Nevertheless, pedaling and walking without effort is commonly taken for granted and can be executed with a high degree of automaticity. Furthermore, the movement pattern can be easily adapted to environmental requirements, e.g. when the surface is getting uneven or the traffic light is suddenly changing to red. Once learned, both types of movement can be mostly carried out without the need for conscious control. However, having in mind the effort and time children spend learning how to walk or to bike, one can imagine that locomotion is more difficult than we usually think. It is the result of a complex interplay between different brain regions, spinal cord, and muscles. In this regard, neural oscillations, periodic fluctuations in the membrane potential of a neuronal population, serve as an important mechanism of communication between these brain regions (reviewed by Schnitzler and Gross, 2005). As in an orchestra, timing and scaling of movement is crucial to enable smooth output. But what if the conductor, the striato-thalamo-cortical loop, is no longer able to perform its job satisfactorily? This might be the case in patients with freezing of gait (FOG), a common symptom in advanced Parkinson's disease (PD). FOG is an episodic lack of intended forward progression, characterized by the feeling of the feet being glued on the floor (reviewed by Nutt et al., 2011a). Although numerous theoretical models have been developed, each focusing on specific aspects of FOG, a comprehensive model is still missing. It has been postulated that freezing is not limited to gait but the result of a core motor control problem affecting different kinds of movement (reviewed by Vercruysse et al., 2014). Surprisingly, bicycling abilities are apparently preserved in patients with FOG (Snijders and Bloem, 2010; Snijders et al., 2011b, 2012b). This is puzzling with respect to our understanding of the human motor system and strongly suggests that, despite the similarity in their rhythm and involved muscle groups (Raasch and Zajac, 1999), bicycling and walking may involve the motor network in different ways.

This thesis aimed to contrast neural oscillations underlying bicycling and walking in healthy subjects and PD patients in order to provide insight into both cortical and subcortical control of movement and how this is related to the preserved bicycling ability in PD patients.

1.1 Neural control of locomotion

Locomotion is an integral part of our everyday life and based on the temporally precisely coordinated activation and inhibition of muscles, multisensory integration, and postural control. Besides descending motor commands, afferent feedback is an indispensable aspect of locomotor control as it serves the regulation of ongoing movements with respect to changing environmental conditions (Nielsen and Sinkjaer, 2002).

In order to move safely in our environment, a fine-tuned, hierarchically organized system has developed that enables efficient, fast and flexible control of locomotion (reviewed by Jahn et al., 2008a; Nutt et al., 2011b; Takakusaki, 2013). Cortical locomotor commands are primarily transmitted via the basal ganglia (BG) and the mesencephalic locomotor region (MLR) to lower level brainstem regions such as the pontomedullary reticular formation (PMRF), and spinal cord. Descending motor commands are modulated by further input from the cerebellum (Fig. 1).

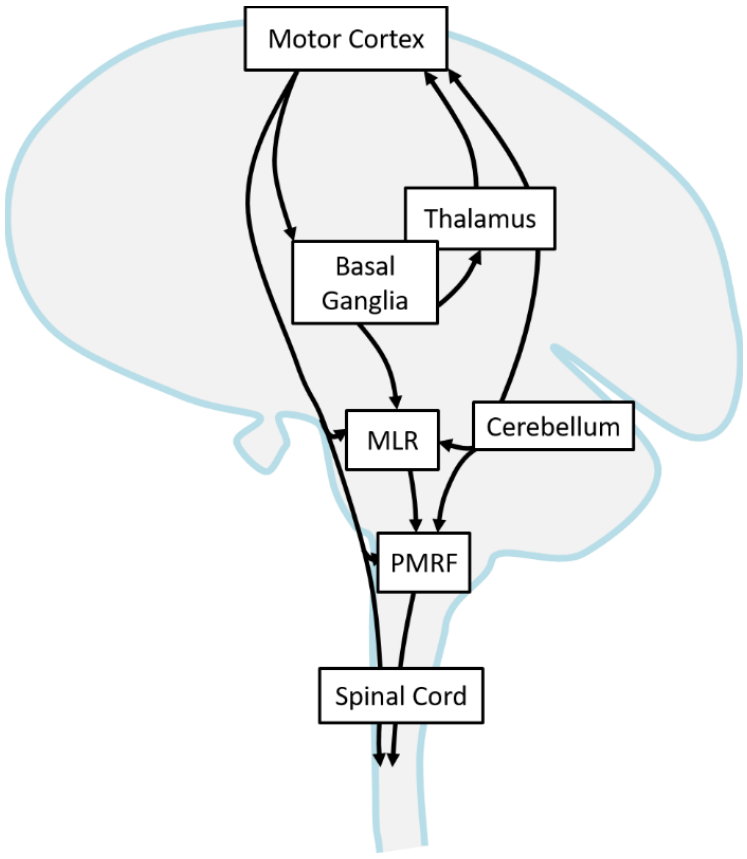

Figure 1: The locomotor network. Simplified schematic illustration of the most important brain regions involved in supraspinal control of human locomotion. Hierarchically organized locomotor control from the cortex to the spinal cord is mainly exerted via the basal ganglia and modulated by the cerebellum. Information is integrated at the level of the mesencephalic locomotor region (MLR) and the pontomedullary reticular formation (PMRF) and conveyed to the spinal cord. Adapted and modified from Jahn et al. (2008a); Nutt et al. (2011b) and Takakusaki (2013).

1.1.1 Cerebral cortex

Cortical motor areas exert the highest level of locomotor control and enable the dynamical and volitional adaptation of complex, coordinated movements. In this regard, activation of an extensive network has been shown including the premotor cortex (PMC), supplementary motor area (SMA), sensorimotor cortex, and the parietal cortex (reviewed by Swinnen, 2002).

The primary motor cortex (M1) is especially associated with movement execution while the SMA is particularly dedicated to planning, initiation, and coordination of voluntary movements (Christensen et al., 2000; Miyai et al., 2001; Sahyoun et al., 2004; la Fougère et al., 2010). In this regard, neuroimaging studies including positron emission tomography or functional near infrared spectroscopy revealed pronounced SMA activity during more complex locomotor tasks, such as avoiding obstacles (Malouin et al., 2003) and backwards walking (Kurz et al., 2012).

An important dissociation exists with respect to cortical involvement in internally and externally guided movements. The SMA is part of the striato-thalamo-cortical loop connecting BG, thalamus, and cortex and associated with internally generated movements. Externally triggered movements are thought to rely on the cerebello-thalamo-cortical loop connecting the cerebellum with frontoparietal areas including the PMC and parietal cortex (Debaere et al., 2003; Taniwaki et al., 2006). In line with this it was shown that walking in a virtual reality guided by interactive feedback elicited increased activity in PMC and parietal cortex as measured with electroencephalography (EEG; Wagner et al., 2014). The posterior parietal cortex (PPC) was observed to react to auditory pacing cues during treadmill walking (Wagner et al., 2016). This supports the general assumption of multisensory integration and matching of anticipated and real sensorimotor feedback being a hallmark of PPC functioning (Buneo and Andersen, 2006).

1.1.2 Basal ganglia

The BG are a key hub in the motor system. They consist of highly interconnected nuclei, i.e., the striatum, the external and internal segment of the globus pallidus (GPe and GPi), the subthalamic nucleus (STN), and the compact and reticular compartment of the substantia nigra (SNc and SNr). The most outstanding feature of the BG is that they form segregated, parallel loops with the cortex (Alexander et al., 1986). These striato-thalamo-cortical loops convey information from different domains, e.g. limbic, motor, and associative information, depending on the involved cortical region. Due to this unique architecture, the BG are suited to integrate information from multiple modalities and thus contribute to a variety of functions ranging from movement selection and inhibition (Mink, 1996) to learning and habit formation (reviewed by Ashby et al., 2010). As they are thought to

mediate both automatic and volitional control of movements (reviewed by Redgrave et al., 2010), gait impairments are closely linked to BG dysfunctions (reviewed by Takakusaki et al., 2008).

In addition to the parallel loop architecture, the intrinsic connections of the BG are organized in form of a direct and indirect pathway (Albin et al., 1989; DeLong, 1990). Cortical input enters the BG primarily via the striatum, whereas GPi and SNr are the main output nuclei. Information is either conveyed directly or indirectly via GPe and STN. This architecture enables precise and flexible adjustment of the tonic inhibitory control over thalamus and brainstem. Activity in the direct pathway inhibits the BG output structures, leading to a decrease of the thalamic inhibition. Conversely, activity in the indirect pathway excites the BG output structures via inhibition of the GPe and subsequent disinhibition of the STN, thus thalamic inhibition is increased. Although this model is simplified, it provides a generally accepted framework for investigation function and disorders of the BG.

The STN deserves special attention. It is the only glutamatergic nucleus in the system and the primary target for therapeutic deep brain stimulation (DBS) in PD patients. The surgical procedure for DBS permits to record pathological alterations of STN activity in PD. This was also done in study 2 of the thesis at hand. The STN receives direct cortical projections from cortical motor areas via the so-called hyperdirect pathway (Nambu et al., 1996). The pivotal role of this pathway in PD pathophysiology is becoming increasingly more recognized (de Hemptinne et al., 2013; Oswal et al., 2016). It is suitable to control response inhibition and switching of behavior due to environmental changes, especially in the presence of conflict (Aron and Poldrack, 2006; Frank, 2006; Cavanagh and Frank, 2013).

1.1.3 Mesencephalic locomotor region

The MLR is one of the most important locomotor centers located in the brainstem. It consists of the cuneiform and subcuneiform nuclei, and the pedunculopontine nucleus (PPN). Especially the latter has gained much attention with regard to normal and pathological gait (reviewed by Jenkinson et al., 2009). The PPN is a heterogeneous structure that contains cholinergic and glutamatergic neurons and has tight reciprocal connections with the BG, cerebellum, and lower brainstem regions (reviewed by Martinez-Gonzalez et al., 2011). The PPN is considered to be involved in balance, postural control, initiation, and maintenance of gait (Jahn et al., 2008b; Karachi et al., 2010; Tattersall et al., 2014). Evidence has accumulated that it is more than a simple relay station between BG and brainstem but is involved in motor planning and information integration via descending and ascending pathways (Tattersall et al., 2014; Lau et al., 2015).

1.1.4 Cerebellum

A further important player in the control of locomotion is the cerebellum. It is primarily involved in motor adaptation based on sensory prediction errors (Tseng et al., 2007; Schlerf et al., 2012) with cerebellar damage leading to e.g. impaired predictive locomotor adaption during walking on a split-belt treadmill (Morton and Bastian, 2006). The cerebellum is further involved in coordination (Debaere et al., 2004) and control of posture and balance (reviewed by Morton and Bastian, 2004). It has direct reciprocal connections with the BG (reviewed by Bostan et al., 2013). Yet, BG and cerebellum were shown to form distinct loops with the cortex, i.e. the cerebello-thalamo-cortical and the striato-thalamo-cortical loops (reviewed by Middleton and Strick, 2000).

1.2 Neural oscillations

Exchange of information within the distributed locomotor network is essential for successful motor performance. Oscillatory activity is an important mechanism suited for local and long-range communication between brain areas (reviewed by Varela et al., 2001; Schnitzler and Gross, 2005).

1.2.1 Measurement of neural oscillations

Neural oscillations are periodic voltage fluctuations in the membrane potential of neuronal populations. As such, they can be identified at different scales using non-invasive and invasive electrophysiological techniques (Fig. 2). Both have been applied in the current thesis.

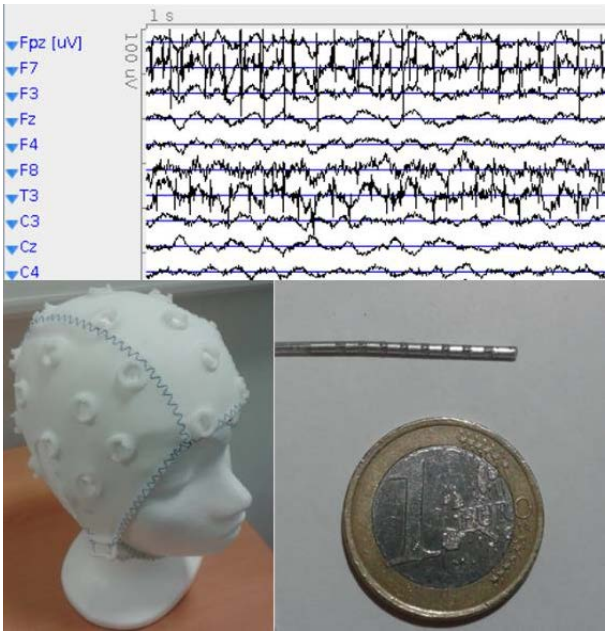

Figure 2: Electrophysiological techniques to measure oscillatory activity. Rhythmic variations in the electrical activity of the brain (upper panel) can be measured in form of EEG and local field potential (LFP) signals. EEG signals are recorded with an electrode cap covering the scalp with the underlying cerebral cortex (lower left panel). LFP signals can be recorded from DBS electrodes that are implanted for subsequent therapeutic stimulation of subcortical brain regions (lower right panel). The number of electrode contacts depends on the manufacturer. Electrodes with 8 contacts were used in study 2.

EEG is an established non-invasive method to measure electrical potentials from outside the skull. Although EEG provides great temporal resolution, it lacks spatial resolution and is more suitable for

cortical activity. Oscillatory activity can also be observed in local field potentials (LFPs) recorded from deep brain structures such as the BG. This is done during or immediately after the therapeutic implantation of electrodes for DBS in the context of neurological diseases such as PD. Such a DBS electrode is depicted in Fig. 2 (lower right panel). This way, LFPs can be assessed that encompass all transmembrane currents but mainly represent extracellularly-recorded synaptic activities of a neuronal population (reviewed by Buzsáki et al., 2012).

1.2.2 Analysis of neural oscillations

Oscillatory activity can be analyzed by transforming the recorded electrophysiological signal into the frequency domain by means of Fourier transformation. This results in information about phase and amplitude as a function of frequency. Importantly, all three parameters provide information about the communication within and between brain networks.

Spectral power is defined as squared amplitude at a given frequency. It is assumed to reflect the degree of synchronization within a neuronal population but is also affected by the number of neurons that engage in this rhythmic activity. The latter may also be related to the oscillation frequency. Low frequency oscillations are associated with large neuronal populations, whereas high frequency oscillations likely originate from more focal populations. Traditionally, oscillation frequencies are divided into five frequency bands: delta (<4 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13-30 Hz), and gamma (>30 Hz). Research has revealed even faster oscillatory activity in deep brain structures, the so-called high-frequency oscillations (HFOs >200 Hz) (Foffani et al., 2003; Özkurt et al., 2011; Wang et al., 2014). Interestingly, oscillations at different frequencies do interact with each other. For example, the amplitude of HFOs was shown to be coupled to the phase of beta oscillations in PD patients (López-Azcárate et al., 2010; Özkurt et al., 2011; Yang et al., 2014; Storzer et al., 2015).

Notably, these frequency bands are associated with specific functions and disease states. While e.g. activity in the gamma band has been related to attention and memory (reviewed by Jensen et al., 2007), beta oscillations are tightly linked to sensorimotor functions.

1.2.3 Modulation of beta oscillations by movement

Investigating oscillatory dynamics in the context of movement has led to the finding of a stable oscillatory pattern in the motor network that has been extensively studied since then. Power in the alpha and beta band is suppressed immediately before and during movement execution and increases above baseline level after movement termination (reviewed by Pfurtscheller and Lopes da Silva, 1999). These dynamics have traditionally been labeled event-related desynchronization and event-related synchronization referring to the assumed underlying neural processes. For the sake of

brevity, this section will focus on cortical beta power changes, while subcortical beta power changes will be elucidated in the section dedicated to PD (section 1.3.2).

Beta oscillations have been assumed to be an indicator of sensorimotor cortex activity (reviewed by Neuper and Pfurtscheller, 2001). Along these lines, the increase of beta power after movement termination, the so-called beta rebound, was thought to reflect the shift from an active to an idling state or even inhibited state of the motor cortex (Pfurtscheller et al., 1996; Solis-Escalante et al., 2012). However, evidence indicates beta power modulation to be more than a simple by-product of movement execution. For example, beta power modulation can also be elicited in the absence of real movement during passive and imagined movements (Alegre et al., 2002; Müller-Putz et al., 2007), and tactile stimulation (van Ede and Maris, 2013).

What is the functional role of beta oscillations? Engel and Fries (2010) proposed beta power to represent maintenance of the current motor state. Deviating from the traditional perspective, the authors reasoned beta oscillations to reflect an active process that promotes the existing motor state at the expense of new voluntary movement. Based on this widely accepted model, beta power suppression has been further related to the likelihood of a subsequent movement (Jenkinson and Brown, 2011) and to the control of computational capacity within the striato-thalamo-cortical network (reviewed by Brittain et al., 2014).

1.2.4 Oscillatory activity underlying bicycling and walking

Given the importance of locomotion for our everyday life, relatively little is known about oscillatory dynamics subserving locomotion. Hitherto, previous studies have consistently shown that sensorimotor alpha and beta power are suppressed during a diversity of walking tasks (e.g. Presacco et al., 2011; Wagner et al., 2012; Seeber et al., 2014). Strikingly, natural overground walking has not yet been investigated with EEG. It was already demonstrated that behavioral and cortical activity is affected by differences in the experimental setup as by using a treadmill or a robotic gait orthosis (Bulea et al., 2015; Knaepen et al., 2015a). This emphasizes the need for investigating locomotor control in the most natural setting for the sake of a high external validity.

Generally, increasing sensorimotor demands during walking resulted in a stronger sensorimotor alpha and beta power suppression (Presacco et al., 2011; Wagner et al., 2012, 2014; Sipp et al., 2013). Thus, stronger power suppression might reflect increased cortical engagement during more complex tasks. In addition to the sustained movement-related alpha and beta power suppression, Gwin et al. (2011) were the first to demonstrate that cortical power is dynamically modulated relative to the phase of the gait cycle, i.e., the interval between two consecutive right heel strikes. Although initially suspected to reflect artifacts rather than real cortical processing,

gait cycle-dependent sensorimotor power modulation in the 24-40 Hz range has been consistently replicated by different groups (Wagner et al., 2012; Seeber et al., 2014; Bulea et al., 2015). As can be derived from Fig. 3, power in the 24-40 Hz range decreases and subsequently increases twice in the gait cycle. Similarly, positive and negative movement-related potentials have been shown to be locked to the gait cycle (Wieser et al., 2010; Knaepen et al., 2015b). Seeber and colleagues (2014) nicely illustrated that movement-related beta power suppression and gait cycle-dependent power modulation are separate but superimposed phenomena, prompting the hypothesis that they reflect different neuronal processes. While beta power suppression likely reflects a sustained active state of the sensorimotor cortex during walking, gait cycle-dependent modulation can be related both to motor planning and subsequent sensorimotor processing (Wagner et al., 2012; Seeber et al., 2014).

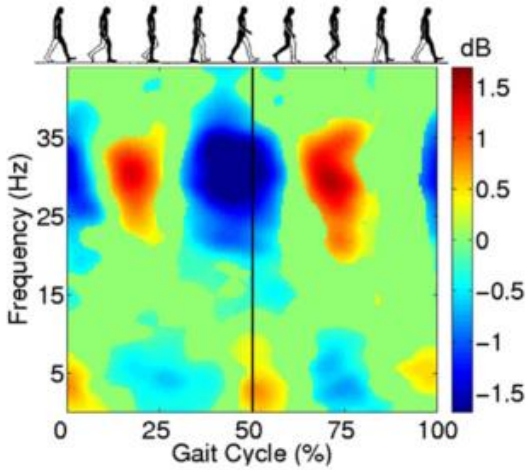

Figure 3: Gait cycle-dependent power modulation. Grand average plot showing changes of spectral power in premotor cortex during the gait cycle. Non-significant differences relative to the full gait cycle baseline ($p \leq 0.05$) are masked in green (0 dB). The right heel strike marks the start and end of the gait cycle. Power in the 24-40 Hz range decreases at the end of the swing phase, before the leading food is touching the ground and the trailing food is pushing off. This is followed by power increases coinciding with the stance phase of each leg, respectively. Adapted from Wagner et al. (2012).

Evidence for cortical involvement in locomotion is more abundant in walking. However, Jain et al. (2013) investigated cortical activity underlying recumbent bicycling on a stationary bicycle. They were able to confirm previous findings in the context of walking by demonstrating sustained sensorimotor beta power suppression and alternating negative and positive cortical potentials that are locked to the pedal cycle. Moreover, they demonstrated sensorimotor activity to be correlated with electromyographic (EMG) activity of the leg muscles. These results are not unexpected given the vast similarity between bicycling and walking in their rhythm and involved muscle groups (Raasch and Zajac, 1999). Yet, active walking was accompanied by stronger gait cycle-dependent power modulations (Wagner et al., 2012), while active bicycling was found to lead to an attenuation of pedal cycle-dependent cortical potentials (Jain et al., 2013). It was assumed that the corticospinal drive in bicycling led to gating of sensory input (Duysens et al., 2013; Jain et al., 2013). These results emphasize movement specific differences in the cortical control of locomotion.

1.3 Parkinson's disease

PD is a progressive neurodegenerative disease that was first described by James Parkinson in 1817 (Parkinson, 1817). It is the second most common neurodegenerative disorder after Alzheimer's disease (reviewed by de Lau and Breteler, 2006) and characterized by a spectrum of motor as well as non-motor symptoms.

1.3.1 Clinical characteristics

PD is primarily associated with a combination of the cardinal motor symptoms: bradykinesia, rest tremor, rigidity, and postural instability. These symptoms are especially relevant for clinical diagnosis but secondary motor symptoms such as dysarthria and FOG and non-motor symptoms such as cognitive and behavioral problems coexist with the cardinal symptoms (reviewed by Jankovic, 2008). Motor symptom severity is clinically rated according to the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS III; Goetz et al., 2008). Progression of PD is further classified by means of the Hoehn and Yahr scale with stage 1 covering the initial symptom lateralization and stage 5 characterizing patients' complete immobility (Hoehn and Yahr, 1967).

PD is a heterogeneous disease that can be divided into two clinical subtypes, i.e., the tremor-dominant and akinetic-rigid or postural instability and gait difficulty (PIGD) subtype, respectively (reviewed by Thenganatt and Jankovic, 2014). The tremor-dominant subtype suffers predominantly from rest tremor and has a relative good prognosis with slow progression. Opposed to this, the PIGD subtype is mainly affected by bradykinesia and rigidity and has a rather rapid progression. This subtype is also more closely related to continuous gait difficulties, a hallmark of PD. It has been shown that PD gait disturbances are evident in five domains: pace, rhythm, variability, asymmetry, and postural control (Galna et al., 2015).

To sum up, PD patients walk slowly, with a high temporal and spatial variability and asymmetry, and they have poor postural control.

1.3.2 Pathophysiology

PD symptoms result from a progressive death of dopaminergic cells which is most prominent in the SNc. The cause of this cell death remains to be clarified; yet, a complicated interplay of genetic and environmental factors was suggested (reviewed by Kalia and Lang, 2015). Lewy bodies that are aggregates of abnormally folded proteins are especially associated with the pathophysiology of PD. As an example for a genetic factor, mutation of the α-synuclein encoding gene causes accumulation of Lewy bodies in the brain, spinal cord, and peripheral nervous system.

Loss of dopaminergic neurons in the SNc disrupts the functionality of the BG. According to the classical rate model of PD, dysfunctions are the result of imbalance between the direct and indirect pathway within the basal ganglia-cortical loop (Albin et al., 1989; DeLong, 1990). Dopamine depletion leads to less activity within the direct pathway mediated by D1 dopamine receptors, while activity increases in the indirect pathway mediated by D2 dopamine receptors. As a consequence, thalamic inhibition is increased which leads to decreased feedback to the cortex. Many of the basic assumptions of the classical rate model have been experimentally confirmed. The model, however, has its inconsistencies and is oversimplified. For example, it is likely that not only changes in neuronal discharge rates but also changes in temporal discharge patterns and synchronization within and beyond the BG network contribute to the pathophysiology of PD (reviewed by Nelson and Kreitzer, 2014).

With regard to synchronization, oscillatory activity in the striato-thalamo-cortical loop is commonly considered to be altered in Parkinson's disease (reviewed by Schnitzler and Gross, 2005; Hammond et al., 2007; Oswal et al., 2013). Research highlighted activity in the beta band to be abnormally increased and linked to akinesia and rigidity (Kühn et al., 2006, 2009). A causal role between beta oscillations and motor impairment was further illustrated by slowed movements as a consequence of stimulating different nodes in the striatho-thalamo-cortical loop in the beta range (Chen et al., 2007; Pogosyan et al., 2009). This is in line with the proposed functional role of beta oscillations (section 1.2.1), i.e., maintaining the status-quo at the expense of voluntary movement (Engel and Fries, 2010).

1.3.3 Treatment

Dopamine replacement and DBS are widely used therapeutic means for treating Parkinson's disease symptoms. In the early disease stages, dopamine agonists and levodopa, a dopamine precursor, are the most effective treatment options. When pharmacological intervention starts to become ineffective and even induces complications such as dyskinesia and hyperkinesia, DBS is considered the therapy of choice (Deuschl et al., 2006). DBS involves implantation of electrodes preferentially in GPi and STN and applying electrical current pulses typically at 130 Hz that are generated by a subcutaneous stimulator. Although the exact mechanisms of DBS remain uncertain, DBS likely affects neuronal firing, oscillations, and neurotransmitters (reviewed by Benabid et al., 2009). Importantly, DBS was shown to alter beta band activity within the basal ganglia-cortical network (Oswal et al., 2016).

Unfortunately, DBS effects on Parkinsonian gait and postural instability are rather variable, probably due to the involvement of different functional pathways (reviewed by Fasano et al., 2015).

To complement classical treatment options, exercise interventions might be used in PD patients to improve balance and gait. Treadmill training, dancing, forced cycling, and even boxing have been shown to improve motor and cognitive functions (reviewed by Petzinger et al., 2013).

1.3.4 Neural control of locomotion in Parkinson's disease

It is assumed that every structure in the locomotor network (section 1.1) contributes to gait impairments in PD (Fig. 4). More specifically, slowed gait, increased variability, and poor postural control are thought to be independent features that may be attributed to partially distinct neural networks (reviewed by Bohnen and Jahn, 2013; Peterson and Horak, 2016).

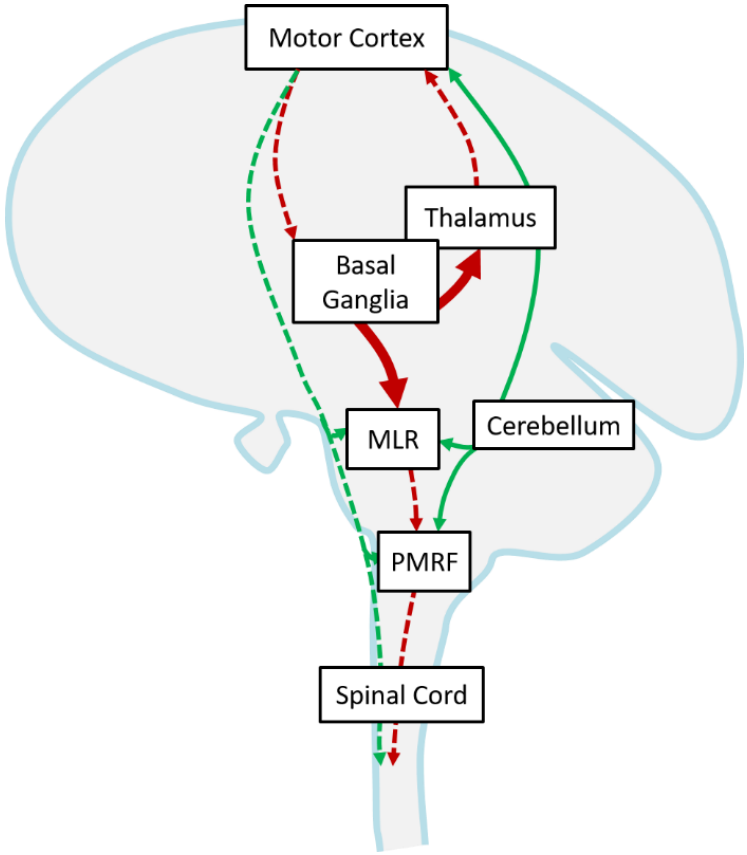

Figure 4: Disturbances in the locomotor network in PD patients. Dopamine depletion leads to increased inhibitory output from the BG to the thalamus and brainstem and thus reduced automatic control of gait. Altered activity in the striato-thalamo-cortical loop is compensated for by increased activity in the cerebello-thalamo-cortical loop as well as by increased cortical control of gait. These alterations are associated with slowed gait, increased gait variability, and poor postural control. Pathological changes are marked in red and compensatory changes in green. Underactive pathways are indicated by dashed lines while the increase of BG output is highlighted by the thicker lines. MLR = mesencephalic locomotor region; PMRF = pontomedullary reticular formation. Adapted and modified from Bohnen and Jahn (2013) and Peterson and Horak (2016).

Altered activity in the striato-thalamo-cortical loop might be related to gait slowness. Based on the classical rate model (section 1.3.2), reduced levels of dopamine cause an increase in BG inhibitory output to the thalamus and brainstem. This in turn might lead to insufficient facilitation of movement especially at the level of the SMA. In line with this hypothesis, reduced activation of the SMA has been observed during imagined gait in PD patients (Hanakawa et al., 1999). Additionally, grey matter atrophy in the SMA was found to be associated with increased severity of postural instability and gait difficulty (Rosenberg-Katz et al., 2013). Importantly, pace-related gait measures could be markedly improved by levodopa (Curtze et al., 2015), which tallies with levodopa-related normalization of SMA activation (Haslinger et al., 2001). Altered activity within the striato-thalamo-cortical loop is also compensated for by a greater dependency on externally guided movements mediated by the cerebello-thalamo-cortical loop (reviewed by Hallett, 2008).

Higher spatiotemporal gait variability might be the consequence of increased cortical control of locomotion compensating for reduced automatic control of locomotion (striato-thalamo-cortical loop). It is widely excepted that PD patients have problems concerning automatic motor control (reviewed by Wu et al., 2015). Conversely, increased dual-task costs during walking hint towards enhanced cortical involvement in locomotion (reviewed by Kelly et al., 2012). Yogev et al. (2005) showed that regulation of gait rhythmicity and variability is an automatic process in healthy adults that becomes attention-demanding in PD patients.

Postural instability has been related to cholinergic dysfunction at the level of the PPN. Lesioning the cholinergic part of the PPN resulted in gait and postural deficits in monkeys (Karachi et al., 2010). Intriguingly, the authors were also able to show that cholinergic neurons degenerated more in PD patients with balance deficits. Consequently, the PPN is considered as an alternative DBS target if gait disturbances are unresponsive to levodopa (reviewed by Collomb-Clerc and Welter, 2015). Results of Weiss and colleagues (2015) even suggest STN-DBS to improve gait by modulating PPN activity.

LFP recordings from electrodes that are implanted for DBS have provided valuable insights into subcortical oscillatory dynamics in the recent past. This way, beta power suppression has been shown in the GPi of dystonic patients (Singh et al., 2011) and the STN of PD patients (Singh et al., 2013) during walking on a treadmill. Intriguingly, the latter study also observed STN low beta power (12-22 Hz) to be paradoxically increased during walking solely in patients with FOG.

1.4 Freezing of Gait

One of the most common, debilitating and also puzzling symptoms in PD is FOG. It is defined as the brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk (reviewed by Nutt et al., 2011a). About 50 % of PD patients suffer from FOG (Giladi et al., 2001b) with up to 80 % experiencing FOG at the later disease stages (Hely et al., 2008; Tan et al., 2011). The psychological strain of these patients is heavy as FOG is associated with an increased risk of falling (Kerr et al., 2010) and imposes a high burden on mobility and quality of life (Moore et al., 2007). Consequently, there is a compelling need for unrevealing the pathophysiological mechanisms leading to FOG in order to develop adequate therapeutic treatments.

1.4.1 Clinical characteristics

FOG is associated with the PIGD rather than the tremor dominant type of PD (Giladi et al., 1992, 2001a). Nevertheless, FOG was shown to be an independent motor symptom (Giladi et al., 2001a; Bartels et al., 2003) that has also been described in other diseases such as progressive supranuclear palsy and normal pressure hydrocephalus (reviewed by Factor, 2008). Freezing is not restricted to gait, but can also be observed during repetitive upper and lower limb movements as well as during speech (reviewed by Vercruysse et al., 2014). Yet, it is still a matter of debate if the underlying pathophysiology is the same (Barbe et al., 2014).

As an outstanding feature, freezing is an episodic phenomenon (reviewed by Nutt et al., 2011a). It can be triggered by movement initiation, turning, narrow spaces, as well as by stressful, emotional, and cognitively demanding situations (Schaafsma et al., 2003; Rahman et al., 2008; Spildooren et al., 2010). On top of this, patients with FOG were found to exhibit spatiotemporal gait abnormalities in between the transient freezing episodes (Nieuwboer et al., 2001; Hausdorff et al., 2003; Chee et al., 2009). Another distinct feature of FOG is trembling of the lower limbs (Moore et al., 2008; Jacobs et al., 2009), illustrating that FOG is characterized by abnormal and inefficient motor output rather than its mere absence.

As an episodic phenomenon, identification of FOG is difficult in a clinical setting. In order to capture patients with FOG, Snijders et al. (2012a) proposed a classification based on subjective reports of patients and their caregivers and on objective confirmation during clinical assessment. The freezing of gait questionnaire (FOG-Q; Giladi et al., 2000) is frequently used to assess subjective reports about FOG. This should be complemented by objective test including rapid 360° turns in both directions that proved to be most efficient to trigger freezing episodes.

1.4.2 Treatment

Therapeutic approaches for the treatment of FOG encompass established treatments in PD such as dopaminergic medication and DBS, as well as attentional and cueing strategies which have proven to be beneficial in FOG (Rahman et al., 2008; Vercruysse et al., 2012). However, optimal treatment is challenging, depending on individual patient characteristics such as symptom severity, circumstances triggering freezing episodes, dopamine responsiveness and comorbidities (reviewed by Nonnekes et al., 2015). Especially the relationship between dopaminergic treatment and FOG is complex with the effect of levodopa ranging from attenuating freezing (Schaafsma et al., 2003; Ferraye et al., 2008) to causing it (Espay et al., 2012). Moreover, FOG becomes less responsive to dopamine in the progression of PD, indicating an extension to non-dopaminergic structures controlling locomotion (reviewed by Nonnekes et al., 2015). In this regard, DBS of the PPN (Stefani et al., 2007; Ferraye et al., 2010) or the SNr (Chastan et al., 2009; Weiss et al., 2013) have been considered as promising means of treating FOG.

1.4.3 Pathophysiology

The pathophysiological models of FOG are as manifold as the freezing phenomenon itself. Its episodic character, symptom heterogeneity, and the complexity of the locomotor network complicate the development of a comprehensive model that can account for all facets of FOG. In the following, this thesis will provide an overview over the most important approaches for the present research question that each focus on different aspects of FOG and are not mutually exclusive (reviewed by Nutt et al., 2011a; Shine et al., 2011a; Nieuwboer and Giladi, 2013).

Threshold model

Plotnik et al. (2012) proposed FOG to be the consequence of multiple gait impairments passing a threshold above which functional gait is no longer possible. Indeed, the walking pattern of freezers is characterized by deficits in the control of amplitude (Chee et al., 2009), cadence (Nieuwboer et al., 2001), rhythm (Hausdorff et al., 2003), and coordination (Plotnik et al., 2008). Notably, exaggerating gait impairments by imposing smaller steps or higher cadence reliably provokes freezing episodes (Moreau et al., 2008). Contrary, ameliorating the walking pattern by unilateral STN stimulation led to less frequent freezing episodes (Fasano et al., 2011).

Impaired automaticity and cognitive control model

Hypoactivation of the SMA has been shown during gait imagery in freezers (Snijders et al., 2011a; Peterson et al., 2014), suggesting FOG to be the result of impaired internally guided movements mediated by the striato-thalamo-cortical loop (reviewed by Hallett, 2008). Likewise, patients with FOG are also prone to impairments within the range of executive functions (reviewed by Heremans

et al., 2013). As gait is highly dependent on attention and executive functions (reviewed by Yogev-Seligmann et al., 2008), FOG may be related to altered cognitive control of gait. This is supported by the higher occurrence of freezing episodes under cognitive load and computationally demanding situations as turning (Spildooren et al., 2010). In this regard, FOG has been associated with a disruption of the frontostriatal circuitry (reviewed by Bartels and Leenders, 2008; Shine et al., 2013c). Structural and functional changes in the frontoparietal network have been observed in freezers (Kostic et al., 2012; Tessitore et al., 2012; Herman et al., 2013; Brugger et al., 2015) as well as a loss of functional connectivity between the BG and prefrontal and parietal areas during freezing in a virtual reality paradigm (Shine et al., 2013b). The interplay between cortical and subcortical regions might be strained in situations requiring a response decision (Vandenbossche et al., 2012). More specifically, deficits in cognitive control will lead to insufficient compensation of the loss of automaticity, and thus to a breakdown of the system.

Decoupling model

Anticipatory postural adjustments (APAs) comprising the preparatory weight shifts preceding the first step were found to be abnormal with respect to timing and amplitude in patients with FOG (reviewed by Delval et al., 2014). Jacobs et al. (2009) even observed multiple APAs preceding stepping in freezers that coexisted with the characteristic knee trembling. The authors concluded step initiation failure to be a consequence of a decoupling between preparatory programming and subsequent release of the motor response. In support of the decoupling model, quick release of pre-programmed motor responses at the brainstem level by loud auditory stimuli, known as the StartReact effect, was shown to be missing in freezers but could be restored by PPN stimulation (Thevathasan et al., 2011).

Common neural pathway model

This model attempts to satisfy all aspects of freezing by assuming over-inhibition of brainstem and thalamic nuclei by exaggerated BG output to be the common neural pathway (Lewis and Barker, 2009; Lewis and Shine, 2016). According to the model, striatal dopamine depletion causes impaired communication between the complementary yet competing BG circuits. Depending on the dopaminergic reserve in combination with the exerted load on the BG, cross-talk might occur between the circuits being associated with excessive synchronization within the major output nuclei of the BG (GPi and SNr). This finally results in over-inhibition of the PPN and thalamus which in turn causes movement cessation. A freezing episode can be further triggered by over-activity within the STN in the presence of conflict. Importantly, the model predicts that movement can be re-established by using preserved pathways involved in externally guided or goal-directed behavior.

In a nutshell, the model allows for pathological impairments at multiple sites within the locomotor network and combines cognitive, motor, and limbic aspects of FOG.

1.4.4 Bicycling ability in PD patients with FOG

Although freezing is a widespread phenomenon affecting different types of movement including upper limb movements and speech (reviewed by Vercruysse et al., 2014), bicycling appears to be an exception (Snijders and Bloem, 2010; Snijders et al., 2011b, 2012b). It has even been suggested that loss of bicycling ability early in the progression of disease strongly supports a diagnosis of atypical parkinsonism rather than PD (Aerts et al., 2011). While there are clear inherent differences between walking and cycling, the pace, involved muscle groups, and cognitive goals are widely overlapping in these two conditions. Hence, there must be some major inherent difference in the activity and interplay of associated brain networks explaining why walking is impaired whereas cycling is preserved.

Snijders and colleagues (2011b, 2012) have proposed several hypotheses why bicycling ability is preserved in the context of impaired walking. First of all, the special conditions of bicycling with the mechanically coupled pedals moving at fixed amplitude may prevent accumulation of spatiotemporal deficits as it may happen during walking (Plotnik et al., 2012). Related to this, these constraints may impose fewer burdens on the impaired striato-thalamo-cortical motor circuit, thereby sparing sufficient resources for efficient motor output. Interestingly, unlocking the pedals of an adapted bicycle ergometer revealed the occurrence of sudden movement cessations similar to a freezing episode in PD patients (Abe et al., 2003).

A further explanatory approach focuses on the potential of bicycling to activate preserved pathways bypassing the BG as it might happen during cueing (reviewed by Nieuwboer, 2008). In this sense, the symmetrically moving pedals together with the constant resistance may provide tactile and auditory cues that enable bicycling to become more externally than internally guided. This may be further supported by the clear affordance of the bike, facilitating goal-directed behavior and hence preclude excessive demands on the BG (Lewis and Barker, 2009).

Moreover, deficient coupling of posture with movement in freezers (Jacobs et al., 2009) might impact both on movement initiation as well as on movement execution. Lateral weight shifts are an integral part of walking, as the body weight needs to be shifted to unload the stepping leg (reviewed by Winter, 1995). This complex sequence is not required in such a way during bicycling. Notably, reducing the demand of postural control and lateral weight shifts during walking with the walk-bicycle, i.e., a bicycle without pedals and a low seat, partly improved FOG (Stummer et al., 2015).

As Snijders et al. (2011b, 2012) have already pointed out, part of the aforementioned aspects unfolds its effect only during movement execution and hence cannot account for differences in movement initiation. It is conceivable that multiple aspects contribute to preserved bicycling ability in FOG which interact and vary in influence depending on the patient's background and the situation.

Despite the wealth of explanatory approaches, brain activity related to bicycling and walking has never been contrasted. Consequently, it is still an open question why both movements are so differently impacted in FOG. Answering this question is of high relevance in the context of rehabilitation because bicycling has been raised as effective therapy for PD, improving motor control (Ridgel et al., 2009) and cognitive performance (Ridgel et al., 2011), as well as attenuating tremor and bradykinesia (Ridgel et al., 2012). Strikingly, functional magnetic resonance imaging (fMRI) studies revealed forced exercise on a stationary bicycle to lead to similar cortical and subcortical activity as well as connectivity changes in PD patients as medication (Beall et al., 2013; reviewed by Alberts et al., 2011).

2 Aims

The purpose of this thesis was to contrast the modulation of cortical and subcortical oscillatory activity by bicycling and walking in healthy participants and PD patients.

Study 1 aimed to examine cortical oscillatory dynamics related to bicycling and walking in healthy participants. Recordings were performed during rest, bicycling on a stationary bicycle, and walking. In particular, the study focused at identifying sensorimotor oscillatory changes locked to a change of the movement state, i.e., from rest to move and *vice versa*. Furthermore, modulation of cortical activity within the movement cycle as well as its relationship to muscular activity was explored.

Study 2 investigated oscillatory changes in the BG of PD patients during bicycling and walking. To this end, LFPs were recorded directly from electrodes implanted in the STN for therapeutic stimulation. Special emphasis was put on activity within the beta band because of its high relevance in the pathophysiology of PD. Thus, potential alterations of beta activity by bicycling and walking were contrasted. Importantly, the study included patients with and without FOG. The aim was to identify oscillatory signatures that are related to or predictive of freezing behavior.

Clarifying the mechanism through which PD patients suffering from FOG retain the ability to bicycle has the potential to provide insight into the pathophysiology underlying FOG. The research question is of high relevance for symptom treatment and rehabilitation. Identifying mechanisms leading to FOG and the mechanism mediating the therapeutic benefits of bicycling may lead to improved therapeutic treatments alleviating FOG. Furthermore, knowledge about the neural basis of cortical control of bicycling and walking might be valuable for brain-machine interface based rehabilitation.

3 Paradigm

The same experimental paradigm was used in both studies. It was designed to characterize the oscillatory patterns as participants and patients initiated, sustained, and terminated pedaling. These were compared to the corresponding patterns associated with free walking at about the same pace.

The experiment consisted of two conditions, i.e., bicycling and walking. The order of conditions was pseudorandomized and counterbalanced across participants. Each condition started with a baseline rest period of 2 min, i.e., sitting on the bike or standing, respectively. This was followed by an alternating sequence containing 10 s of rest and 10 s of movement. Start and end of the movement phase was indicated by an acoustic signal (beep of 500 ms duration with a frequency of 1000 Hz for start and 1500 Hz for end), prompting participants to initiate and terminate pedaling and walking, respectively. The sequence was repeated, with the number of repetitions depending on the population under study. Healthy participants performed 50 repetitions. Patients solely performed 30 repetitions because of fatigue after surgery. The last part within each condition was moving continuously for 2 min (Fig. 5A).

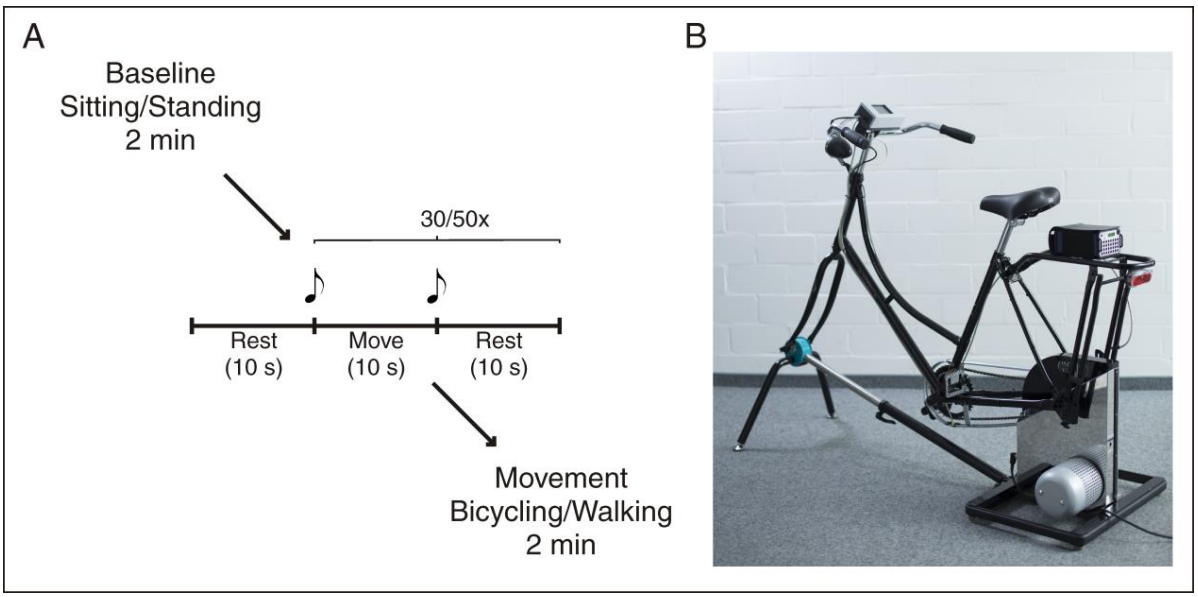

Figure 5: Experimental setup. (A) Schematic illustration of the experimental paradigm. Each condition started with a 2 min baseline rest period, i.e., sitting on the bicycle or standing, respectively. This was followed by repeatedly alternating 10 s movement and 10 s rest with further 10 s of rest at the beginning. This way, 30 or 50 instances of acoustically cued movement initiation and termination were captured dependent on the population under study. Subsequently, data were recorded during continuous walking or pedaling for 2 min. **(B)** The bicycle simulator consisted of a Dutch-style bicycle frame mounted on an ergometer. Pedal position was recorded simultaneously with all electrophysiological signals. Adapted and modified from Storzer et al. (2016).

While the walking condition was conducted in a 50 m long hallway, bicycling took place on a custom-made stationary bicycle (Fig. 5B). Originally developed to analyze bicycling performance parameters (Dahmen et al., 2011), it was upgraded with sensors to record parameters such as pedal position simultaneously with all electrophysiological signals. In addition, a computer-controlled brake to set pedaling resistance was added **(Appendix 5)**. Resistance was kept constant at 30 N at a target cadence of 40 revolutions per minute. Participants were instructed to walk with the same cadence, i.e., 40 strides per minute. The movement pattern was monitored with bilateral electronic goniometers that continuously tracked the knee angle and with footswitches placed under both feet during walking.

Electrophysiological data were recorded with a portable EEG/EMG amplifier (Porti amplifier, TMSi, Enschede, The Netherlands) and controlled by a combination of the open source software packages OpenBCI and Svarog (Durka et al., 2012). In both studies, EMG was recorded bilaterally from three leg muscles (*tibialis anterior*, *biceps femoris*, and *rectus femoris*) by bipolar surface electrodes. Whereas in study 1 cortical EEG was acquired in healthy participants with an 18-electrode cap, study 2 assessed LFPs from the STN in PD patients. The LFP signal was recorded by two bilaterally implanted DBS electrodes with externalized leads. That is, recordings were performed in the 1 to 5 day interval between electrode and stimulator implantation in the OFF medication state. Importantly, electrophysiological signals were recorded with actively shielded cables attenuating movement artifacts.

4 STUDY 1: Bicycling and Walking are Associated with Different Cortical Oscillatory Dynamics

Study 1 **(Appendix 1)** investigated cortical oscillatory dynamics involved in bicycling and walking in healthy participants. The aim was to clarify extent and aspects of cortical involvement in motor control. In particular, functional differences in the motor network subserving bicycling and walking were addressed. The comparison of these two distinct types of locomotion is especially interesting as it may help to understand why PD patients with severe FOG retain the ability to bicycle, which was investigated in the subsequent study 2.

4.1 Introduction

Previous work in this field has revealed sensorimotor alpha and beta power to be suppressed both during bicycling (Jain et al., 2013) and during walking (Gwin et al., 2011; Wagner et al., 2012; Seeber et al., 2014). These EEG studies further demonstrated modulation of cortical activity to be locked to specific phases within the movement cycle during both types of movement. Notably, Jain et al. (2013) found the alternating positive and negative cortical potentials in bicycling to be correlated with EMG activity of the leg muscles. However, only one EEG study has investigated power during the switch from standing to walking signifying a change of the movement state (Severens et al., 2012). The corresponding change back, i.e., from walking to standing is still unexplored.

As a direct comparison of brain activity related to bicycling and walking has never been performed, this study contrasted both movement state-dependent as well as movement phase-dependent EEG power changes underlying bicycling and walking. In addition, a possible relation between cortical and muscle activity was investigated.

4.2 Methods

15 healthy subjects participated in the study. EEG, EMG of the leg muscles, and movement kinematics were recorded simultaneously. One participant was excluded from the analysis due to severe movement and muscle artifacts. Data were recorded with the above described paradigm (Fig. 1 of Appendix 1), in which participants were asked to initiate, sustain, and terminate bicycling and walking after a baseline rest period, i.e., sitting and standing. Analysis was focused on the Cz electrode overlying the leg area of both motor cortices and the SMA. The goniometer signal was used to determine movement initiation and termination as well as the maximum knee flexion of the right knee that defined the starting point of the movement cycle. Averaged and time resolved movement state-related power changes were investigated with regard to three different frequency bands, i.e.,

alpha (8-12 Hz), low beta (13-22 Hz), and high beta (23-35 Hz) based on previous studies (López-Azcárate et al., 2010; Singh et al., 2013; Toledo et al., 2014). Movement phase-dependent power changes were compared between bicycling and walking with respect to phase and strength.

4.3 Results

4.3.1 Movement-related power changes

EEG data showed broadband power suppression during bicycling and walking relative to the baseline rest conditions with distinctive peaks in the alpha, low beta, and high beta band (Fig. 2 of Appendix 1). Frequencies of maximal suppression did not differ between conditions. However, walking was accompanied by stronger alpha power suppression, whereas the power decrease in the high beta band was stronger for bicycling. Regarding the time course of oscillatory activity (Fig. 3 of Appendix 1), the same pattern of a stronger high beta power suppression starting shortly before movement initiation in bicycling relative to walking could be observed. Opposed to this, walking was marked by a prompter alpha power decrease upon movement initiation. Furthermore, bicycling and walking differed significantly in the time course of the alpha power recovery after movement termination, with only a gradual recovery in walking. In contrast, beta power increased relative to the baseline rest condition immediately after movement termination in both conditions. This post-movement beta rebound was more pronounced and prolonged in bicycling compared to walking.

4.3.2 Movement cycle locked power modulations

Movement cycle-dependent power modulation in the 24-40 Hz range was evident for bicycling and walking (Fig. 4 of Appendix 1). Although, power modulation in the movement cycle followed a sinusoidal pattern in both conditions, it was stronger in walking with a phase lag between conditions. Power decreases occurred at 29.8 % and 79.1 % of the gait cycle and at 48.9 % and 92.1 % of the pedal cycle, respectively. These phases coincided with movement transitions from stance to swing in walking and flexion to extension in bicycling. Furthermore, these phase coincided with the maximum EMG activity of the legs for both conditions. In general, EMG activity was stronger in walking than bicycling. EEG and EMG activity within the movement cycle were found to be correlated for both conditions.

4.4 Discussion

Study 1 aimed to describe oscillatory correlates of cortical control of bicycling and walking. The present results revealed stronger movement state-dependent power modulations in the beta range (13-35 Hz) in bicycling, whereas alpha power suppression was more pronounced in walking.

Moreover, walking, as opposed to bicycling, expressed stronger movement phase-dependent power modulations in the 24-40 Hz range.

Why is bicycling accompanied by stronger sustained modulations of beta band activity? Generally speaking, sensorimotor beta power decrease has been related to an active state of the sensorimotor cortex (Seeber et al., 2014) and to a change of the current motor state (Engel and Fries, 2010). Consequently, bicycling seems to promote the switch from a resting state to a dynamic state and *vice versa*. A key difference between bicycling and walking that might be associated with the stronger beta power suppression could be the more continuous nature of bicycling, which lacks the stationary phases that are part of walking. Indeed, beta power was found to remain suppressed during continuous movements (Erbil and Ungan, 2007; Gwin and Ferris, 2012), whereas it recovered during isometric movements (Cassim et al., 2000; Gwin and Ferris, 2012). Along these lines, the continuous motor output in bicycling might also result in stronger inhibition processes at movement termination that are thought to be reflected by the beta rebound (Solis-Escalante et al., 2012).

As a further aspect, the present results indicated walking to be accompanied by a stronger alpha power suppression compared to bicycling. This difference was evident at movement initiation and especially after movement termination due to a slow alpha power recovery in walking. In line with the association between alpha activity and attentional information processing (reviewed by Klimesch, 2012), alpha power suppression was especially observed during walking with interactive movement-related feedback (Wagner et al., 2014) or during precision walking (Presacco et al., 2011). Thus, stronger alpha power suppression in walking than bicycling may reflect enhanced sensory and attentional demands.

Higher computational load in walking relative to bicycling is also emphasized by the stronger movement phase-dependent power modulation in the 24-40 Hz range. The current results contribute to the growing evidence that oscillations in the 24-40 Hz range are closely connected to motor planning and sensorimotor processing (Wagner et al., 2012, 2014, Seeber et al., 2014, 2015). Irrespective of the movement type, power decreases occurred during movement transition phases, i.e., transition between the stance and swing phase in walking and flexion and extension in bicycling. Notably, EEG power and EMG activity were found to be correlated, with power decreases coinciding with maximal recruitment of the *tibialis anterior* and *biceps femoris*. Related to this, Petersen et al. (2012) demonstrated that cortical activity at the Cz electrode was leading muscular activity of the *tibialis anterior* in the 24-40 Hz range.

The interesting finding of more pronounced power modulation suggests walking to be associated with more extensive motor planning and sensory processing within the movement-cycle. There are

two complementary explanations for the obtained result: The more continuous and more restricted movement pattern in bicycling with pedals moving at fixed phase difference and circumference may demand less motor planning within the pedal cycle. This is supported by higher dual-tasks costs during walking than bicycling in PD patients (Yogev-Seligmann et al., 2013). Alternatively, integration of sensory information into the motor command might be more pronounced during walking. Almost identical activation patterns in passive and active bicycling and walking (Wagner et al., 2012; Jain et al., 2013) highlight the huge contribution of sensory afferents to sensorimotor activity. Indeed, sensory information might be less required in bicycling due to the predetermined movement pattern. Efferent corticospinal output during bicycling might even lead to sensory gating, thus, attenuation of within-cycle modulations (Duysens et al., 2013; Jain et al., 2013).

The current study may shed some light on the puzzling finding of preserved bicycling abilities in PD patients suffering from FOG (Snijders and Bloem, 2010; Snijders et al., 2011b, 2012b). Abnormal activity in the high beta band over central, parietal, and occipital regions has been shown to be associated with gait initiation failure in PD patients (Ly et al., 2016), freezing during turning (Handojoseno et al., 2015), and the transition from walking to freezing (Shine et al., 2014). It has to be noted that the study at hand investigated oscillatory changes in healthy participants, and hence revealed physiological processes that may or may not be altered in PD patients. Nevertheless, it is tempting to reason that stronger cortical high beta power suppression is part of the reason why bicycling is less prone to abnormal motor output relative to walking. This hypothesis was specifically addressed in study 2.

The presence of muscle artifacts contaminating the EEG especially during walking is a major drawback of the present study. These artifacts were found to be restricted to lower frequencies only up to 10 Hz, and so could not influence the presented results in the higher beta frequency band. Nevertheless, these artifacts precluded the analysis of theta band activity that has recently gained attention in the context of FOG (Shine et al., 2014; Handojoseno et al., 2015; Scholten et al., 2016).

4.5 Conclusion

Study 1 revealed that bicycling and walking are associated with different cortical oscillatory dynamics. Movement state-dependent high beta power modulation was more pronounced in bicycling as opposed to walking. Conversely, movement phase-dependent power modulation in the 24-40 Hz range was found to be stronger in walking relative to bicycling. In conclusion, the results suggest that, relative to walking, bicycling is characterized by a stronger sustained cortical activation and less phase-dependent sensorimotor processing.

5 STUDY 2: Stronger subthalamic beta power suppression in bicycling relative to walking in Parkinson's disease

In study 1, it was shown that bicycling is accompanied by stronger cortical beta power suppression relative to walking. This is particularly interesting as abnormally increased beta band activity in the striato-thalamo-cortical loop is related to motor impairment in PD patients (reviewed by Oswal et al., 2013). This raises the question *if* and *how* beta band oscillations are modulated by bicycling relative to walking in the BG of PD patients, especially in the context of FOG. Therefore, study 2 **(Appendix 2)** aimed to characterize the relationship between both types of movement and deep brain activity to clarify the mechanisms through which bicycling ability is less affected in Parkinson's disease patients, in particular in freezers.

5.1 Introduction

LFP recordings from implanted DBS electrodes in the BG have revealed that walking modulates beta band oscillations (Singh et al., 2011, 2013). Notably, Singh et al. (2013) observed a broadband beta power suppression in the STN of non-freezers during walking, while oscillatory activity was specifically increased in the low beta band (12-22 Hz) in freezers. These results support the notion of excessive synchronization in the BG to lead to paroxysmal movement cessation (Lewis and Barker, 2009). However, the physiological mechanism behind this oscillatory profile remains elusive. It might even be the case that it is not specifically related to gait impairment in freezers but a general signature of altered BG activity that distinguishes freezers from non-freezers. Thus, it is of high relevance to investigate oscillatory activity subserving similar types of movement that provoke and lack freezing, respectively, such as walking and bicycling. Moreover, preserved bicycling ability in freezers implies that the associated brain networks in these patients somehow remain intact in pedaling but are compromised when attempting to walk. However, to the best of my knowledge, no study has recorded oscillatory activity of the BG during bicycling.

Therefore, this study compared oscillatory differences between bicycling and walking in PD patients with DBS electrodes implanted in the STN, with the aim of revealing how each movement type is associated with beta band modulations. We hypothesized that bicycling would attenuate pathological beta oscillations within the basal ganglia as compared to walking.

5.2 Methods

13 PD patients clinically selected for DBS participated in this study. Recordings took place 1-5 days after electrode implantation in the OFF medication state (except for one patient who was recorded in the ON medication state). STN LFPs, cortical EEG electrodes covering the sensorimotor cortex, and EMG of bilateral leg muscles were recorded simultaneously while patients engaged in bicycling and walking (Fig. 1 of Appendix 2). One patient did not complete the paradigm due to fatigue and hence data of two STN were not included in the analysis. Additionally, four STNs of two patients and four further STNs had to be excluded due to a non-functional extension or movement artifact contamination. Thus, 16 STNs of 10 PD patients were included in the analysis (Table 1 of Appendix 2). Analysis was focused on the bipolar STN channel showing the strongest beta power modulation (pooled over conditions).

Effects of movement ('rest' vs. 'move') and posture ('on bike' vs. 'on foot') on beta power were tested by repeated measures analysis of variance. Beta power changes were further analyzed locked to movement initiation and termination. Analysis was conducted with respect to the patients' classification as freezer or non-freezer based on the FOG-Q question #3: "Do you feel that your feet get glued to the floor while walking, turning or when trying to initiate walking?". This way, four patients were classified as freezers, six patients as non-freezers.

5.3 Results

5.3.1 Effect of movement and posture on beta power

STN beta power was significantly decreased during movement irrespective of posture (Fig. 2 of Appendix 2). The strongest beta power suppression was observed on average at 22.5 Hz (*SD* = 6.1 Hz). Furthermore, the power decrease from sitting to pedaling was stronger as compared to the power decrease from standing to walking.

5.3.2 Beta power changes locked to movement initiation and termination

Beta power relative to the baseline rest conditions was found to decrease upon the initiation of bicycling and walking. Bicycling reduced broadband beta power (10-30 Hz) relative to walking in both PD populations (Fig. 3 and 4 of Appendix 2). A high beta power increase occurring immediately after movement termination was evident in both movement conditions and of similar magnitude. It has to be noted that the baseline rest conditions, i.e., sitting and standing, were found to be significantly different in the 19-28 Hz range with higher beta power during sitting relative to walking.

5.3.3 Movement-related beta power changes in patients with freezing of gait

Patients with a history of FOG exhibited an abnormal narrowband power increase at ∼18 Hz in the STN that was not present in PD patients without FOG (Fig. 4 of Appendix 2). Importantly, this power increase was observed in the absence of actual freezing episodes. This oscillation was clearly intensified during walking, whereas it was of smaller amplitude at the initiation of bicycling and even vanished after 2 seconds. Importantly, this ~18 Hz oscillation was anti-correlated with the remaining beta band specifically during walking, and was particularly enhanced at initiation and termination of walking (Fig. 5 of Appendix 2).

5.4 Discussion

While study 1 looked at cortical involvement in locomotor control, the present study is one of the rare contributions to the investigation of BG oscillatory dynamics underlying bicycling and walking. Implantation of electrodes for DBS therapy in PD patients provides the extraordinarily valuable opportunity to examine neural activity from the BG, the primary brain structure implicated in PD. Study 2 revealed bicycling to be marked by stronger suppression of beta oscillations in the STN of PD patients compared to walking. Strikingly, results clearly indicated a relationship between a patient's susceptibility to freezing and an abnormal ∼18 Hz oscillation.

Study 2 extends the findings of study 1 by demonstrating stronger beta power suppression during bicycling compared to walking in the BG of PD patients. Unlike in study 1, STN beta rebound after movement termination was of similar magnitude. Thus, the functional difference in BG activity between bicycling and walking was specific to beta power suppression during movement. A particularly intriguing possibility is that bicycling suppresses the pathological beta oscillations in the BG. It is not unlikely that this is part of the reason why PD symptoms, especially freezing, are less severe on a bike. Furthermore, this is plausibly explaining why bicycling has therapeutic effects regarding both motor and cognitive functions (Ridgel et al., 2009, 2011, 2012).

What are the potential reasons for the difference in STN beta power suppression between bicycling and walking? In this respect one might again consider the continuous nature of bicycling as opposed to the alternating stance and swing phases in walking. A continuous movement pattern implicates a higher likelihood of the subsequent movement which has been related to beta power suppression (Jenkinson and Brown, 2011). This may be reinforced by the high predictability of bicycling with few degrees of freedom due to the circular pedal trajectory. Consequently, stronger beta power suppression in bicycling than walking might reflect the more continuous and more predictable movement pattern in bicycling that is likely imposing a lower computational load on the motor

system. This may also prevent 'overloading' the networks involved in locomotion which has been related to FOG (Lewis and Barker, 2009; Lewis and Shine, 2016).

As the most outstanding finding in the present study, synchronized activity at about 18 Hz appears to be a clear marker that identifies patients with freezing of gait. This abnormal oscillation is remarkably intensified during walking whereas in bicycling, it is not only greatly reduced in amplitude but also restricted to the first two seconds of pedaling initiation. One of the few previous studies recording LFPs in patients with FOG also found a selective low beta STN power (12-22 Hz) increase during walking (Singh et al., 2013). Moreover, Quinn et al. (2015) observed walking to be accompanied by a power decrease in the STN, leaving a peak of about 18 Hz in akinetic-rigid patients. Crucially, the abnormal ∼18 Hz oscillation was anti-correlated with the remaining beta band specifically during walking in the study at hand.

The mechanism behind the abnormal ∼18 Hz oscillation remains to be clarified. First of all, the synchronized activity during walking might reflect a movement-inhibiting signal in a subcortical network. This is supported by the pathological significance of synchronization in the lower beta range with respect to bradykinesia and rigidity (reviewed by Brown, 2007; Brittain and Brown, 2014). Moreover, the STN is assumed to be part of a stopping network, in which frontal cortical areas exert top-down control via the hyperdirect pathway, yielding inhibition of the motor output by the STN (Aron and Poldrack, 2006; Frank, 2006; Cavanagh and Frank, 2013). Interestingly, Wagner et al. (2016) found step shortening due to cued tempo shifts in healthy subjects to be associated with a frontal narrowband low beta power increase, thought to reflect a top down motor inhibition signal. Moreover, Scholten et al. (2016) found phase synchronization in the beta band over the left prefrontal area to be associated with increased susceptibility to upper limb freezing. Thus, an excessive cortically driven inhibitory signal might manifest as abnormal ~18 Hz oscillation in the STN of freezing patients.

However, it has also been proposed that beta oscillations emerge from the interaction between STN and GPe (Holgado et al., 2010). Simultaneous recordings from the STN, PPN, and M1 in hemiparkinsonian rats support the STN as potential source of excessive beta activity during walking as it was driving beta activity in both PPN and M1 (Li et al., 2016). Intriguingly, McCarthy et al. (2011) found a 17 Hz oscillation originating in the striatum due to increased levels of cholinergic drive as a consequence of dopamine depletion. In a follow-up study the authors further demonstrated that optogenetic stimulation of striatal cholinergic interneurons in mice leads to elevated beta oscillations in the striatum and M1, inducing hypokinetic motor deficits (Kondabolu et al., 2016).

A point which warrants a comment in this discussion is that albeit patients defined as freezers selectively displayed the abnormal ~18 Hz oscillation during walking, they did not freeze. One possible explanation might be that this oscillatory signature reflects susceptibility to freezing and might be boosted during actual freezing episodes. These might be potentially triggered by response conflict or additional motor, cognitive, and limbic load on the striato-thalamo-cortical loop (Lewis and Barker, 2009; Lewis and Shine, 2016). Alternatively, the ~18 Hz oscillation might be reflective of a compensatory mechanism. It has been suggested that FOG might result from altered brain activity and the inability to compensate for this alteration (reviewed by Snijders et al., 2016). For example, Snijders et al., (2011a) reasoned increased activity of the PPN to compensate for cortical alterations in freezers. As PPN stimulation is most effective in the beta range (Thevathasan et al., 2010), especially for ameliorating FOG (Thevathasan et al., 2012a), the 18 Hz oscillation might originate in the PPN. Yet, this is rather unlikely as PPN oscillations show different characteristics regarding the dominant peak frequency, bandwidth, and timing of movement-related modulation (Tsang et al., 2010; Thevathasan et al., 2012b).

Interpreting the results one has to keep in mind that patients were identified as freezers according to the FOG-Q, i.e., based on subjective reports which is a shortcoming of the study. Future studies should definitely include an objective examination of freezing behavior and include only patients with definite acute FOG (Snijders et al., 2012a). Furthermore, due to the small sample sizes of the present study we did not test for differences between freezers and non-freezers. Nevertheless, our data are in line with previous research (Singh et al., 2013) and provide a promising starting point for future studies. Such work should include a representative number of patients with and without freezing of gait allowing adequate statistical testing.

5.5 Conclusion

The study demonstrated bicycling to be accompanied by a stronger movement-related suppression of pathological STN beta oscillations compared to walking. Moreover, the results strongly suggest that FOG arises from a specific movement-inhibiting signal in subcortical networks that is lessened in bicycling. It is likely that the continuous and computationally less demanding nature of bicycling compared to walking lowers the susceptibility to 'overloading' the networks involved in locomotion.

6 General Discussion

The present thesis focused on functional differences in the motor network controlling bicycling and walking. The aim of this thesis was to contribute to understanding why bicycling and walking, two similar types of movement, are differently affected in PD patients with FOG. For this purpose, oscillatory activity subserving bicycling and walking was contrasted both at the cortical level in healthy participants (study 1) and at the subcortical level in PD patients (study 2) using the same paradigm. This way, this thesis revealed new insights into movement-specific brain dynamics at different brain areas and in different populations.

The significance of oscillatory activity in the beta band subserving bicycling and walking was revealed in study 1 and 2. More specifically, stronger beta power suppression in bicycling compared to walking turned out to be the key functional difference in the motor network subserving both types of movement. This is especially interesting as excessive synchronization in the beta band is a hallmark of PD (reviewed by Oswal et al., 2013) and has been linked to FOG in particular (Singh et al., 2013; Shine et al., 2014; Handojoseno et al., 2015; Ly et al., 2016; Scholten et al., 2016). Intriguingly, the difference in beta power suppression was seen irrespective of the population under study, i.e., healthy participants, freezers, and non-freezers, and the recording site, i.e., cortex or BG. Thus, it can be concluded that bicycling promotes a widespread attenuation of beta oscillations in the striato-thalamo-cortical network.

Furthermore, the present work highlighted the role of various, distinct beta rhythms. On the one side, study 1 showed that the difference in sensorimotor oscillatory activity between bicycling and walking was evident in the high beta range. On the other side, study 2 demonstrated bicycling to be accompanied by a broadband beta power decrease compared to walking in the parkinsonian STN. However, a closer look at patients with FOG revealed an oscillatory signature in the low beta range during walking signifying the susceptibility to freezing.

These observations are well in line with the current knowledge about beta oscillations and their modulation by DBS. It was shown that DBS suppresses oscillatory activity in the STN in the low beta range (Whitmer et al., 2012; Oswal et al., 2016) with the attenuation being maximal at 18 Hz (Whitmer et al., 2012). Furthermore, DBS-related suppression of low beta band activity was found to correlate with motor improvement (Oswal et al., 2016). However, functional coupling between the STN and mesial cortical motor areas was typically observed in the high beta range with the cortex driving the STN likely via the hyperdirect pathway (Hirschmann et al., 2011; Litvak et al., 2011; Oswal et al., 2016). Increased activity within the hyperdirect pathway has even been proposed as a prerequisite for excessive STN beta band synchronization (Holgado et al., 2010). Yet, DBS-related

suppression of the coupling was not correlated with motor improvement (Oswal et al., 2016) which is consistent with the assumption that the therapeutic effects of DBS are mediated by suppressing low beta activity locally in the STN (reviewed by Eusebio et al., 2012). Thus, bicycling-related modulation of spatially and spectrally distinct motor hubs could be one possible explanation why patients with FOG remain able to bicycle effortlessly and why bicycling has a therapeutic effect.

The question is, why bicycling is accompanied by stronger beta power suppression, whereas walking is prone to synchronization in the BG? Study 1 suggests a lower computational load for bicycling compared to walking. Walking requires extensive motor planning and sensorimotor processing with every step as it is indicated by the prominent 24-40 Hz modulation within the movement cycle. Stronger alpha power suppression in walking that is associated with attention and information processing (reviewed by Klimesch, 2012) supports the idea of a higher computational load in walking. Conversely, the motor output in bicycling is more continuously and thereby more predictable once pedaling has successfully commenced. These aspects have been linked to beta power suppression (Engel and Fries, 2010; Jenkinson and Brown, 2011).

The current results add valuable information to the discussion about the paradoxical bicycling ability in patients with FOG. The data suggest the lower computational load for bicycling as the critical factor for the ability to bike. Therefore, this thesis supports the assumption of Snijders et al. (2011b, 2012) that bicycling imposes fewer burdens on the impaired striato-thalamo-cortical loop, thereby sparing sufficient resources for efficient motor output. The thesis extends this line of thinking by underlining the pivotal role of BG synchronous oscillations. It can be hypothesized that the low demands during bicycling decrease the risk of interference between the parallel but separated cortico-BG circuits. According to the common neural pathway model (Lewis and Barker, 2009; Lewis and Shine, 2016), reduced interference should result in less pathological synchronization in the BG. Indeed, this is exactly what study 2 revealed, namely smaller amplitude of the abnormal 18 Hz oscillation that even ceases during pedaling. Conversely, walking is susceptible to synchronization in the BG because of its inherent high computational load. As such, walking is prone to an ‘overload’ of the motor network involved in locomotion. This vulnerability may even be intensified because of lower cognitive capacities in patients with FOG (reviewed by Heremans et al., 2013) and accumulation of gait impairments reaching a saturation point triggering freezing episodes (Plotnik et al., 2012).

However, it remains an open question why patients with FOG do not freeze when attempting to initiate bicycling but walking. Lower computational load during bicycling is only effective once pedaling has successfully begun. Furthermore, synchronization at ∼18 Hz was also evident during the first two seconds of bicycling, though to a smaller extent. One possible explanation is that movement

initiation is in general a potential trigger for freezing episodes. Yet, initiation failure is more likely during walking because of the required coupling of posture and gait (Jacobs et al., 2009). Furthermore, it can be hypothesized that the tactile feedback of the pedals affects beta power suppression (Cassim et al., 2001; van Ede and Maris, 2013). This in turn might enable to initiate pedaling, or to use pathways involved in externally guided movements. Future studies are needed to clarify if different mechanisms contribute to freezing during movement initiation and movement execution.

Although the present thesis provided electrophysiological correlates of both motor control and the risk of freezing, the conducted studies do not allow drawing causal conclusions. Bicycling and walking differ in several aspects, e.g. sensorimotor input, postural control, and coordination. Based on current theories, functional differences in the motor network underlying bicycling and walking have been related to differences in the movement pattern. Yet, a causal link between movement continuity and beta oscillations remains to be demonstrated. Moreover, both studies concentrated on modulation of beta oscillations which is the most obvious frequency band involved in motor control and PD pathophysiology. However, HFOs and their coupling to the phase of beta oscillations have been suggested to be of clinical relevance (Foffani et al., 2003; López-Azcárate et al., 2010; Özkurt et al., 2011; Yang et al., 2014; Hirschmann et al., 2016). It has even been argued that HFOs might serve as a complementary electrophysiological marker to beta oscillations that might be used for closed-loop DBS (Hirschmann et al., 2016). Consequently, investigating the modulation of HFO activity by bicycling and walking might be a promising attempt to further clarify the questions why freezers are able to bicycle.

In summary, this thesis made valuable contributions to research on neural oscillations underlying bicycling and walking. Novel findings regarding cortical and subcortical control of bicycling were demonstrated and the neural control of bicycling was contrasted with the neural control of walking. In addition, an electrophysiological signature of freezing susceptibility was revealed. Together, this is highly relevant in the context of therapy for PD. The more we know about physiological and pathological brain activity, the more treatment options can be improved.

7 Outlook

This thesis contributed to the understanding of functional differences in the motor network between bicycling and walking and provides clear avenues for further research and potential therapies.

Neural control of locomotion is dependent on a distributed but tightly connected network comprising cortical and subcortical brain regions. It is also assumed that FOG might be caused by pathological impairments at multiple sites within the locomotor network including the PPN (reviewed by Nutt et al., 2011a). This strongly emphasizes the need to record electrophysiological data from cortical and subcortical brain regions simultaneously to reveal faulty motor network activity associated with FOG. In this regard, investigating functional connectivity within the motor network might provide valuable insight into the direction of information flow between the target brain regions. It would be desirable to identify brain states associated with normal locomotion, the transition to freezing, and actual freezing episodes to elucidate the exact mechanism behind the paroxysmal movement cessation.

Simultaneous magnetoencephalography (MEG) and LFP recordings in PD patients selected for therapeutic DBS have already been successfully performed (Hirschmann et al., 2011; Litvak et al., 2011). MEG has a good spatial resolution and can be combined with state-of-the-art source localization techniques that enable a satisfying localization of cortical sources. Investigating neural activity while patients are moving is, however, not possible with MEG. This problem can be dealt with by using MEG compatible pedaling and stepping devices similar to the ones used in previous fMRI studies (Mehta et al., 2009; Shine et al., 2011b). Movements based on these devices would be qualitatively different from actual bicycling and walking. Nevertheless, computational load would still be different between bicycling and walking due to locked vs. unlocked pedals, respectively. As this thesis suggests the lower computational load for bicycling as the critical factor for the ability to bike these movements might be adequate surrogates. Likewise, freezing behavior might be investigated using a finger tapping paradigm (Barbe et al., 2014; Scholten et al., 2016).

The effect of computational load on brain activity and freezing behavior can be further examined using a virtual environment (Shine et al., 2011b). This allows for flexible manipulation of motor and cognitive load by including e.g. obstacles or dual-task situations. Patients with FOG were characterized by a deficient activation of cortical and subcortical brain regions in response to higher cognitive load as measured with fMRI (Shine et al., 2013a). Yet, the blood-oxygen-level dependent contrast is only an indirect measurement of brain activity while MEG signals are direct correlates of neuronal activity. Examining brain activity by means of MEG allows to test the hypothesis that FOG is linked to excessive synchronization in the BG of PD patients (Lewis and Barker, 2009; Lewis and

Shine, 2016). Moreover, it might reveal differential oscillatory patterns in bicycling and walking during the performance of simultaneous cognitive and motor functions that may be related to the preserved bicycling ability in freezers.

The bicycle simulator that was used in the present studies is already equipped to play videos synchronized to pedaling. This would be a great opportunity to investigate the effect of sensory input, optic flow, and higher demand on motor control due to winding pathways or obstacles on brain activity during pedaling on the bicycle simulator. The ability to record EEG and LFP data during pedaling on the bicycle simulator was already exploited in the second study but without using the video option. So far, EEG recordings are limited in the number of EEG channels due to head bandages that patients still have the days after surgery. As a solution, DBS devices can be used that transmit data recorded from deep brain electrodes via wireless data transfer (e.g. Medtronic Activa PC+S in Quinn et al., 2015; Neumann et al., 2016). This way, data could be acquired month after DBS surgery with a chronically implanted neurostimulator because physical access to the electrodes is no longer needed. Usage of such a device would greatly expand opportunities such as simultaneous recording of LFPs from the BG and cortical activity with high-density EEG covering the whole scalp. Using high-density EEG would allow for more sophisticated artefact rejection approaches (Bulea et al., 2015; Seeber et al., 2015; Wagner et al., 2016). This would permit to investigate modulation in the theta range that has been linked to FOG (Shine et al., 2014) but is frequently contaminated by movement artefacts.

As a further step, cortical brain activity can be modulated by means of transcranial magnetic stimulation or transcranial direct/alternating current stimulation. This would allow causal interferences about the functional role of cortical oscillatory activity in motor control and FOG. Similarly, brain activity can be contrasted between DBS OFF and DBS ON using newly developed artefact rejection methods (Abbasi et al., 2016). This way, the effect of stimulating different target regions such as the STN, SNr, or PPN on oscillatory activity measured with MEG might be explored and correlated with gait improvement.

Identifying mechanisms leading to FOG and oscillatory signatures indicative of freezing susceptibility should lead to improved therapeutic treatments alleviating FOG. This line of research might be complemented by recording oscillatory activity during different kinds of physical training, such as treadmill walking, dancing, and bicycling. Although feasibility of physical activity as potential therapy for PD patients is already being studied (reviewed by Petzinger et al., 2013), this is not yet combined with investigating brain activity. With DBS devices that enable wireless data transfer patients will be able to participate in more comprehensive experiments after they have recovered from the surgical procedure. This way, oscillatory activity could be monitored during different cycling training regimen,

such as during forced exercise (Ridgel et al., 2009; reviewed by Alberts et al., 2011) and could be correlated with the therapeutic outcome.

Altogether, these future projects will enrich the therapeutic options for PD patients with and without FOG. This is of high relevance as treatment of gait impairment is still challenging but indispensable for improving mobility and quality of life of PD patients.

8 References

Abbasi O, Hirschmann J, Schmitz G, Schnitzler A, Butz M (2016) Rejecting deep brain stimulation artefacts from MEG data using ICA and mutual information. J Neurosci Methods 268:131–141.

Abe K, Asai Y, Matsuo Y, Nomura T, Sato S, Inoue S, Mizukura I, Sakoda S (2003) Classifying lower limb dynamics in Parkinson's disease. Brain Res Bull 61:219–226.

Aerts M, Abdo W, Bloem B (2011) The "bicycle sign" for atypical parkinsonism. Lancet 377:125–126.

Alberts JL, Linder SM, Penko AL, Lowe MJ, Phillips M (2011) It Is Not About the Bike , It Is About the Pedaling. Exerc Sport Sci Rev 39:177–186.

Albin RL, Young AB, Penney JB (1989) The functional anatomy of basal ganglia disorders. Trends Neurosci 12:366–375.

Alegre M, Labarga A, Gurtubay IG, Iriarte J, Malanda A, Artieda J (2002) Beta electroencephalograph changes during passive movements: sensory afferences contribute to beta event-related desynchronization in humans. Neurosci Lett 331:29–32.

Alexander GE, DeLong MR, Strick PL (1986) Parallel Organization of Functionally Segregated Circuits Linking Basal Ganglia and Cortex. Annu Rev Neurosci 9:357–381.

Aron AR, Poldrack RA (2006) Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. J Neurosci 26:2424–2433.

Ashby FG, Turner BO, Horvitz JC (2010) Cortical and basal ganglia contributions to habit learning and automaticity. Trends Cogn Sci 14:208–215.

Barbe MT, Amarell M, Snijders AH, Florin E, Quatuor E-L, Schönau E, Fink GR, Bloem BR, Timmermann L (2014) Gait and upper limb variability in Parkinson's disease patients with and without freezing of gait. J Neurol 261:330–342.

Bartels AL, Balash Y, Gurevich T, Schaafsma JD, Hausdorff JM, Giladi N (2003) Relationship between freezing of gait (FOG) and other features of Parkinson's: FOG is not correlated with bradykinesia. J Clin Neurosci 10:584–588.

Bartels AL, Leenders KL (2008) Brain imaging in patients with freezing of gait. Mov Disord 23:461–467.

Beall EB, Lowe MJ, Alberts JL, Frankemolle AMM, Thota AK, Shah C, Phillips MD (2013) The Effect of Forced-Exercise Therapy for Parkinson's Disease on Motor Cortex Functional Connectivity. Brain Connect 3:190–198.

Benabid AL, Chabardes S, Mitrofanis J, Pollak P (2009) Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol 8:67–81.

Bohnen NI, Jahn K (2013) Imaging: What can it tell us about parkinsonian gait? Mov Disord 28:1492–1500.

Bostan AC, Dum RP, Strick PL (2013) Cerebellar networks with the cerebral cortex and basal ganglia. Trends Cogn Sci 17:241–254.

Brittain J-S, Brown P (2014) Oscillations and the basal ganglia: Motor control and beyond. Neuroimage 85:637–647.

Brittain J-S, Sharott A, Brown P (2014) The highs and lows of beta activity in cortico-basal ganglia loops. Eur J Neurosci 39:1951–1959.

Brown P (2007) Abnormal oscillatory synchronisation in the motor system leads to impaired movement. Curr Opin Neurobiol 17:656–664.

Brugger F, Abela E, Hägele-Link S, Bohlhalter S, Galovic M, Kägi G (2015) Do executive dysfunction and freezing of gait in Parkinson's disease share the same neuroanatomical correlates? J Neurol Sci 356:184–187.

Bulea TC, Kim J, Damiano DL, Stanley CJ, Park H-S (2015) Prefrontal, posterior parietal and sensorimotor network activity underlying speed control during walking. Front Hum Neurosci 9:247.

Buneo CA, Andersen RA (2006) The posterior parietal cortex: Sensorimotor interface for the planning and online control of visually guided movements. Neuropsychologia 44:2594–2606.

Buzsáki G, Anastassiou CA, Koch C (2012) The origin of extracellular fields and currents--EEG, ECoG, LFP and spikes. Nat Rev Neurosci 13:407–420.

Cassim F, Monaca C, Szurhaj W, Bourriez JL, Defebvre L, Derambure P, Guieu JD (2001) Does post-movement beta synchronization reflect an idling motor cortex? Neuroreport 12:3859–3863.

Cassim F, Szurhaj W, Sediri H, Devos D, Bourriez JL, Poirot I, Derambure P, Defebvre L, Guieu JD (2000) Brief and sustained movements: Differences in event-related (de)synchronization (ERD/ERS) patterns. Clin Neurophysiol 111:2032–2039.

Cavanagh JF, Frank MJ (2013) Stop! Stay tuned for more information. Exp Neurol 247:289–291.

Chastan N, Westby GWM, Yelnik J, Bardinet E, Do MC, Agid Y, Welter ML (2009) Effects of nigral stimulation on locomotion and postural stability in patients with Parkinson's disease. Brain 132:172–184.

Chee R, Murphy A, Danoudis M, Georgiou-Karistianis N, Iansek R (2009) Gait freezing in Parkinson's disease and the stride length sequence effect interaction. Brain 132:2151–2160.

Chen CC, Litvak V, Gilbertson T, Kühn A, Lu CS, Lee ST, Tsai CH, Tisch S, Limousin P, Hariz M, Brown P (2007) Excessive synchronization of basal ganglia neurons at 20 Hz slows movement in Parkinson's disease. Exp Neurol 205:214–221.

Christensen LOD, Johannsen P, Sinkjaer T, Petersen N, Pyndt HS, Nielsen JB (2000) Cerebral activation during bicycle movements in man. Exp Brain Res 135:66–72.

Collomb-Clerc A, Welter M-L (2015) Effects of deep brain stimulation on balance and gait in patients with Parkinson's disease: A systematic neurophysiological review. Neurophysiol Clin Neurophysiol 45:371–388.

Curtze C, Nutt JG, Carlson-Kuhta P, Mancini M, Horak FB (2015) Levodopa Is a Double-Edged Sword for Balance and Gait in People With Parkinson's Disease. Mov Disord 30:1361–1370.

Dahmen T, Byshko R, Saupe D, Röder M, Mantler S (2011) Validation of a model and a simulator for road cycling on real tracks. Sport Eng 14:95–110.

de Hemptinne C, Ryapolova-Webb ES, Air EL, Garcia PA, Miller KJ, Ojemann JG, Ostrem JL, Galifianakis NB, Starr PA (2013) Exaggerated phase-amplitude coupling in the primary motor cortex in Parkinson disease. Proc Natl Acad Sci 110:4780–4785.

de Lau LM, Breteler MM (2006) Epidemiology of Parkinson's disease. Lancet Neurol 5:525–535.

Debaere F, Wenderoth N, Sunaert S, Van Hecke P, Swinnen SP (2003) Internal vs external generation of movements: Differential neural pathways involved in bimanual coordination performed in the presence or absence of augmented visual feedback. Neuroimage 19:764–776.

Debaere F, Wenderoth N, Sunaert S, Van Hecke P, Swinnen SP (2004) Cerebellar and premotor function in bimanual coordination: Parametric neural responses to spatiotemporal complexity and cycling frequency. Neuroimage 21:1416–1427.

DeLong MR (1990) Primate models of movement disorders of basal ganglia origin. Trends Neurosci 13:281–285.

Delval A, Tard C, Defebvre L (2014) Why we should study gait initiation in Parkinson's disease. Neurophysiol Clin Neurophysiol 44:69–76.

Deuschl G et al. (2006) A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med 355:896–908.

Durka PJ, Kuś R, Żygierewicz J, Michalska M, Milanowski P, Łabęcki M, Spustek T, Laszuk D, Duszyk A, Kruszyński M (2012) User-centered design of brain-computer interfaces: OpenBCI.pl and BCI Appliance. Bull Polish Acad Sci Tech Sci 60:427–431.

Duysens J, Severens M, Nienhuis B (2013) How can active cycling produce less brain activity than passive cycling? Clin Neurophysiol 124:217–218.

Engel AK, Fries P (2010) Beta-band oscillations—signalling the status quo? Curr Opin Neurobiol 20:156–165.

Erbil N, Ungan P (2007) Changes in the alpha and beta amplitudes of the central EEG during the onset, continuation, and offset of long-duration repetitive hand movements. Brain Res 1169:44–56.

Espay AJ, Fasano A, Van Nuenen BFL, Payne MM, Snijders AH, Bloem BR (2012) "On" state freezing of gait in Parkinson disease: A paradoxical levodopa-induced complication. Neurology 78:454–457.

Eusebio A, Cagnan H, Brown P (2012) Does suppression of oscillatory synchronisation mediate some of the therapeutic effects of DBS in patients with Parkinson's disease? Front Integr Neurosci 6:47.

Factor SA (2008) The clinical spectrum of freezing of gait in atypical Parkinsonism. Mov Disord 23:6–8.

Fasano A, Aquino CC, Krauss JK, Honey CR, Bloem BR (2015) Axial disability and deep brain stimulation in patients with Parkinson disease. Nat Rev Neurol 11:98–110.

Fasano A, Herzog J, Seifert E, Stolze H, Falk D, Reese R, Volkmann J, Deuschl G (2011) Modulation of gait coordination by subthalamic stimulation improves freezing of gait. Mov Disord 26:844–851.

Ferraye MU et al. (2010) Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. Brain 133:205–214.

Ferraye MU, Debû B, Fraix V, Xie-Brustolin J, Chabardès S, Krack P, Benabid A-L, Pollak P (2008) Effects of subthalamic nucleus stimulation and levodopa on freezing of gait in Parkinson Disease. Neurology 70:1431–1437.

Foffani G, Priori A, Egidi M, Rampini P, Tamma F, Caputo E, Moxon KA, Cerutti S, Barbieri S (2003) 300-Hz subthalamic oscillations in Parkinson's disease. Brain 126:2153–2163.

Frank MJ (2006) Hold your horses: a dynamic computational role for the subthalamic nucleus in decision making. Neural Netw 19:1120–1136.

Galna B, Lord S, Burn DJ, Rochester L (2015) Progression of gait dysfunction in incident Parkinson's disease: impact of medication and phenotype. Mov Disord 30:359–367.

Giladi N, McDermott MP, Fahn S, Przedborski S, Jankovic J, Stern M, Tanner C (2001a) Freezing of gait in PD: prospective assessment in the DATATOP cohort. Neurology 56:1712–1721.

Giladi N, Mcmahon D, Przedborski S, Flaster E, Guillory S (1992) Motor blocks in Parkinson' s disease. Neurology 42:333–339.

Giladi N, Shabtai H, Simon E, Biran S, Tal J, Korczyn A (2000) Construction of freezing of gait questionnaire for patients with Parkinsonism. Parkinsonism Relat Disord 6:165–170.

Giladi N, Treves TA, Simon ES, Shabtai H, Orlov Y, Kandinov B, Paleacu D, Korczyn AD (2001b) Freezing of gait in patients with advanced Parkinson's disease. J Neural Transm 108:53–61.

Goetz CG et al. (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 23:2129–2170.

Gwin JT, Ferris DP (2012) An EEG-based study of discrete isometric and isotonic human lower limb muscle contractions. J Neuroeng Rehabil 9:35.

Gwin JT, Gramann K, Makeig S, Ferris DP (2011) Electrocortical activity is coupled to gait cycle phase during treadmill walking. Neuroimage 54:1289–1296.

Hallett M (2008) The intrinsic and extrinsic aspects of freezing of gait. Mov Disord 23:439–443.

Hammond C, Bergman H, Brown P (2007) Pathological synchronization in Parkinson's disease: networks, models and treatments. Trends Neurosci 30:357–364.

Hanakawa T, Katsumi Y, Fukuyama H, Honda M, Hayashi T, Kimura J, Shibasaki H (1999) Mechanisms underlying gait disturbance in Parkinson's disease: A single photon emission computed tomography study. Brain 122:1271–1282.

Handojoseno AMA, Gilat M, Ly QT, Chamtie H, Shine JM, Nguyen TN, Tran Y, Lewis SJG, Nguyen HT (2015) An EEG study of turning freeze in Parkinson's disease patients: The alteration of brain dynamic on the motor and visual cortex. In: 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), pp 6618–6621. IEEE.

Haslinger B, Erhard P, Ka N, Boecker H, Rummeny E, Schwaiger M, Conrad B (2001) Event-related functional magnetic resonance imaging in Parkinson ' s disease before and after levodopa. Brain 124:558–570.

Hausdorff JM, Schaafsma JD, Balash Y, Bartels AL, Gurevich T, Giladi N (2003) Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. Exp Brain Res 149:187–194.

Hely MA, Reid WGJ, Adena MA, Halliday GM, Morris JGL (2008) The Sydney Multicenter Study of Parkinson's disease: The inevitability of dementia at 20 years. Mov Disord 23:837–844.

Heremans E, Nieuwboer A, Spildooren J, Vandenbossche J, Deroost N, Soetens E, Kerckhofs E, Vercruysse S (2013) Cognitive aspects of freezing of gait in Parkinson's disease: a challenge for rehabilitation. J Neural Transm 120:543–557.

Herman T, Rosenberg-Katz K, Jacob Y, Giladi N, Hausdorff JM (2013) Gray matter atrophy and freezing of gait in Parkinson's disease: Is the evidence black-on-white? Mov Disord 29:134–139.

Hirschmann J, Butz M, Hartmann CJ, Hoogenboom N, Özkurt TE, Vesper J, Wojtecki L, Schnitzler A (2016) Parkinsonian Rest Tremor Is Associated With Modulations of Subthalamic High-Frequency Oscillations. Mov Disord 31:1551–1559.

Hirschmann J, Özkurt TE, Butz M, Homburger M, Elben S, Hartmann CJ, Vesper J, Wojtecki L, Schnitzler A (2011) Distinct oscillatory STN-cortical loops revealed by simultaneous MEG and local field potential recordings in patients with Parkinson's disease. Neuroimage 55:1159–1168.

Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. Neurology 17:427–442.

Holgado AJN, Terry JR, Bogacz R (2010) Conditions for the Generation of Beta Oscillations in the Subthalamic Nucleus-Globus Pallidus Network. J Neurosci 30:12340–12352.

Jacobs JV, Nutt JG, Carlson-Kuhta P, Stephens M, Horak FB (2009) Knee trembling during freezing of gait represents multiple anticipatory postural adjustments. Exp Neurol 215:334–341.

Jahn K, Deutschländer A, Stephan T, Kalla R, Hüfner K, Wagner J, Strupp M, Brandt T (2008a) Supraspinal locomotor control in quadrupeds and humans. Prog Brain Res 171:353–362.

Jahn K, Deutschländer A, Stephan T, Kalla R, Wiesmann M, Strupp M, Brandt T (2008b) Imaging human supraspinal locomotor centers in brainstem and cerebellum. Neuroimage 39:786–792.

Jain S, Gourab K, Schindler-Ivens S, Schmit BD (2013) EEG during pedaling: Evidence for cortical control of locomotor tasks. Clin Neurophysiol 124:379–390.

Jankovic J (2008) Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 79:368–376.

Jenkinson N, Brown P (2011) New insights into the relationship between dopamine, beta oscillations and motor function. Trends Neurosci 34:611–618.

Jenkinson N, Nandi D, Muthusamy K, Ray NJ, Gregory R, Stein JF, Aziz TZ (2009) Anatomy, physiology, and pathophysiology of the pedunculopontine nucleus. Mov Disord 24:319–328.

Jensen O, Kaiser J, Lachaux JP (2007) Human gamma-frequency oscillations associated with attention and memory. Trends Neurosci 30:317–324.

Kalia LV, Lang AE (2015) Parkinson's disease. Lancet 386:896–912.

Karachi C, Grabli D, Bernard FA, Tandé D, Wattiez N, Belaid H, Bardinet E, Prigent A, Nothacker H-P, Hunot S, Hartmann A, Lehéricy S, Hirsch EC, François C (2010) Cholinergic mesencephalic neurons are involved in gait and postural disorders in Parkinson disease. J Clin Invest 120:2745–2754.

Kelly VE, Eusterbrock AJ, Shumway-Cook A (2012) A review of dual-task walking deficits in people with Parkinson's disease: motor and cognitive contributions, mechanisms, and clinical implications. Parkinsons Dis 2012:918719.

Kerr GK, Worringham CJ, Cole MH, Lacherez PF, Wood JM, Silburn PA (2010) Predictors of future falls in Parkinson disease. Neurology 75:116–124.

Klimesch W (2012) Alpha-band oscillations, attention, and controlled access to stored information. Trends Cogn Sci 16:606–617.

Knaepen K, Mierau A, Swinnen E, Fernandez Tellez H, Michielsen M, Kerckhofs E, Lefeber D, Meeusen R (2015a) Human-Robot Interaction: Does Robotic Guidance Force Affect Gait-Related Brain Dynamics during Robot-Assisted Treadmill Walking? PLoS One 10:e0140626.

Knaepen K, Mierau A, Tellez HF, Lefeber D, Meeusen R (2015b) Temporal and spatial organization of gait-related electrocortical potentials. Neurosci Lett 599:75–80.

Kondabolu K, Roberts EA, Bucklin M, McCarthy MM, Kopell N, Han X (2016) Striatal cholinergic interneurons generate beta and gamma oscillations in the corticostriatal circuit and produce motor deficits. Proc Natl Acad Sci U S A 113:E3159–E3168.

Kostic VS, Agosta F, Pievani M, Stefanova E, Jecmenica-Lukic M, Scarale A, Spica V, Filippi M (2012) Pattern of brain tissue loss associated with freezing of gait in Parkinson disease. Neurology 78:409–416.

Kühn AA, Kupsch A, Schneider G-H, Brown P (2006) Reduction in subthalamic 8-35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. Eur J Neurosci 23:1956–1960.

Kühn AA, Tsui A, Aziz T, Ray N, Brücke C, Kupsch A, Schneider G-H, Brown P (2009) Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. Exp Neurol 215:380–387.

Kurz MJ, Wilson TW, Arpin DJ (2012) Stride-time variability and sensorimotor cortical activation during walking. Neuroimage 59:1602–1607.

la Fougère C, Zwergal A, Rominger A, Förster S, Fesl G, Dieterich M, Brandt T, Strupp M, Bartenstein P, Jahn K (2010) Real versus imagined locomotion: a [18F]-FDG PET-fMRI comparison. Neuroimage 50:1589–1598.

Lau B, Welter M-L, Belaid H, Fernandez Vidal S, Bardinet E, Grabli D, Karachi C (2015) The integrative role of the pedunculopontine nucleus in human gait. Brain 138:1284–1296.

Lewis SJG, Barker RA (2009) A pathophysiological model of freezing of gait in Parkinson's disease. Parkinsonism Relat Disord 15:333–338.

Lewis SJG, Shine JM (2016) The Next Step: A Common Neural Mechanism for Freezing of Gait. Neuroscientist 22:72–82.

Li M, Zhou M, Wen P, Wang Q, Yang Y, Xiao H, Xie Z, Li X, Wang N, Wang J, Luo F, Chang J, Zhang W (2016) The network of causal interactions for beta oscillations in the pedunculopontine nucleus, primary motor cortex, and subthalamic nucleus of walking parkinsonian rats. Exp Neurol 282:27–36.

Litvak V, Jha A, Eusebio A, Oostenveld R, Foltynie T, Limousin P, Zrinzo L, Hariz MI, Friston K, Brown P (2011) Resting oscillatory cortico-subthalamic connectivity in patients with Parkinson's disease. Brain 134:359–374.

López-Azcárate J, Tainta M, Rodríguez-Oroz MC, Valencia M, González R, Guridi J, Iriarte J, Obeso JA, Artieda J, Alegre M (2010) Coupling between beta and high-frequency activity in the human subthalamic nucleus may be a pathophysiological mechanism in Parkinson's disease. J Neurosci 30:6667–6677.

Ly QT, Handojoseno AMA, Gilat M, Nguyen N, Chai R, Tran Y, Lewis SJG, Nguyen HT (2016) Detection of Gait Initiation Failure in Parkinson's disease patients using EEG signals. In: 2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), pp 1599–1602. IEEE.

Malouin F, Richards CL, Jackson PL, Dumas F, Doyon J (2003) Brain activations during motor imagery of locomotor-related tasks: a PET study. Hum Brain Mapp 19:47–62.

Martinez-Gonzalez C, Bolam JP, Mena-Segovia J (2011) Topographical organization of the pedunculopontine nucleus. Front Neuroanat 5:22.

McCarthy MM, Moore-Kochlacs C, Gu X, Boyden ES, Han X, Kopell N (2011) Striatal origin of the pathologic beta oscillations in Parkinson's disease. Proc Natl Acad Sci U S A 108:11620–11625.

Mehta JP, Verber MD, Wieser JA, Schmit BD, Schindler-Ivens SM (2009) A novel technique for examining human brain activity associated with pedaling using fMRI. J Neurosci Methods 179:230–239.

Middleton FA, Strick PL (2000) Basal ganglia and cerebellar loops. Brain Res Rev 31:236–250.

Mink JW (1996) The basal ganglia: Focused selection and inhibition of competing motor programs. Prog Neurobiol 50:381–425.

Miyai I, Tanabe HC, Sase I, Eda H, Oda I, Konishi I, Tsunazawa Y, Suzuki T, Yanagida T, Kubota K (2001) Cortical Mapping of Gait in Humans: A Near-Infrared Spectroscopic Topography Study. Neuroimage 14:1186–1192.

Moore O, Peretz C, Giladi N (2007) Freezing of gait affects quality of life of peoples with Parkinson's disease beyond its relationships with mobility and gait. Mov Disord 22:2192–2195.

Moore ST, MacDougall HG, Ondo WG (2008) Ambulatory monitoring of freezing of gait in Parkinson's disease. J Neurosci Methods 167:340–348.

Moreau C, Defebvre L, Bleuse S, Blatt JL, Duhamel A, Bloem BR, Destée A, Krystkowiak P (2008) Externally provoked freezing of gait in open runways in advanced Parkinson's disease results from motor and mental collapse. J Neural Transm 115:1431–1436.

Morton SM, Bastian AJ (2004) Cerebellar control of balance and locomotion. Neuroscientist 10:247–259.

Morton SM, Bastian AJ (2006) Cerebellar Contributions to Locomotor Adaptations during Splitbelt Treadmill Walking. J Neurosci 26:9107–9116.

Müller-Putz GR, Zimmermann D, Graimann B, Nestinger K, Korisek G, Pfurtscheller G (2007) Event-related beta EEG-changes during passive and attempted foot movements in paraplegic patients. Brain Res 1137:84–91.

Nambu A, Takada M, Inase M, Tokuno H (1996) Dual somatotopical representations in the primate subthalamic nucleus: evidence for ordered but reversed body-map transformations from the primary motor cortex and the supplementary motor area. J Neurosci 16:2671–2683.

Nelson AB, Kreitzer AC (2014) Reassessing Models of Basal Ganglia Function and Dysfunction. Annu Rev Neurosci 37:117–135.

Neumann W-J, Staub F, Horn A, Schanda J, Mueller J, Schneider G-H, Brown P, Kühn AA (2016) Deep Brain Recordings Using an Implanted Pulse Generator in Parkinson's Disease. Neuromodulation 19:20–24.

Neuper C, Pfurtscheller G (2001) Event-related dynamics of cortical rhythms: frequency-specific features and functional correlates. Int J Psychophysiol 43:41–58.

Nielsen JBB, Sinkjaer T (2002) Afferent feedback in the control of human gait. J Electromyogr Kinesiol 12:213–217.

Nieuwboer A (2008) Cueing for freezing of gait in patients with Parkinson's disease: A rehabilitation perspective. Mov Disord 23:475–481.

Nieuwboer A, Dom R, De Weerdt W, Desloovere K, Fieuws S, Broens-Kaucsik E (2001) Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. Mov Disord 16:1066–1075.

Nieuwboer A, Giladi N (2013) Characterizing freezing of gait in Parkinson's disease: Models of an episodic phenomenon. Mov Disord 28:1509–1519.

Nonnekes J, Snijders AH, Nutt JG, Deuschl G, Giladi N, Bloem BR (2015) Freezing of gait: a practical approach to management. Lancet Neurol 14:768–778.

Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A (2011a) Freezing of gait: moving forward on a mysterious clinical phenomenon. Lancet Neurol 10:734–744.

Nutt JG, Horak FB, Bloem BR (2011b) Milestones in gait, balance, and falling. Mov Disord 26:1166–1174.

Oswal A, Beudel M, Zrinzo L, Limousin P, Hariz M, Foltynie T, Litvak V, Brown P (2016) Deep brain stimulation modulates synchrony within spatially and spectrally distinct resting state networks in Parkinson's disease. Brain 139:1482–1496.

Oswal A, Brown P, Litvak V (2013) Synchronized neural oscillations and the pathophysiology of Parkinson's disease. Curr Opin Neurol 26:662–670.

Özkurt TE, Butz M, Homburger M, Elben S, Vesper J, Wojtecki L, Schnitzler A (2011) High frequency oscillations in the subthalamic nucleus: a neurophysiological marker of the motor state in Parkinson's disease. Exp Neurol 229:324–331.

Parkinson J (1817) An Essay on the Shaking Palsy. Sherwood, Neely, and Jones. London.

Petersen TH, Willerslev-Olsen M, Conway BA, Nielsen JB (2012) The motor cortex drives the muscles during walking in human subjects. J Physiol 590:2443–2452.

Peterson DS, Horak FB (2016) Neural Control of Walking in People with Parkinsonism. Physiology 31:95–107.

Peterson DS, Pickett K a., Duncan R, Perlmutter J, Earhart GM (2014) Gait-related brain activity in people with Parkinson disease with freezing of gait. PLoS One 9:e90634.

Petzinger GM, Fisher BE, McEwen S, Beeler JA, Walsh JP, Jakowec MW (2013) Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. Lancet Neurol 12:716–726.

Pfurtscheller G, Lopes da Silva FH (1999) Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin Neurophysiol 110:1842–1857.

Pfurtscheller G, Stancák Jr. A, Neuper C (1996) Post-movement beta synchronization. A correlate of an idling motor area? Electroencephalogr Clin Neurophysiol 98:281–293.

Plotnik M, Giladi N, Hausdorff JM (2008) Bilateral coordination of walking and freezing of gait in Parkinson's disease. Eur J Neurosci 27:1999–2006.

Plotnik M, Giladi N, Hausdorff JM (2012) Is freezing of gait in Parkinson's disease a result of multiple gait impairments? Implications for treatment. Parkinsons Dis 2012:459321.

Pogosyan A, Gaynor LD, Eusebio A, Brown P (2009) Boosting cortical activity at Beta-band frequencies slows movement in humans. Curr Biol 19:1637–1641.

Presacco A, Goodman R, Forrester L, Contreras-Vidal JL (2011) Neural decoding of treadmill walking from noninvasive electroencephalographic signals. J Neurophysiol 106:1875–1887.

Quinn EJ, Blumenfeld Z, Velisar A, Koop MM, Shreve LA, Trager MH, Hill BC, Kilbane C, Henderson JM, Brontë-Stewart H (2015) Beta oscillations in freely moving Parkinson's subjects are attenuated during deep brain stimulation. Mov Disord 30:1750–1758.

Raasch CC, Zajac FE (1999) Locomotor strategy for pedaling: muscle groups and biomechanical functions. J Neurophysiol 82:515–525.

Rahman S, Griffin HJ, Quinn NP, Jahanshahi M (2008) The Factors that Induce or Overcome Freezing of Gait in Parkinson's Disease. Behav Neurol 19:127–136.

Redgrave P, Rodriguez M, Smith Y, Rodriguez-Oroz MC, Lehericy S, Bergman H, Agid Y, DeLong MR, Obeso JA (2010) Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease. Nat Rev Neurosci 11:760–772.

Ridgel AL, Kim C, Fickes EJ, Muller MD, Alberts JL (2011) Changes in Executive Function After Acute Bouts of Passive Cycling in Parkinson ' s Disease. J Aging Phys Act 19:87–98.

Ridgel AL, Peacock CA, Fickes EJ, Kim C (2012) Active-Assisted Cycling Improves Tremor and Bradykinesia in Parkinson ' s Disease. Arch Phys Med Rehabil 93:2049–2054.

Ridgel AL, Vitek JL, Alberts JL (2009) Forced, not voluntary, exercise improves motor function in Parkinson's disease patients. Neurorehabil Neural Repair 23:600–608.

Rosenberg-Katz K, Herman T, Jacob Y, Giladi N, Hendler T, Hausdorff JM (2013) Gray matter atrophy distinguishes between Parkinson disease motor subtypes. Neurology 80:1476–1484.

Sahyoun C, Floyer-Lea A, Johansen-Berg H, Matthews PM (2004) Towards an understanding of gait control: brain activation during the anticipation, preparation and execution of foot movements. Neuroimage 21:568–575.

Schaafsma JD, Balash Y, Gurevich T, Bartels AL, Hausdorff JM, Giladi N (2003) Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease. Eur J Neurol 10:391–398.

Schlerf J, Ivry RB, Diedrichsen J (2012) Encoding of Sensory Prediction Errors in the Human Cerebellum. J Neurosci 32:4913–4922.

Schnitzler A, Gross J (2005) Normal and pathological oscillatory communication in the brain. Nat Rev Neurosci 6:285–296.

Scholten M, Govindan RB, Braun C, Bloem BR, Plewnia C, Krüger R, Gharabaghi A, Weiss D (2016) Cortical correlates of susceptibility to upper limb freezing in Parkinson's disease. Clin Neurophysiol 127:2386–2393.

Seeber M, Scherer R, Wagner J, Solis-Escalante T, Müller-Putz GR (2014) EEG beta suppression and low gamma modulation are different elements of human upright walking. Front Hum Neurosci 8:485.

Seeber M, Scherer R, Wagner J, Solis-Escalante T, Müller-Putz GR (2015) High and low gamma EEG oscillations in central sensorimotor areas are conversely modulated during the human gait cycle. Neuroimage 112:318–326.

Severens M, Nienhuis B, Desain P, Duysens J (2012) Feasibility of measuring event Related Desynchronization with electroencephalography during walking. In: 2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society, pp 2764–2767. IEEE.

Shine JM, Handojoseno AMA, Nguyen TN, Tran Y, Naismith SL, Nguyen H, Lewis SJG (2014) Abnormal patterns of theta frequency oscillations during the temporal evolution of freezing of gait in Parkinson's disease. Clin Neurophysiol 125:569–576.

Shine JM, Matar E, Ward PB, Bolitho SJ, Pearson M, Naismith SL, Lewis SJG (2013a) Differential Neural Activation Patterns in Patients with Parkinson's Disease and Freezing of Gait in Response to Concurrent Cognitive and Motor Load. PLoS One 8:e52602.

Shine JM, Matar E, Ward PB, Frank MJ, Moustafa AA, Pearson M, Naismith SL, Lewis SJG (2013b) Freezing of gait in Parkinson's disease is associated with functional decoupling between the cognitive control network and the basal ganglia. Brain 136:3671–3681.

Shine JM, Moustafa AA, Matar E, Frank MJ, Lewis SJG (2013c) The role of frontostriatal impairment in freezing of gait in Parkinson's disease. Front Syst Neurosci 7:61.

Shine JM, Naismith SL, Lewis SJG (2011a) The pathophysiological mechanisms underlying freezing of gait in Parkinson's Disease. J Clin Neurosci 18:1154–1157.

Shine JM, Ward PB, Naismith SL, Pearson M, Lewis SJG (2011b) Utilising functional MRI (fMRI) to explore the freezing phenomenon in Parkinson's disease. J Clin Neurosci 18:807–810.

Singh A, Kammermeier S, Plate A, Mehrkens JH, Ilmberger J, Bötzel K (2011) Pattern of local field potential activity in the globus pallidus internum of dystonic patients during walking on a treadmill. Exp Neurol 232:162–167.

Singh A, Plate A, Kammermeier S, Mehrkens JH, Ilmberger J, Bötzel K (2013) Freezing of gait-related oscillatory activity in the human subthalamic nucleus. Basal Ganglia 3:25–32.

Sipp AR, Gwin JT, Makeig S, Ferris DP (2013) Loss of balance during balance beam walking elicits a multifocal theta band electrocortical response. J Neurophysiol 110:2050–2060.

Snijders AH, Bloem BR (2010) Cycling for Freezing of Gait. N Engl J Med 362:e46.

Snijders AH, Haaxma CA, Hagen YJ, Munneke M, Bloem BR (2012a) Freezer or non-freezer: clinical assessment of freezing of gait. Parkinsonism Relat Disord 18:149–154.

Snijders AH, Leunissen I, Bakker M, Overeem S, Helmich RC, Bloem BR, Toni I (2011a) Gait-related cerebral alterations in patients with Parkinson's disease with freezing of gait. Brain 134:59–72.

Snijders AH, Takakusaki K, Debu B, Lozano AM, Krishna V, Fasano A, Aziz TZ, Papa SM, Factor SA, Hallett M (2016) Physiology of freezing of gait. Ann Neurol.

Snijders AH, Toni I, Ružička E, Bloem BR (2011b) Bicycling breaks the ice for freezers of gait. Mov Disord 26:367–371.

Snijders AH, van Kesteren M, Bloem BR (2012b) Cycling is less affected than walking in freezers of gait. J Neurol Neurosurg Psychiatry 83:575–576.

Solis-Escalante T, Müller-Putz GR, Pfurtscheller G, Neuper C (2012) Cue-induced beta rebound during withholding of overt and covert foot movement. Clin Neurophysiol 123:1182–1190.

Spildooren J, Vercruysse S, Desloovere K, Vandenberghe W, Kerckhofs E, Nieuwboer A (2010) Freezing of gait in Parkinson's disease: the impact of dual-tasking and turning. Mov Disord 25:2563–2570.

Stefani A, Lozano AM, Peppe A, Stanzione P, Galati S, Tropepi D, Pierantozzi M, Brusa L, Scarnati E, Mazzone P (2007) Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. Brain 130:1596–1607.

Storzer L, Burgers S, Hirschmann J (2015) Are Beta Phase-Coupled High-Frequency Oscillations and Beta Phase-Locked Spiking Two Sides of the Same Coin? J Neurosci 35:1819–1820.

Storzer L, Butz M, Hirschmann J, Abbasi O, Gratkowski M, Saupe D, Schnitzler A, Dalal SS (2016) Bicycling and Walking are Associated with Different Cortical Oscillatory Dynamics. Front Hum Neurosci 10:61.

Stummer C, Dibilio V, Overeem S, Weerdesteyn V, Bloem BR, Nonnekes J (2015) The walk-bicycle: A new assistive device for Parkinson's patients with freezing of gait? Parkinsonism Relat Disord 21:755–757.

Swinnen SP (2002) Intermanual coordination: from behavioural principles to neural-network interactions. Nat Rev Neurosci 3:348–359.

Takakusaki K (2013) Neurophysiology of gait: From the spinal cord to the frontal lobe. Mov Disord 28:1483–1491.

Takakusaki K, Tomita N, Yano M (2008) Substrates for normal gait and pathophysiology of gait disturbances with respect to the basal ganglia dysfunction. J Neurol 255:19–29.

Tan DM, McGinley JL, Danoudis ME, Iansek R, Morris ME (2011) Freezing of gait and activity limitations in people with parkinson's disease. Arch Phys Med Rehabil 92:1159–1165.

Taniwaki T, Okayama A, Yoshiura T, Togao O, Nakamura Y, Yamasaki T, Ogata K, Shigeto H, Ohyagi Y, Kira J, Tobimatsu S (2006) Functional network of the basal ganglia and cerebellar motor loops in vivo: Different activation patterns between self-initiated and externally triggered movements. Neuroimage 31:745–753.

Tattersall TL, Stratton PG, Coyne TJ, Cook R, Silberstein P, Silburn PA, Windels F, Sah P (2014) Imagined gait modulates neuronal network dynamics in the human pedunculopontine nucleus. Nat Neurosci 17:449–454.

Tessitore A, Amboni M, Esposito F, Russo A, Picillo M, Marcuccio L, Pellecchia MT, Vitale C, Cirillo M, Tedeschi G, Barone P (2012) Resting-state brain connectivity in patients with Parkinson's disease and freezing of gait. Parkinsonism Relat Disord 18:781–787.

Thenganatt MA, Jankovic J (2014) Parkinson Disease Subtypes. JAMA Neurol 71:499–504.

Thevathasan W, Cole MH, Graepel CL, Hyam JA, Jenkinson N, Brittain J-S, Coyne TJ, Silburn PA, Aziz TZ, Kerr G, Brown P (2012a) A spatiotemporal analysis of gait freezing and the impact of pedunculopontine nucleus stimulation. Brain 135:1446–1454.

Thevathasan W, Pogosyan A, Hyam JA, Jenkinson N, Bogdanovic M, Coyne TJ, Silburn PA, Aziz TZ, Brown P (2011) A block to pre-prepared movement in gait freezing, relieved by pedunculopontine nucleus stimulation. Brain 134:2085–2095.

Thevathasan W, Pogosyan A, Hyam JA, Jenkinson N, Foltynie T, Limousin P, Bogdanovic M, Zrinzo L, Green AL, Aziz TZ, Brown P (2012b) Alpha oscillations in the pedunculopontine nucleus correlate with gait performance in parkinsonism. Brain 135:148–160.

Thevathasan W, Silburn PA, Brooker H, Coyne TJ, Khan S, Gill SS, Aziz TZ, Brown P (2010) The impact of low-frequency stimulation of the pedunculopontine nucleus region on reaction time in parkinsonism. J Neurol Neurosurg Psychiatry 81:1099–1104.

Toledo JB, López-Azcárate J, Garcia-Garcia D, Guridi J, Valencia M, Artieda J, Obeso J, Alegre M, Rodriguez-Oroz M (2014) High beta activity in the subthalamic nucleus and freezing of gait in Parkinson's disease. Neurobiol Dis 64:60–65.

Tsang EW, Hamani C, Moro E, Mazzella F, Poon YY, Lozano AM, Chen R (2010) Involvement of the human pedunculopontine nucleus region in voluntary movements. Neurology 75:950–959.

Tseng YW, Diedrichsen J, Krakauer JW, Shadmehr R, Bastian AJ (2007) Sensory Prediction Errors Drive Cerebellum-Dependent Adaptation of Reaching. J Neurophysiol 98:54–62.

van Ede F, Maris E (2013) Somatosensory Demands Modulate Muscular Beta Oscillations, Independent of Motor Demands. J Neurosci 33:10849–10857.

Vandenbossche J, Deroost N, Soetens E, Coomans D, Spildooren J, Vercruysse S, Nieuwboer A, Kerckhofs E (2012) Freezing of gait in Parkinson's disease: disturbances in automaticity and control. Front Hum Neurosci 6:356.

Varela F, Lachaux J, Rodriguez E, Martinerie J (2001) The BrainWeb : Phase Large-Scale Integration. Nat Neurosci 2:229–239.

Vercruysse S, Gilat M, Shine JM, Heremans E, Lewis S, Nieuwboer A (2014) Freezing beyond gait in Parkinson's disease: a review of current neurobehavioral evidence. Neurosci Biobehav Rev 43:213–227.

Vercruysse S, Spildooren J, Heremans E, Vandenbossche J, Wenderoth N, Swinnen SP, Vandenberghe W, Nieuwboer A (2012) Abnormalities and cue dependence of rhythmical upper-limb movements in Parkinson patients with freezing of gait. Neurorehabil Neural Repair 26:636–645.

Wagner J, Makeig S, Gola M, Neuper C, Muller-Putz G (2016) Distinct Band Oscillatory Networks Subserving Motor and Cognitive Control during Gait Adaptation. J Neurosci 36:2212–2226.

Wagner J, Solis-Escalante T, Grieshofer P, Neuper C, Müller-Putz G, Scherer R (2012) Level of participation in robotic-assisted treadmill walking modulates midline sensorimotor EEG rhythms in able-bodied subjects. Neuroimage 63:1203–1211.

Wagner J, Solis-Escalante T, Scherer R, Neuper C, Müller-Putz G (2014) It's how you get there: walking down a virtual alley activates premotor and parietal areas. Front Hum Neurosci 8:93.

Wang J, Hirschmann J, Elben S, Hartmann CJ, Vesper J, Wojtecki L, Schnitzler A (2014) High-frequency oscillations in Parkinson's disease: spatial distribution and clinical relevance. Mov Disord 29:1265–1272.

Weiss D, Walach M, Meisner C, Fritz M, Scholten M, Breit S, Plewnia C, Bender B, Gharabaghi A, Wächter T, Krüger R (2013) Nigral stimulation for resistant axial motor impairment in Parkinson's disease? A randomized controlled trial. Brain 136:2098–2108.

Weiss PH, Herzog J, Pötter-Nerger M, Falk D, Herzog H, Deuschl G, Volkmann J, Fink GR (2015) Subthalamic nucleus stimulation improves Parkinsonian gait via brainstem locomotor centers. Mov Disord 30:1121–1125.

Whitmer D, de Solages C, Hill B, Yu H, Henderson JM, Bronte-Stewart H (2012) High frequency deep brain stimulation attenuates subthalamic and cortical rhythms in Parkinson's disease. Front Hum Neurosci 6:155.

Wieser M, Haefeli J, Bütler L, Jäncke L, Riener R, Koeneke S (2010) Temporal and spatial patterns of cortical activation during assisted lower limb movement. Exp Brain Res 203:181–191.

Winter DA (1995) Human blance and posture control during standing and walking. Gait Posture 3:193–214.

Wu T, Hallett M, Chan P (2015) Motor automaticity in Parkinson's disease. Neurobiol Dis 82:226–234.

Yang AI, Vanegas N, Lungu C, Zaghloul KA (2014) Beta-Coupled High-Frequency Activity and Beta-Locked Neuronal Spiking in the Subthalamic Nucleus of Parkinson's Disease. J Neurosci 34:12816–12827.

Yogev G, Giladi N, Peretz C, Springer S, Simon ES, Hausdorff JM (2005) Dual tasking, gait rhythmicity, and Parkinson's disease: Which aspects of gait are attention demanding? Eur J Neurosci 22:1248–1256.

Yogev-Seligmann G, Giladi N, Gruendlinger L, Hausdorff JM (2013) The contribution of postural control and bilateral coordination to the impact of dual tasking on gait. Exp Brain Res 226:81–93.

Yogev-Seligmann G, Hausdorff JM, Giladi N (2008) The role of executive function and attention in gait. Mov Disord 23:329–342.

9 Erklärung

Hiermit erkläre ich, dass ich die vorliegende 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

Lena Storzer

10 Danksagung

Die letzten Jahre waren wie eine Achterbahnfahrt und ich möchte mich an dieser Stelle bei allen bedanken, die mich in dieser Zeit begleitet haben.

Zuallererst möchte ich meinem Doktorvater Prof. Dr. Alfons Schnitzler danken. Vielen Dank für die Möglichkeit, an diesem spannenden Forschungsprojekt zu arbeiten und für all die Unterstützung und anregenden Gespräche während dieser Zeit.

Prof. Dr. Tobias Kalenscher danke ich herzlich für die Zweitbetreuung dieser Doktorarbeit. Darüber hinaus möchte ich dir für deine Förderung und dein Engagement bereits im Vorfeld der Doktorarbeit danken, durch die vieles erst möglich geworden ist.

Ganz besonders möchte ich dem gesamten BrainBike Team danken: Dr. Markus Butz, Dr. Jan Hirschmann, Omid Abbasi, Prof. Dr. Sarang S. Dalal, Dr. Maciej Gratkowski und Prof. Dr Dietmar Saupe. Markus, danke für deine wunderbare Betreuung und für dein Vertrauen. Du hast mir immer die Möglichkeit gegeben selbstständig zu arbeiten, meine Ideen auszuprobieren und dabei immer ohne zu Zögern als Versuchskaninchen zur Verfügung gestanden. Jan und Sarang, euch danke ich vor allem für eure fachliche Unterstützung und Anregungen, die meine Arbeit sehr bereichert haben. Omid, we've been a good team – of course ;-) Thank you for your willingness to help and your kindness. Danke Maciej für deine Freude am Weiterentwickeln des Powerbikes und immer schnelle Hilfe trotz der vielen Kilometer zwischen uns.

Für immer große Hilfsbereitschaft und Herzlichkeit möchte ich mich auch bei allen Kollegen bedanken. Was wären die letzten Jahre ohne gemeinsame Mittagspausen und Fußballspielen nach Feierabend? Insbesondere möchte ich Dr. Vanessa Krause und Dr. Katja Biermann-Ruben danken. Ihr habt mir immer mit Rat und Tat zur Seite gestanden und mit netten Gesprächen den Arbeitstag bereichert.

Besonders möchte ich meiner Familie danken. Ihr seid immer für mich da gewesen, habt an mich geglaubt, mich ermutigt, mir Kraft gegeben und mich getröstet. Niels, du bist ein ganz wunderbarer Mensch und ich kann dir gar nicht genug danken. Dein Fingerabdruck ist auf dieser Arbeit.

11 Appendix

This work is based on:

Appendix 1:

Storzer L, Butz M, Hirschmann J, Abbasi O, Gratkowski M, Saupe D, Schnitzler A, Dalal SS (2016) Bicycling and Walking are Associated with Different Cortical Oscillatory Dynamics. Front Hum Neurosci 10:61.

Impact factor (2016): 3.634
Personal contribution: 80 %, experimental design, data acquisition, data analysis, data interpretation, manuscript writing and revision

Appendix 2:

Storzer L, Butz M, Hirschmann J, Abbasi O, Gratkowski M, Saupe D, Dalal SS, Schnitzler A (submitted) Stronger subthalamic beta power suppression in bicycling relative to walking in Parkinson's disease.

Personal contribution: 80 %, experimental design, data acquisition, data analysis, data interpretation, manuscript writing and revision

Other aspects are taken from:

Appendix 3:

Storzer L, Burgers S, Hirschmann J (2015) Are Beta Phase-Coupled High-Frequency Oscillations and Beta Phase-Locked Spiking Two Sides of the Same Coin? J Neurosci 35:1819–1820.

Impact factor (2015): 6.92

Personal contribution: 35 %, manuscript writing and revision

Appendix 4:

Seinstra M, Wojtecki L, Storzer L, Schnitzler A, Kalenscher T (2016) No Effect of Subthalamic Deep Brain Stimulation on Intertemporal Decision-Making in Parkinson Patients. eNeuro 3.

Impact factor: New journal without an impact factor yet

Personal contribution: 20 %, data acquisition, manuscript revision

Appendix 5:

Gratkowski M, Storzer L, Butz M, Schnitzler A, Saupe D, Dalal SS (under review)
BrainCycles: Experimental setup for the combined measurement of cortical and subcortical activity in Parkinson's disease patients during cycling. Front Hum Neurosci.

Impact factor (2016): 3.634

Personal contribution: 30 %, experimental design, data acquisition, data analysis, data interpretation, manuscript revision

frontiers in Human Neuroscience

ORIGINAL RESEARCH
published: 19 February 2016
doi: 10.3389/fnhum.2016.00061

Bicycling and Walking are Associated with Different Cortical Oscillatory Dynamics

Lena Storzer[1], Markus Butz[1], Jan Hirschmann[1], Omid Abbasi[1,2], Maciej Gratkowski[3], Dietmar Saupe[3], Alfons Schnitzler[1] and Sarang S. Dalal[4]*

[1] Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany, [2] Department of Medical Engineering, Ruhr-University Bochum, Bochum, Germany, [3] Department of Computer and Information Science, University of Konstanz, Konstanz, Germany, [4] Zukunftskolleg and Department of Psychology, University of Konstanz, Konstanz, Germany

Although bicycling and walking involve similar complex coordinated movements, surprisingly Parkinson's patients with freezing of gait typically remain able to bicycle despite severe difficulties in walking. This observation suggests functional differences in the motor networks subserving bicycling and walking. However, a direct comparison of brain activity related to bicycling and walking has never been performed, neither in healthy participants nor in patients. Such a comparison could potentially help elucidating the cortical involvement in motor control and the mechanisms through which bicycling ability may be preserved in patients with freezing of gait. The aim of this study was to contrast the cortical oscillatory dynamics involved in bicycling and walking in healthy participants. To this end, EEG and EMG data of 14 healthy participants were analyzed, who cycled on a stationary bicycle at a slow cadence of 40 revolutions per minute (rpm) and walked at 40 strides per minute (spm), respectively. Relative to walking, bicycling was associated with a stronger power decrease in the high *beta* band (23–35 Hz) during movement initiation and execution, followed by a stronger *beta* power increase after movement termination. Walking, on the other hand, was characterized by a stronger and persisting *alpha* power (8–12 Hz) decrease. Both bicycling and walking exhibited movement cycle-dependent power modulation in the 24–40 Hz range that was correlated with EMG activity. This modulation was significantly stronger in walking. The present findings reveal differential cortical oscillatory dynamics in motor control for two types of complex coordinated motor behavior, i.e., bicycling and walking. Bicycling was associated with a stronger sustained cortical activation as indicated by the stronger high *beta* power decrease during movement execution and less cortical motor control within the movement cycle. We speculate this to be due to the more continuous nature of bicycling demanding less phase-dependent sensory processing and motor planning, as opposed to walking.

Keywords: EEG, bicycling, walking, motor control, oscillations, sensorimotor cortex

OPEN ACCESS

Edited by:
Klaus Gramann, Berlin Institute of Technology, Germany

Reviewed by:
Johanna Wagner, Graz University of Technology, Austria
Pedro M. R. Reis, Friedrich-Alexander Universität Erlangen-Nürnberg, Germany
Helen Jingi Huang, University of Michigan, USA

****Correspondence:***
Lena Storzer
lena.storzer@hhu.de

Received: *23 November 2015*
Accepted: *08 February 2016*
Published: *19 February 2016*

Citation:
Storzer L, Butz M, Hirschmann J, Abbasi O, Gratkowski M, Saupe D, Schnitzler A and Dalal SS (2016) Bicycling and Walking are Associated with Different Cortical Oscillatory Dynamics. Front. Hum. Neurosci. 10:61. doi: 10.3389/fnhum.2016.00061

INTRODUCTION

Walking abilities are severely impaired in patients suffering from freezing of gait, a common phenomenon in advanced Parkinson's disease (for a review, see Nutt et al., 2011). Surprisingly, bicycling abilities are apparently preserved in the very same patients (Snijders et al., 2011b, 2012). Moreover, bicycling has been put forward as a therapy for Parkinson's disease, improving motor control, cognitive performance, tremor, and bradykinesia (Ridgel et al., 2009, 2011, 2012). Consequently, contrasting cortical activation during bicycling and walking starting in healthy participants may offer valuable insights into extent and aspects of cortical involvement in motor control of these two distinct types of movement. In addition, it may help to understand why Parkinsonian patients with severe freezing of gait retain the ability to bicycle and it may lead to improved therapeutic applications of bicycling in this patient population.

Vertical ergometer bicycling and walking are characterized by the alternating extension and flexion of the lower limbs that are suggested to be controlled by a shared subset of co-exited muscles (Raasch and Zajac, 1999). Moreover, both are complex movements that recruit a network of motor associated brain regions. Using near-infrared spectroscopy (NIRS; Miyai et al., 2001) and single-photon emission computed tomography (SPECT; Fukuyama et al., 1997), walking was associated with activity in sensorimotor regions, the supplementary motor area (SMA), and cerebellum. Activity within these movement-related brain areas was also reported during recumbent bicycling using functional magnetic resonance imaging (fMRI; Mehta et al., 2009) and positron emission tomography (PET; Christensen et al., 2000). Interestingly, imagination of bicycling compared to rest led to activation in the SMA, while active bicycling compared to passive bicycling was accompanied by a stronger recruitment of the primary motor cortex (Christensen et al., 2000). Furthermore, brain activity was shown to be influenced by exercise intensity and preference (Christensen et al., 2000; Brümmer et al., 2011a,b). This illustrates that the specific functional involvement of movement-related brain areas varies substantially with the task. In this sense, we can expect bicycling and walking to induce different cortical activities as both movements differ, e.g., in the requirement of postural control and coordination. In line with this, a behavioral study by Yogev-Seligmann et al. (2013) indicated that walking depends more on cognitive resources than bicycling. This was indicated by higher interference caused by the additional demand of a secondary task. It remains an open question, however, how exactly walking and bicycling differ on the electrophysiological level.

Previous work in this field using EEG has mainly focused on investigating neural oscillations underlying walking movements and resulted in two main findings.

First, *alpha* (8–12 Hz) and *beta* band (13–30 Hz) activity over the sensorimotor cortex are decreased during active motor execution compared to rest or passive movement (Wieser et al., 2010; Presacco et al., 2011; Severens et al., 2012; Wagner et al., 2012, 2014; Seeber et al., 2014). This tallies with previous findings of power decrease during motor execution, preparation and even during passive and imagined movements (Stančák and Pfurtscheller, 1996; Alegre et al., 2002; Müller-Putz et al., 2007). The decrease is followed by a *beta* power increase (rebound) after movement termination (Pfurtscheller et al., 1996; Parkes et al., 2006; Solis-Escalante et al., 2012). In this sense, *beta* power is modulated dependent on a change of the movement state, i.e., it decreases during the switch from rest to movement and rebounds after the reverse switch from movement to rest.

Second, power modulations are locked to the phase of the gait cycle in the 24–40 Hz and 70–90 Hz range, respectively (Wagner et al., 2012, 2014; Seeber et al., 2014, 2015). Gwin et al. (2011) were the first to show that power is modulated in a cyclic fashion during the gait cycle. Notably, Petersen et al. (2012) found activity at the Cz electrode and the TA muscle to be coherent in the 24–40 Hz range before the heel strike during walking. Although sustained *beta* decrease and transient power modulation in the 24–40 Hz range overlap in the frequency domain, they are thought to be two separate phenomena (Seeber et al., 2014). While sustained *beta* decrease is linked to a sustained active state of the sensorimotor cortex (Seeber et al., 2014; for a review, see Neuper and Pfurtscheller, 2001), phase-dependent power modulation in the 24–40 Hz range is associated with phasic gait cycle-dependent sensorimotor processing and motor planning (Wagner et al., 2012, 2014; Seeber et al., 2014).

Notably, cortical involvement in motor control has also been studied with EEG during recumbent bicycling on a stationary bicycle (Jain et al., 2013). This approach revealed similar findings to the results obtained in the context of walking studies. Active lower leg movements as opposed to passive movements led to a stronger power decrease in the *beta* band over the sensorimotor cortex. Additionally, bicycling was associated with alternating positive and negative cortical potentials, occurring twice in the pedal cycle and correlated with EMG activity of the leg muscles.

In the present study, we contrasted cortical activity underlying bicycling and walking to address the extent and aspects of cortical involvement in motor control. Furthermore, we aimed to clarify which aspects differ across these two distinct types of movement. We investigated movement state-dependent EEG power changes, i.e., the switch from rest to movement and back again. Moreover, we studied movement phase-dependent EEG power changes, i.e., power modulations that are locked to specific phases within the movement cycle.

MATERIALS AND METHODS

Participants

Fifteen healthy right-handed volunteers participated in this study. One participant was excluded from the analyses because of severe contamination of the EEG by muscle artifacts. Thus, data are presented from the remaining 14 participants (24.9 $\pm$ 3.0 years, six females). The study was approved by the local ethics committee of the Medical Faculty of the Heinrich Heine University Düsseldorf (study number: 4294) and was performed

in accordance with the Declaration of Helsinki. All participants gave their prior written informed consent.

Experimental Design and Procedure

Participants started either in the bicycling or in the walking condition (**Figure 1A**). The order of conditions was pseudorandomized and counterbalanced across subjects. Each condition started with a baseline rest period of 2 min, i.e., sitting on the bicycle or standing, respectively. In order to investigate movement initiation and termination, subjects performed an alternating sequence containing 10 s of movement, i.e., bicycling or walking, and 10 s of rest. The sequence was repeated 50 times. Subjects started with one additional rest phase before continuing with the alternating sequence to capture each of the 50 initiations and terminations. Start and end of the movement phase was indicated by an acoustic signal (beep of 500 ms duration with a frequency of 1000 Hz for start and 1500 Hz for end). Participants were allowed to start with their preferred leg but asked to keep this constant across trials and conditions. Finally, participants engaged in continuous movement for 2 min. The definition of number of repetitions and recording times was based on pilot recordings. Thus, we could ensure to acquire a sufficient data quantity for power analyses. Participants were instructed to bicycle or to walk at a comfortable slow cadence of 40 revolutions per minute (rpm) or strides per minute (spm), respectively. Prior to the experiment, they were given a short trial period to get accustomed to the intended cadence.

Bicycling took place on a basic version of the stationary bicycle simulator originally developed to analyze bicycling performance parameters (Dahmen et al., 2011; **Figure 1B**). This simulator combines a common bicycle frame with a commercial Cyclus 2 ergometer (RBM Elektronik-Automation GmbH, Leipzig, Germany) based on an eddy current brake. The brake force of the ergometer, controlled by custom-made PC-based software, was kept constant over participants. Bicycling with 40 rpm at a pedal force of 30 N resulted in a power of 23 W. Furthermore, custom Arduino-based electronics and optical sensors tracked pedal position that was recorded simultaneously with all electrophysiological signals. The bicycle simulator was the same for all participants with the saddle height adapted to the individual body height, i.e., the fully stretched leg was matching the distance from the saddle to the lowest pedal position. The walking condition was conducted in a 50 m long hallway with no obstacles or additional cues. Turnings made during continuous walking for 2 min were excluded from the analysis.

Data Acquisition

Data were recorded with the maximum sampling rate of 2048 Hz using a portable EEG amplifier (Porti amplifier, TMSi, Enschede, Netherlands) and controlled by a combination of the open source software packages OpenBCI and Svarog (Durka et al., 2012). EEG was acquired with an 18-electrode cap (TMSi, Enschede, Netherlands) attached according to the international 10–20 system. EEG signals were referenced against an average reference and a water-based ground electrode integrated in a wristband was used. Bipolar surface EMG activity of three leg muscles (TA, *tibialis anterior*; BF, *biceps femoris*; and RF, *rectus femoris*) was recorded bilaterally using the EEG amplifier and disposable Ag/AgCl electrodes (Covidien, Dublin, Ireland). Electrodes were placed 2 cm apart on the belly of each muscle. Electrode placement was instructed by an expert neurologist in line with the SENIAM guidelines (Hermens et al., 1999). EMG and scalp EEG were recorded with actively shielded cables attenuating movement artifacts. The knee angle was continuously tracked by bilateral electronic goniometers.

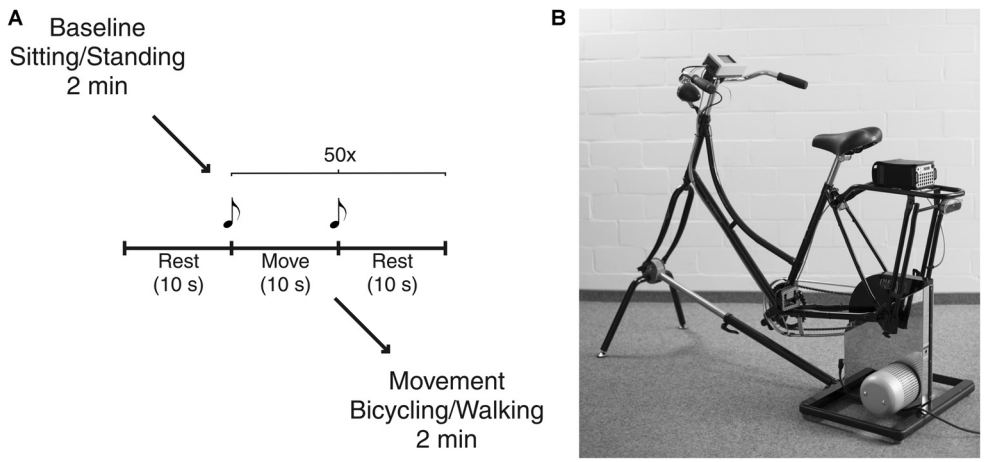

FIGURE 1 | Experimental setup. (A) Schematic illustration of the experimental paradigm. Each condition started with a baseline rest period of 2 min, i.e., sitting on the bicycle or standing, respectively. After further 10 s of rest participants performed an alternating sequence containing 10 s of movement, i.e., bicycling or walking, and 10 s of rest. This was repeated 50 times. Start and end of the movement phase were indicated by an acoustic signal. Finally, participants engaged in continuous movement for 2 min. **(B)** The bicycle simulator compromises a Dutch-style bicycle frame mounted on an ergometer. Custom-made software electronics and optical sensors tracked pedal position that was recorded simultaneously with all electrophysiological signals.

Footswitches placed under both feet monitored stepping (TMSi, Enschede, Netherlands).

Artifact Rejection

Data were analyzed with the Matlab-based FieldTrip toolbox (Oostenveld et al., 2011) using Matlab R2014a (The Mathworks, Natick, MA, USA). EEG signals were band-pass filtered offline (1–100 Hz). A band-stop filter was applied (49–51 Hz) to remove power line noise. To account for movement and muscle artifacts contaminating the EEG, the following steps were taken: first, data were visually inspected and times including artifacts such as jumps or transient high frequency activity excluded from further analysis. Second, data were decomposed using independent component analysis (ICA) with the extended Infomax algorithm implemented in the FieldTrip toolbox. The Infomax algorithm has been shown to be superior to two other ICA algorithms, SOBI and FastICA (Delorme et al., 2007). Components showing the spatial or temporal signatures of eye blinks were rejected (1.93 ± 0.47 components per participant; range 1–3) and the remaining components projected back to the scalp channels. Finally, data were re-referenced against the common average of nine central electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4). By restricting the average reference to these electrodes we were able to minimize the influence of artifacts arising from neck muscles.

Continuous Movement, Initiation, and Termination of Movement

Power changes during continuous movement were expressed as the relative power change in dB to the baseline rest condition, i.e., sitting and standing, respectively. This was assessed by dividing data into 1 s segments with an overlap of 50% and calculating the fast Fourier transform (FFT) for each segment. Subsequently, spectra were averaged over segments.

The goniometer signal was used to determine movement initiation and termination. The relevant events were defined by the following procedure. First, goniometer amplitude range during movement was determined and set to 100%. Next, baseline levels were calculated for each 2 s period before the acoustic signal which indicated start. A threshold was defined at 2% above the respective baseline level. Movement initiation was then defined as crossing of the predefined threshold. An analogous threshold was defined for movement termination based on the period from 3 to 5 s after the acoustic signal which indicated stop. The accuracy of the selected initiations as well as terminations were verified visually afterwards and adapted if necessary (0% of initiations and 11.60% of terminations).

Movement initiation and termination were analyzed by performing time-frequency decomposition with a sliding Hanning window of 1 s duration and a step size of 0.05 s. Again, power changes were expressed as the relative power change in dB to the baseline rest condition. In order to draw conclusions about differences in relative power between bicycling and walking we checked that baselines were not significantly different using the non-parametric cluster-based permutation test implemented in the FieldTrip toolbox (Maris and Oostenveld, 2007).

Movement Cycle

The movement cycle was defined as the interval between two consecutive maximum knee flexions of the right knee. The maximum knee flexion is an event occurring both in bicycling and in walking. Therefore, this approach facilitates the comparison between the two types of movement. However, this definition deviates from previous walking studies which used the heel strike as the boundary of the gait cycle (Gwin et al., 2011; Wagner et al., 2012; Seeber et al., 2014). The maximum knee flexion occurs between toe off and heel strike. Power modulations locked to the movement cycle based on the knee flexion precede the ones based on the heel strike by approximately 30% of the movement cycle.

To avoid confounds due to acceleration or deceleration, we solely incorporated cycles deriving from the continuous movement condition and from the period between 2 s after movement start and 2 s before movement stop. This resulted in an average of 202.1 ± 22.2 movement cycles (range 160–240). Time-frequency spectra were calculated per movement cycle with a sliding Hanning window. The window had a length of 0.5 s and was moved in steps of 0.01 s. Individual spectra were interpolated to the length of the longest cycle and subsequently averaged. This procedure standardized the same time frame for all subjects and conditions. Power within the movement cycle was normalized by the temporal average of the entire cycle for each frequency.

Rhythmicity of power modulations within the movement cycle was quantified by the gait phase modulation measure introduced by Seeber et al. (2014) and modified by Trenado (2015). This index can take values between 0 and 1 reflecting the similarity of the power modulation within the movement cycle with a sinusoid. The calculation is based on two periods of the sinusoid representing the modulation with every single leg movement within the movement cycle. The frequency and peak value of maximal sinusoidal modulation within the 24–40 Hz range was computed for every subject and condition. The choice of the frequency range of interest was based on prior studies (Wagner et al., 2012; Seeber et al., 2014). Peak values of the modulation measure did not differ between conditions, i.e., power modulation within the movement cycle had the same similarity with a sinusoid in bicycling and walking (Bicycling: $M = 0.78$, $SD = 0.13$, Walking: $M = 0.83$, $SD = 0.10$, paired t-test, $p > 0.05$). The resulting frequency was further used for fitting a sine wave to the corresponding power modulation. Again, a two-period pattern of the sine wave was assumed. This allowed comparing both phase and amplitude of rhythmic power modulations between bicycling and walking.

EMG Analysis

One of the 14 subjects had to be excluded from the EMG analysis for all muscles and a further subject for one muscle (BF) due to poor data quality. EMG data was band-pass filtered (20–450 Hz) and full-wave rectified. These filter cut-off frequencies were chosen in order to maintain the relevant information and avoiding artifact contamination, especially at lower frequencies (van Boxtel, 2001; De Luca et al., 2010). Average EMG activity

was obtained by computing the sum per unit of time. As we did not observe a power difference between body sides in any of the muscles (Bicycling: TA_left M = 18.18, SD = 15.03, TA_right M = 13.93, SD = 6.03, BF_left M = 19.77, SD = 8.34, BF_right M = 18.42, SD = 8.21, RF_left M = 23.41, SD = 10.97, RF_right M = 21.84, SD = 9.50, Walking: TA_left M = 49.04, SD = 15.26, TA_right M = 47.52, SD = 10.08, BF_left M = 30.70, SD = 16.32, BF_right M = 31.34, SD = 13.32, RF_left M = 39.09, SD = 23.70, RF_right M = 34.47, SD = 20.55; paired t-tests, all $p > 0.05$; for bicycling TA and walking RF Wilcoxon signed-rank test, all $p > 0.05$), we averaged EMG activity over sides.

Muscle activity within the movement cycle was analyzed as described in Jain et al. (2013). EMG activity was smoothed using a 4th order low-pass Butterworth filter with a cut-off at 5 Hz. EMG activity was summed over left and right muscles, yielding the composite EMG. In contrast to Jain et al. (2013), we interpolated EMG cycles in line with the EEG and computed grand average composite EMG as well as EEG on z-score transformed EEG and EMG data. Z-score transformed data were obtained by subtracting the mean and dividing by the standard deviation in order to account for scaling differences between subjects. Then, the correlation coefficient was determined between EEG power and EMG activity within the movement cycle.

Statistics

All analyses were focused on the Cz electrode overlying the leg area of both motor cortices and the SMA. We restricted the analysis to the Cz electrode as previous studies in the context of bicycling and walking were able to demonstrate movement-related activity especially in central sensorimotor areas (Wieser et al., 2010; Gwin et al., 2011; Wagner et al., 2012; Jain et al., 2013; Seeber et al., 2014). Changes of spectral power during continuous movement relative to the baseline rest period were evaluated in three different frequency bands: 8–12 Hz (alpha), 13–22 Hz (low beta), and 23–35 Hz (high beta) based on previous studies (López-Azcárate et al., 2010; Singh et al., 2013; Toledo et al., 2014). The frequency of maximal decrease was obtained for each frequency band and average power at the peak frequency (±1 Hz) compared between bicycling and walking using paired-samples t-tests implemented in IBM SPSS statistics, version 22 (IBM Deutschland GmbH, Ehningen, Germany). Differences in time-frequency spectra were evaluated by non-parametric cluster-based permutation testing implemented in the FieldTrip toolbox (Maris and Oostenveld, 2007). The calculation of mean and standard deviation of phase values were performed using the circular variants of these operations using the Circular Statistics Toolbox (Berens, 2009). For evaluation of phase differences between power modulations within the movement cycle we applied a non-parametric permutation test based on Watson's U^2 statistic (Zar, 1999). All other variables were tested with SPSS. We tested for normality using the Kolmogorov-Smirnov test. Two-sided paired-samples t-tests were performed in case of normally distributed data. Otherwise, we used the non-parametric Wilcoxon signed-rank test. For all tests, the significance level was set to 0.05. We corrected for multiple comparisons using the adaptive Bonferroni correction (Holm, 1979).

RESULTS

Movement-Related Power Changes

The average cadence across participants was 40.9 rpm (SD = 1.72) for bicycling and 41.5 spm (SD = 2.88) for walking. Both bicycling and walking led to a broadband decrease of oscillatory activity relative to the baseline rest condition with minima in the *alpha* (8–12 Hz), low *beta* (13–22 Hz) and high *beta* band (23–35 Hz; **Figure 2**). For bicycling relative to sitting, *alpha* power decreased about 1.81 dB (SD = 1.99) at 10.00 Hz (SD = 1.30), low *beta* power about 1.63 dB (SD = 1.27) at 18.21 Hz (SD = 2.49), and high *beta* power about 3.58 dB (SD = 2.27) at 26.71 Hz (SD = 2.13). For walking relative to standing, *alpha* power decreased about 4.49 dB (SD = 4.06) at 10.14 Hz (SD = 1.29), low *beta* power about 1.95 dB (SD = 1.98) at 17.71 Hz (SD = 1.98), and high *beta* power about 2.30 dB (SD = 1.95) at 27.36 Hz (SD = 2.84). Frequencies of maximal decrease in the *alpha*, low and high *beta* range didn't differ between bicycling and walking (all $p > 0.05$), but the pattern of power decreases during movement relative to baseline rest condition was different between the two conditions. While *alpha* power decrease was stronger for walking than for bicycling (p = 0.031), the power decrease in the high *beta* band was stronger for bicycling (p = 0.046).

Power decreases relative to the baseline rest condition could be observed in the *alpha*, low, and high *beta* band at movement initiation in bicycling and walking (**Figure 3**, upper panel). Furthermore, *theta* power (4–7 Hz) increased both in bicycling and walking relative to the baseline rest condition before movement initiation. For the walking condition, this was followed by a prompt *alpha* power decrease immediately

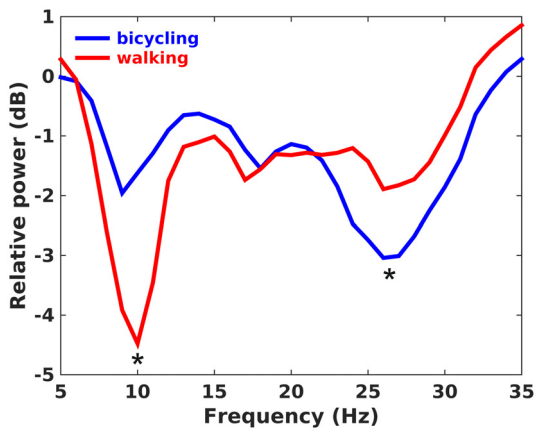

FIGURE 2 | Power ratio. Grand average plot showing changes of spectral power in dB during continuous movement relative to the baseline rest period. Positive values indicate a power increase during movement relative to baseline, whereas negative values indicate a power decrease. *Alpha* power decrease was stronger in walking, whereas high *beta* power decrease was stronger in bicycling as indicated by the asterisks.

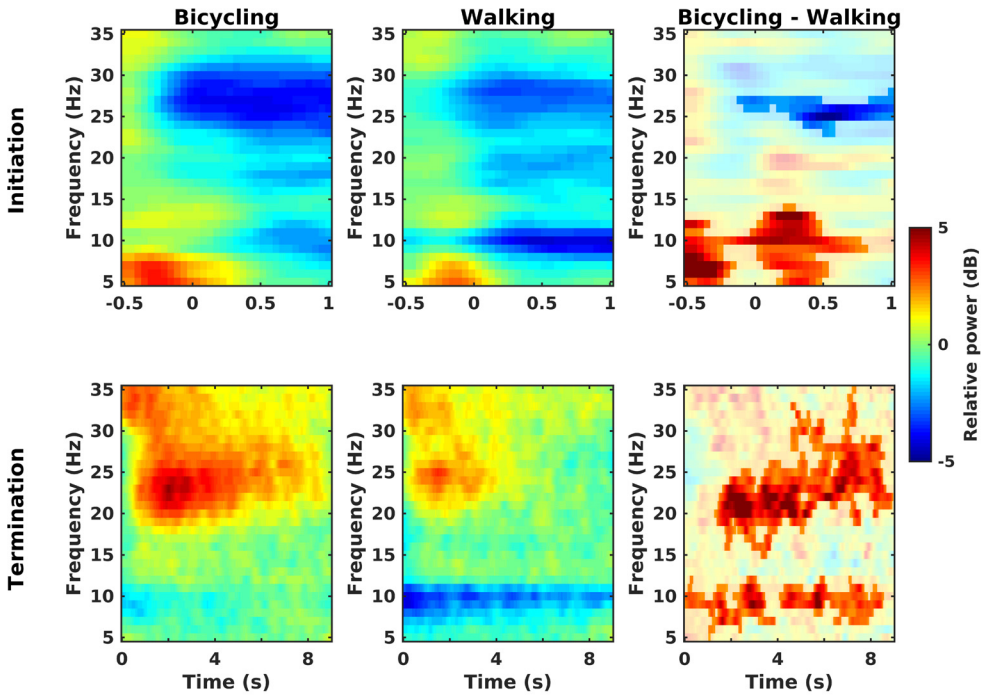

FIGURE 3 | Initiation and termination of movement. Grand average time-frequency representations of power changes locked to a change of the movement state relative to the baseline rest period (in dB) for bicycling, walking, and the difference between both (non-significant differences masked). Upper row: Movement initiation is at $t = 0$. In both conditions power decreases (blue) occur in the *alpha*, low and high *beta* band, but with a stronger high *beta* power decrease in bicycling and a stronger *alpha* power decrease in walking. Lower row: Movement termination is at $t = 0$. In both conditions power increase (red) occurs in the *beta* band. Contrasting bicycling and walking revealed a difference in the temporal evolution both of the *beta* rebound and of the *alpha* power recovery.

after movement initiation, whereas *alpha* power decreased approximately 500 ms after movement initiation in the bicycling condition. Contrasting relative power between bicycling and walking revealed two significant clusters (**Figure 3**, upper right panel). One cluster was found in the high *beta* band starting approximately 110 ms before movement start and indicating a stronger power decrease in bicycling compared to walking ($p = 0.044$). Additionally, we observed a significant cluster in the *theta-alpha* range (5–14 Hz, $p = 0.003$) during movement initiation, reflecting a stronger *theta* power increase and weaker subsequent *alpha* power decrease in bicycling compared to walking.

Post-movement *beta* power increase relative to the baseline rest condition could be observed in both conditions about 500 ms after movement termination covering the low and high *beta* range (**Figure 3**, lower panel). Furthermore, relative *alpha* power recovered immediately after movement stop in bicycling whereas it recovered only gradually after walking. Contrasting relative power between bicycling and walking (**Figure 3**, lower right panel) showed the post-movement *beta* power increase to be more pronounced and prolonged in bicycling compared to walking ($p < 0.001$). Furthermore, we observed two significant clusters in the *alpha* range (earlier cluster around 0–3.5 s, $p = 0.036$; later cluster around 4–8.5 s, $p = 0.042$) reflecting the persistent post-movement *alpha* power decrease in walking.

Movement-Cycle Locked Modulations

Time-frequency spectra clearly showed movement cycle-dependent power modulation in the 24–40 Hz range for both bicycling and walking, but with a phase lag between conditions (**Figure 4A**). There was a significant difference in amplitude (Bicycling: $M = 0.42$, $SD = 0.17$, Walking: $M = 0.63$, $SD = 0.36$, $p = 0.026$) and phase (Bicycling: $M = -1.09$ rad, $SD = 0.74$, Walking: $M = 1.55$ rad, $SD = 1.06$, $p < 0.001$) of the sine wave fitted to the strongest power modulation within the movement cycle (**Figure 4B**). Power decreases occurred at 29.80% ($SD = 13.79$) and 79.10% ($SD = 9.71$) of the gait cycle when the leading foot was touching the ground and the trailing foot was pushing off. Within the pedal cycle, power decreases occurred shortly before top and bottom pedal positions at 48.87% ($SD = 12.92$) and 92.12% ($SD = 8.44$) of the pedal cycle.

As can been seen in **Figure 5**, the time points of EEG power decreases coincided with the maximum EMG activity for both conditions. Testing a temporal relationship between the grand average composite bilateral EMG and EEG revealed a negative correlation for all muscles in the bicycling condition (TA: $r = -0.92$, $p < 0.001$; RF: $r = -0.95$, $p < 0.001$; BF: $r = -0.89$, $p < 0.001$). For the walking condition, the TA ($r = -0.45$, $p < 0.001$) and the BF ($r = -0.44$, $p < 0.001$) were correlated with the cortical power envelope. Walking relative to bicycling was accompanied by a stronger average EMG activity of the TA (Bicycling: $M = 16.06$, $SD = 9.82$, Walking: $M = 48.28$, $SD = 11.40$,

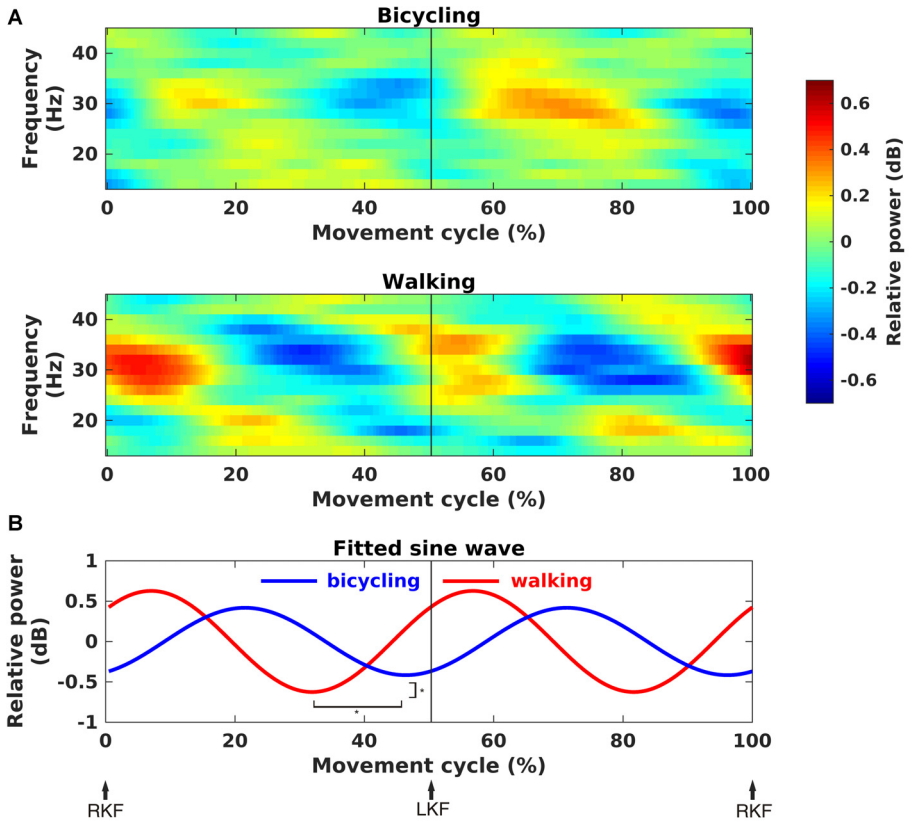

FIGURE 4 | Movement phase-dependent power modulations. **(A)** Grand average time-frequency representations of power changes within the movement cycle relative to the movement cycle mean power (in dB). Sinusoidal power modulations can be observed in the frequency range 24–40 Hz in bicycling (upper panel) and walking (lower panel). **(B)** Grand average sine wave fitted to the power modulation within the movement cycle. The fit was performed for the frequency of maximal movement phase modulation in each individual. It was based on a two-period pattern representing the power modulation with every single leg movement, i.e., right knee flexion (RKF) to left knee flexion (LKF) and LKF to RKF. Sine waves differed significantly in phase and amplitude as indicated by the asterisks.

$p = 0.006$) and the BF (Bicycling: $M = 19.10$, $SD = 7.76$, Walking: $M = 31.02$, $SD = 12.43$, $p = 0.012$). No difference was observed for the average EMG activity of the RF (Bicycling: $M = 22.62$, $SD = 9.91$, Walking: $M = 36.78$, $SD = 19.46$, $p > 0.05$).

DISCUSSION

Our data demonstrate different cortical oscillatory dynamics subserving bicycling and walking, giving rise to movement specific aspects of cortical involvement in motor control. Bicycling was marked by movement state-dependent power modulations in the *beta* range (13–35 Hz), whereas walking exhibited stronger movement phase-dependent power modulations in the 24–40 Hz range.

Stronger Movement State-Dependent *Beta* Power Modulation in Bicycling

Beta decrease during movement execution as well as *beta* rebound at movement termination was stronger in bicycling than in walking. This is particularly interesting as *beta* power decrease is related to an active state of the sensorimotor cortex associated with increased cortical excitability (Seeber et al., 2014; for a review, see Neuper and Pfurtscheller, 2001), and *beta* rebound to the shift from an active to an idling or even inhibited state of the motor cortex (Pfurtscheller et al., 1996; Solis-Escalante et al., 2012). Overall, *beta* activity is believed to represent maintenance of the current motor state (Engel and Fries, 2010). In this sense, the oscillatory profile of bicycling seems to be dominated by the switch from a resting state to a dynamic state and *vice versa*.

What are the potential reasons for the difference in *beta* power between bicycling and walking? During bicycling, pedals are locked to each other and hence, both legs are moving continuously. In contrast, in walking, each leg is independent with alternating stance and swing phases; i.e., the movement is divided into short and distinct independent entities. In fact, *beta* power was shown to remain suppressed during continuous movements (Erbil and Ungan, 2007; Gwin and Ferris, 2012), whereas it recovered during isometric and sustained movements (Cassim et al., 2000; Gwin and Ferris, 2012). The more continuous motor output in bicycling may therefore result in the stronger *beta* power decrease during movement execution and in a stronger inhibition process at movement termination.

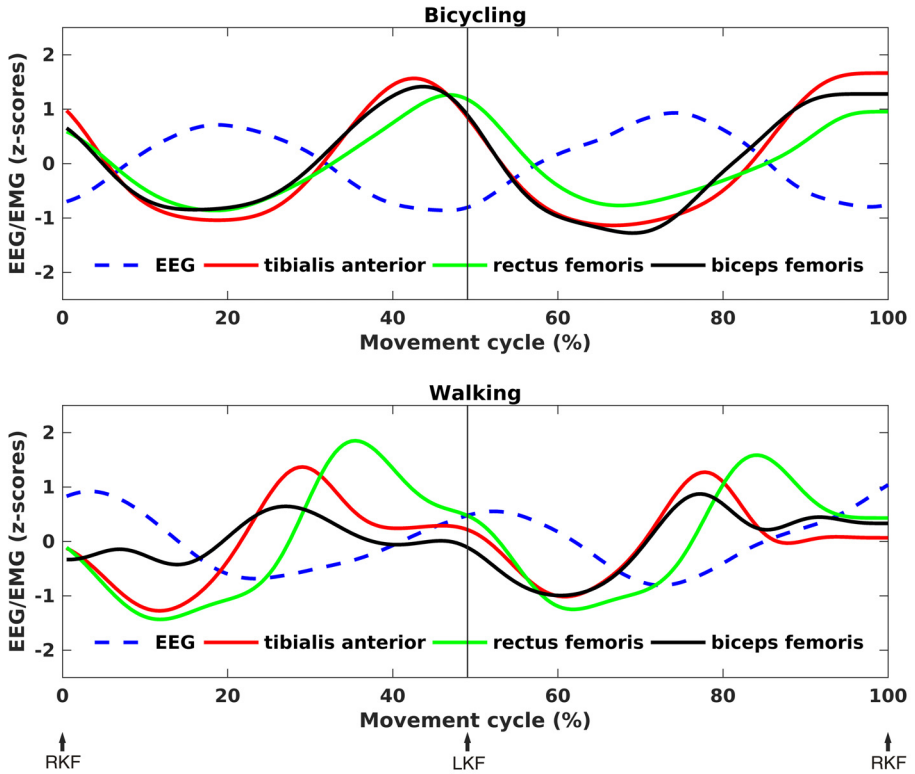

FIGURE 5 | Correlation between EEG power and EMG activity. Grand average *z*-score transformed, time-resolved EEG power and EMG activity for bicycling (upper panel) and walking (lower panel). The frequency was subject-specific, i.e., the frequency of maximal movement phase modulation in each individual. An anti-phasic relationship between EEG and EMG can be seen, with EMG activity peaks coinciding with EEG power troughs.

Moreover, differences in sensory feedback accompanying motor output might also affect movement state-dependent *beta* power modulation in bicycling (Cassim et al., 2001; van Ede and Maris, 2013).

Alternatively, differences in movement kinematics could have accounted for the difference in *beta* power decrease. Cadence was kept constant across conditions. Still, we were not able to control for differences in velocity, as walking velocity can change at constant cadence by adapting step length. However, central *beta* power decrease was found not to be affected by movement velocity (Stančák and Pfurtscheller, 1996; Bulea et al., 2015). Investigations on the effect of muscular effort on brain activity yielded inconsistent results (Stančák et al., 1997; Christensen et al., 2000; Gwin and Ferris, 2012; Pistohl et al., 2012). In the present study, muscular effort of the TA and the BF were stronger in walking while *beta* decrease was stronger in bicycling. Accordingly, it is quite unlikely that the stronger *beta* decrease in bicycling resulted from stronger muscular effort.

Alpha Power Modulations

Bicycling and walking were associated with different oscillatory dynamics in the *alpha* band. Walking, as opposed to bicycling, was associated with a stronger *alpha* power decrease. Furthermore, *alpha* decrease occurred earlier during initiation of walking, but it was also found to recover later after movement termination. In line with this, Leocani et al. (1997) investigated self-paced finger movements and found cortical areas showing fast *alpha* suppression to be the ones showing late recovery. *Alpha* decrease was shown to persist after movement termination and localized to the postcentral gyrus (Salmelin and Hari, 1994; Salmelin et al., 1995; Leocani et al., 1997; Jurkiewicz et al., 2006). Consequently, *alpha* decrease is assumed to be closely linked to somatosensory processing. This tallies with the findings by Wagner et al. (2012) who showed *alpha* power to decrease during active compared to passive walking in the sensory cortex, probably related to the increased sensory feedback from the muscles. Interestingly, *alpha* power was also reported to decrease in parietal areas during walking with interactive movement related feedback compared to movement unrelated feedback (Wagner et al., 2014). This difference in *alpha* power decrease was suggested to be related to sensorimotor integration during visually guided walking in a virtual environment. Moreover, Presacco et al. (2011) found *alpha* power to decrease during precision walking, i.e., when participants were required to control their foot placement based on visual feedback. As *alpha* band activity is generally associated with attention and information processing (for a review, see Klimesch, 2012), this may point to enhanced sensory and attentional demands in walking.

Stronger Movement Phase-Dependent Power Modulation in the 24–40 Hz Range in Walking

We report movement phase-dependent power modulation in the 24–40 Hz range for the first time in bicycling and overground walking. Within-cycle power modulation in walking agrees with previous results and has been related to motor planning and sensorimotor processing (Wagner et al., 2012, 2014; Seeber et al., 2014, 2015). However, the exact role remained elusive.

Here, we provide further evidence for cortical oscillatory activity being involved in motor control. For both movement types, power decreases occurred during movement transition phases, i.e., transition between stance and swing phase in walking and flexion and extension in bicycling. Since transition phases occur at different time points in the movement cycle in bicycling and walking if defined according to the maximum right knee flexion (RKF), the corresponding power modulation significantly differed between conditions. This adds to previous results demonstrating strongest negative movement-evoked potentials during transition phases in bicycling and walking, emphasizing highest cortical control during changes of movement direction (Wieser et al., 2010; Jain et al., 2013; Knaepen et al., 2015). In line with this idea, negative potentials have been associated with activity in the cingulate and prefrontal cortex and subsequent positive potentials with activity in sensorimotor regions, thought to reflect processing of afferent feedback (Knaepen et al., 2015). Interestingly, Petersen et al. (2012) found corticomuscular coherence in the 24–40 Hz range between Cz and the TA muscle before the heel strike during walking. Importantly, cortical activity was leading muscular activity, as indicated by the negative sign of the imaginary part of coherency. Together, this may indicate power modulations in the 24–40 Hz range to reflect movement phase-dependent planning processes as an aspect of cortical motor control.

Although bicycling and walking both exhibited movement phase-dependent power modulation with power decreases occurring during movement transition phases, power modulation was found to be stronger in walking. This suggests that bicycling and walking differ in cortical involvement in motor control within the movement cycle. Two factors may contribute to this difference. First, the restricted movement pattern in bicycling with symmetrically moving pedals at fixed circumference may demand less motor planning within the pedal cycle. This assumption is strengthened by the finding of higher interference during walking compared to bicycling in a dual task situation in Parkinson's disease patients (Yogev-Seligmann et al., 2013). The authors reasoned bilateral coordination making movement vulnerable to cognitive load. Indeed, the SMA has been shown to be involved in interlimb coordination and to be affected in Parkinson's disease (Wu et al., 2010). Hence, the present difference in cortical activity recorded at the Cz electrode might reflect differences in motor planning due to differing coordination demands.

Second, stronger power modulation in walking might result from stronger muscle recruitment or the integration of related sensory feedback. We found EEG power and EMG activity to be closely correlated in the present study with EEG power decreases coinciding with maximal muscle recruitment of the TA and BF. Notably, average EMG activity of the TA and BF was stronger in walking compared to bicycling. This may be directly related to the difference in cortical power modulation between the two movement types. Moreover, afferent input of the leg muscles was shown to affect cortical activation. Williamson et al. (1997) found passive bicycling to lead to less activation of the motor cortex as compared to active bicycling. However, passive bicycling with additional electrical stimulation of the leg muscles increased the cortical activation in the direction of the level during active bicycling. Somatosensory integration was also suggested to lead to phase specific power increases in the 30–50 Hz range in posterior parietal areas during a speed tracking task on a treadmill when participants had to drive the treadmill speed by themselves, as opposed to a predetermined treadmill speed (Bulea et al., 2015). In agreement with this, integration of sensory information into the motor command was proposed to shift the corticomuscular coherence from the range of 15–30 Hz to higher frequencies, i.e., 30–35 Hz, during dynamic movements (Omlor et al., 2007). Importantly, the huge contribution of sensory afferents to sensorimotor activity was also emphasized by almost identical activation patterns in passive and active bicycling and walking (Wagner et al., 2012; Jain et al., 2013). Interestingly, Wagner et al. (2012) observed a trend for stronger power decreases in active compared to passive walking, whereas Jain et al. (2013) found active compared to passive bicycling to lead to an attenuation of the movement-evoked potentials. They assumed this to be due to sensory gating by efferent corticospinal output. Based on this, phasic sensory input may be more inhibited in bicycling because of the continuous movement pattern and stronger corticospinal drive, respectively.

Methodological Considerations

Artifact contamination is a major issue in EEG studies on movement (Gwin et al., 2011; Castermans et al., 2014; Kline et al., 2015). Recently, several artifact rejection methods, e.g., ICA in combination with dipole analysis, have been applied to study oscillatory activity during walking (Gwin et al., 2011; Wagner et al., 2012). We decided to use ICA solely for rejecting components clearly reflecting eye blinks and not components potentially related to muscle artifacts. Due to the small number of electrodes ICA cannot be expected to isolate muscle artifacts completely, i.e., many of the components will be a mixture of artifacts and brain activity, and should not be discarded. Moreover, we restricted the average reference to the nine central electrodes in order to minimize muscular artifact contamination especially from the neck muscles which mostly affected the lateral and occipital electrodes. However, we cannot rule out that we thereby changed signal localization and power or artifacts remaining in the data. Notably, the similarity between our data and prior results suggests that our conservative procedure yielded comparable data quality. This point is additionally supported by intra-cycle power modulations occurring in a

physiologically limited frequency band (24–40 Hz) and not as broadband activity. This would be expected in case of movement artifact contamination (Castermans et al., 2014) and in particular muscular artifact contamination from the neck muscles (Gwin et al., 2011; Severens et al., 2012).

Interpreting the differences in cortical activity underlying bicycling and walking one has to keep in mind that several factors as e.g., exercise intensity and preference influence brain activity (Brümmer et al., 2011a,b). We controlled for a difference in cadence as Christensen et al. (2000) have shown that cortical activation correlates with cadence but not with pedal resistance during recumbent bicycling. However, as we did not measure heart beat or direct calorimetry, we cannot directly control the influence of physiological load on the power difference between bicycling and walking.

Furthermore, participants had to bicycle and walk with a predetermined cadence of 40 rpm and 40 spm, respectively. The imposed cadence might have deviated from the self-preferred cadence which could have influenced brain activity during both movements, especially cortical control within the movement cycle. A relationship between cortical control and walking cadence is suggested by the findings of slowed walking cadence in the elderly under dual-task load (for a review, see Al-Yahya et al., 2011). Not controlling for a difference in cadence, however, would have caused an obvious mismatch in motor output between bicycling and walking. Furthermore, Gwin et al. (2011) did not find any significant difference comparing gait phase-dependent EEG power modulation for 0.8 and 1.25 m/s walking.

Implications for Freezing of Gait in Parkinson's Disease

The finding of different cortical oscillatory dynamics in bicycling and walking may shed some light on the puzzling finding of preserved bicycling abilities in Parkinson's patients suffering from severe freezing of gait (FOG; Snijders et al., 2011b, 2012). FOG has been associated with impaired temporal and spatial gait control (Nieuwboer et al., 2001; Hausdorff et al., 2003), decreased activity of the SMA (Snijders et al., 2011a), and increased resting state high *beta* power within the subthalamic nucleus (Toledo et al., 2014). Parkinson's disease is generally associated with abnormally increased *beta* band activity in the corticobasal ganglia loop (for a review, see Oswal et al., 2013). Therefore, one may speculate that bicycling may be less hampered in FOG because the more continuous nature of this movement promotes *beta* suppression and demands less sensorimotor processing. Furthermore, the more continuous movement in bicycling may be less vulnerable to interruptions than the independent movement entities in walking. A study specifically addressing this hypothesis is in progress.

CONCLUSION

The present study provides insight into oscillatory dynamics being involved in motor control during both bicycling and walking. We found stronger movement state-dependent high *beta* power modulation but less movement phase-dependent power modulation in the 24–40 Hz range in bicycling as opposed to walking. Our data suggest that, relative to walking, bicycling is characterized by a stronger cortical activation. This may be the result of the more continuous movement pattern, precluding a regular rest period. In contrast, phases of rest and movement alternate all the time in walking and may therefore demand more phase-dependent sensory processing and motor planning.

AUTHOR CONTRIBUTIONS

All authors contributed to the design of the experiment and revised the manuscript. LS, MB, JH, OA, and SSD were involved in data analysis and interpretation and LS further in data acquisition. All authors approved the final version of the manuscript, agreed to be accountable for all aspects of the work and qualify for authorship.

ACKNOWLEDGMENTS

We thank Dr. Carlos Trenado (HHU Düsseldorf) for his support with data analysis and for helpful discussions and comments and Nitin Sharma (University of Konstanz) for assistance with constructing and programming the bicycle simulator.

This work was generously supported by a grant from the Jacques and Gloria Gossweiler Foundation. Further support was received from the Zukunftskolleg of the University of Konstanz [SSD], Heinrich Heine University Strategic Research Funds [MB], the Open Access Publication Fund of the University of Konstanz, and the research commission of the medical faculty of the Heinrich Heine University [9772562 to MB]. LS was supported by a travel grant from the Boehringer Ingelheim Foundation (BIF).

REFERENCES

Alegre, M., Labarga, A., Gurtubay, I. G., Iriarte, J., Malanda, A., and Artieda, J. (2002). Beta electroencephalograph changes during passive movements: sensory afferences contribute to beta event-related desynchronization in humans. *Neurosci. Lett.* 331, 29–32. doi: 10.1016/s0304-3940(02)00825-x

Al-Yahya, E., Dawes, H., Smith, L., Dennis, A., Howells, K., and Cockburn, J. (2011). Cognitive motor interference while walking: a systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* 35, 715–728. doi: 10.1016/j.neubiorev.2010.08.008

Berens, P. (2009). CircStat: a MATLAB toolbox for circular statistics. *J. Stat. Softw.* 31, 1–21. doi: 10.18637/jss.v031.i10

Brümmer, V., Schneider, S., Abel, T., Vogt, T., and Strüder, H. K. (2011a). Brain cortical activity is influenced by exercise mode and intensity. *Med. Sci. Sport. Exerc.* 43, 1863–1872. doi: 10.1249/mss.0b013e3182172a6f

Brümmer, V., Schneider, S., Strüder, H. K., and Askew, C. D. (2011b). Primary motor cortex activity is elevated with incremental exercise intensity. *Neuroscience* 181, 150–162. doi: 10.1016/j.neuroscience.2011.02.006

Bulea, T. C., Kim, J., Damiano, D. L., Stanley, C. J., and Park, H.-S. (2015). Prefrontal, posterior parietal and sensorimotor network activity underlying speed control during walking. *Front. Hum. Neurosci.* 9:247. doi: 10.3389/fnhum.2015.00247

Cassim, F., Monaca, C., Szurhaj, W., Bourriez, J. L., Defebvre, L., Derambure, P., et al. (2001). Does post-movement beta synchronization reflect an idling motor cortex? *Neuroreport* 12, 3859–3863. doi: 10.1097/00001756-200112040-00051

Cassim, F., Szurhaj, W., Sediri, H., Devos, D., Bourriez, J. L., Poirot, I., et al. (2000). Brief and sustained movements: differences in event-related (de)synchronization (ERD/ERS) patterns. *Clin. Neurophysiol.* 111, 2032–2039. doi: 10.1016/s1388-2457(00)00455-7

Castermans, T., Duvinage, M., Cheron, G., and Dutoit, T. (2014). About the cortical origin of the low-delta and high-gamma rhythms observed in EEG signals during treadmill walking. *Neurosci. Lett.* 561, 166–170. doi: 10.1016/j.neulet.2013.12.059

Christensen, L. O. D., Johannsen, P., Sinkjaer, T., Petersen, N., Pyndt, H. S., and Nielsen, J. B. (2000). Cerebral activation during bicycle movements in man. *Exp. Brain Res.* 135, 66–72. doi: 10.1007/s002210000493

Dahmen, T., Byshko, R., Saupe, D., Röder, M., and Mantler, S. (2011). Validation of a model and a simulator for road cycling on real tracks. *Sport Eng.* 14, 95–110. doi: 10.1007/s12283-011-0076-1

De Luca, C. J., Donald Gilmore, L., Kuznetsov, M., and Roy, S. H. (2010). Filtering the surface EMG signal: movement artifact and baseline noise contamination. *J. Biomech.* 43, 1573–1579. doi: 10.1016/j.jbiomech.2010.01.027

Delorme, A., Sejnowski, T., and Makeig, S. (2007). Enhanced detection of artifacts in EEG data using higher-order statistics and independent component analysis. *Neuroimage* 34, 1443–1449. doi: 10.1016/j.neuroimage.2006.11.004

Durka, P. J., Kuś, R., Żygierewicz, J., Michalska, M., Milanowski, P., Łabecki, M., et al. (2012). User-centered design of brain-computer interfaces: open BCI.pl and BCI appliance. *Bull. Polish Acad. Sci. Tech. Sci.* 60, 427–431. doi: 10.2478/v10175-012-0054-1

Engel, A. K., and Fries, P. (2010). Beta-band oscillations—signalling the status quo? *Curr. Opin. Neurobiol.* 20, 156–165. doi: 10.1016/j.conb.2010.02.015

Erbil, N., and Ungan, P. (2007). Changes in the alpha and beta amplitudes of the central EEG during the onset, continuation and offset of long-duration repetitive hand movements. *Brain Res.* 1169, 44–56. doi: 10.1016/j.brainres.2007.07.014

Fukuyama, H., Ouchi, Y., Matsuzaki, S., Nagahama, Y., Yamauchi, H., Ogawa, M., et al. (1997). Brain functional activity during gait in normal subjects: a SPECT study. *Neurosci. Lett.* 228, 183–186. doi: 10.1016/s0304-3940(97)00381-9

Gwin, J. T., and Ferris, D. P. (2012). An EEG-based study of discrete isometric and isotonic human lower limb muscle contractions. *J. Neuroeng. Rehabil.* 9:35. doi: 10.1186/1743-0003-9-35

Gwin, J. T., Gramann, K., Makeig, S., and Ferris, D. P. (2011). Electrocortical activity is coupled to gait cycle phase during treadmill walking. *Neuroimage* 54, 1289–1296. doi: 10.1016/j.neuroimage.2010.08.066

Hausdorff, J. M., Schaafsma, J. D., Balash, Y., Bartels, A. L., Gurevich, T., and Giladi, N. (2003). Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. *Exp. Brain Res.* 149, 187–194. doi: 10.1007/s00221-002-1354-8

Hermens, H. J., Freriks, B., Merletti, R., Stegeman, D., Blok, J., Rau, G., et al. (1999). *European Recommendations for Surface ElectroMyoGraphy*. Enschede: Roessingh Research and Development.

Holm, S. (1979). A simple sequentially rejective multiple test procedure. *Scand. J. Stat.* 6, 65–70.

Jain, S., Gourab, K., Schindler-Ivens, S., and Schmit, B. D. (2013). EEG during pedaling: evidence for cortical control of locomotor tasks. *Clin. Neurophysiol.* 124, 379–390. doi: 10.1016/j.clinph.2012.08.021

Jurkiewicz, M. T., Gaetz, W. C., Bostan, A. C., and Cheyne, D. (2006). Post-movement beta rebound is generated in motor cortex: evidence from neuromagnetic recordings. *Neuroimage* 32, 1281–1289. doi: 10.1016/j.neuroimage.2006.06.005

Klimesch, W. (2012). Alpha-band oscillations, attention and controlled access to stored information. *Trends Cogn. Sci.* 16, 606–617. doi: 10.1016/j.tics.2012.10.007

Kline, J. E., Huang, H. J., Snyder, K. L., and Ferris, D. P. (2015). Isolating gait-related movement artifacts in electroencephalography during human walking. *J. Neural Eng.* 12:046022. doi: 10.1088/1741-2560/12/4/046022

Knaepen, K., Mierau, A., Tellez, H. F., Lefeber, D., and Meeusen, R. (2015). Temporal and spatial organization of gait-related electrocortical potentials. *Neurosci. Lett.* 599, 75–80. doi: 10.1016/j.neulet.2015.05.036

Leocani, L., Toro, C., Manganotti, P., Zhuang, P., and Hallett, M. (1997). Event-related coherence and event-related desynchronization/synchronization in the 10 Hz and 20 Hz EEG during self-paced movements. *Electroencephalogr. Clin. Neurophysiol. Potentials Sect.* 104, 199–206. doi: 10.1016/s0168-5597(96)96051-7

López-Azcárate, J., Tainta, M., Rodríguez-Oroz, M. C., Valencia, M., González, R., Guridi, J., et al. (2010). Coupling between beta and high-frequency activity in the human subthalamic nucleus may be a pathophysiological mechanism in Parkinson's disease. *J. Neurosci.* 30, 6667–6677. doi: 10.1523/JNEUROSCI.5459-09.2010

Maris, E., and Oostenveld, R. (2007). Nonparametric statistical testing of EEG- and MEG-data. *J. Neurosci. Methods* 164, 177–190. doi: 10.1016/j.jneumeth.2007.03.024

Mehta, J. P., Verber, M. D., Wieser, J. A., Schmit, B. D., and Schindler-Ivens, S. M. (2009). A novel technique for examining human brain activity associated with pedaling using fMRI. *J. Neurosci. Methods* 179, 230–239. doi: 10.1016/j.jneumeth.2009.01.029

Miyai, I., Tanabe, H. C., Sase, I., Eda, H., Oda, I., Konishi, I., et al. (2001). Cortical mapping of gait in humans: a near-infrared spectroscopic topography study. *Neuroimage* 14, 1186–1192. doi: 10.1006/nimg.2001.0905

Müller-Putz, G. R., Zimmermann, D., Graimann, B., Nestinger, K., Korisek, G., and Pfurtscheller, G. (2007). Event-related beta EEG-changes during passive and attempted foot movements in paraplegic patients. *Brain Res.* 1137, 84–91. doi: 10.1016/j.brainres.2006.12.052

Neuper, C., and Pfurtscheller, G. (2001). Event-related dynamics of cortical rhythms: frequency-specific features and functional correlates. *Int. J. Psychophysiol.* 43, 41–58. doi: 10.1016/s0167-8760(01)00178-7

Nieuwboer, A., Dom, R., De Weerdt, W., Desloovere, K., Fieuws, S., and Broens-Kaucsik, E. (2001). Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. *Mov. Disord.* 16, 1066–1075. doi: 10.1002/mds.1206

Nutt, J. G., Bloem, B. R., Giladi, N., Hallett, M., Horak, F. B., and Nieuwboer, A. (2011). Freezing of gait: moving forward on a mysterious clinical phenomenon. *Lancet Neurol.* 10, 734–744. doi: 10.1016/s1474-4422(11)70143-0

Omlor, W., Patino, L., Hepp-Reymond, M. C., and Kristeva, R. (2007). Gamma-range corticomuscular coherence during dynamic force output. *Neuroimage* 34, 1191–1198. doi: 10.1016/j.neuroimage.2006.10.018

Oostenveld, R., Fries, P., Maris, E., and Schoffelen, J.-M. (2011). Fieldtrip: open source software for advanced analysis of MEG, EEG and invasive electrophysiological data. *Comput. Intell. Neurosci.* 2011:156869. doi: 10.1155/2011/156869

Oswal, A., Brown, P., and Litvak, V. (2013). Synchronized neural oscillations and the pathophysiology of Parkinson's disease. *Curr. Opin. Neurol.* 26, 662–670. doi: 10.1097/WCO.0000000000000034

Parkes, L. M., Bastiaansen, M. C. M., and Norris, D. G. (2006). Combining EEG and fMRI to investigate the post-movement beta rebound. *Neuroimage* 29, 685–696. doi: 10.1016/j.neuroimage.2005.08.018

Petersen, T. H., Willerslev-Olsen, M., Conway, B. A., and Nielsen, J. B. (2012). The motor cortex drives the muscles during walking in human subjects. *J. Physiol.* 590, 2443–2452. doi: 10.1113/jphysiol.2012.227397

Pfurtscheller, G., Stancák, A., Jr., and Neuper, C. (1996). Post-movement beta synchronization. A correlate of an idling motor area? *Electroencephalogr. Clin. Neurophysiol.* 98, 281–293. doi: 10.1016/0013-4694(95)00258-8

Pistohl, T., Schulze-Bonhage, A., Aertsen, A., Mehring, C., and Ball, T. (2012). Decoding natural grasp types from human ECoG. *Neuroimage* 59, 248–260. doi: 10.1016/j.neuroimage.2011.06.084

Presacco, A., Goodman, R., Forrester, L., and Contreras-Vidal, J. L. (2011). Neural decoding of treadmill walking from noninvasive electroencephalographic signals. *J. Neurophysiol.* 106, 1875–1887. doi: 10.1152/jn.00104.2011

Raasch, C. C., and Zajac, F. E. (1999). Locomotor strategy for pedaling: muscle groups and biomechanical functions. *J. Neurophysiol.* 82, 515–525.

Ridgel, A. L., Kim, C., Fickes, E. J., Muller, M. D., and Alberts, J. L. (2011). Changes in executive function after acute bouts of passive cycling in Parkinson 's disease. *J. Aging Phys. Act.* 19, 87–98.

Ridgel, A. L., Peacock, C. A., Fickes, E. J., and Kim, C.-H. (2012). Active-assisted cycling improves tremor and bradykinesia in Parkinson's disease. *Arch. Phys. Med. Rehabil.* 93, 2049–2054. doi: 10.1016/j.apmr.2012.05.015

Ridgel, A. L., Vitek, J. L., and Alberts, J. L. (2009). Forced, not voluntary, exercise improves motor function in Parkinson's disease patients. *Neurorehabil. Neural Repair* 23, 600–608. doi: 10.1177/1545968308328726

Salmelin, R., and Hari, R. (1994). Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. *Neuroscience* 60, 537–550. doi: 10.1016/0306-4522(94)90263-1

Salmelin, R., Hämäläinen, M., Kajola, M., and Hari, R. (1995). Functional segregation of movement-related rhythmic activity in the human brain. *Neuroimage* 2, 237–243. doi: 10.1006/nimg.1995.1031

Seeber, M., Scherer, R., Wagner, J., Solis-Escalante, T., and Müller-Putz, G. R. (2014). EEG beta suppression and low gamma modulation are different elements of human upright walking. *Front. Hum. Neurosci.* 8:485. doi: 10.3389/fnhum.2014.00485

Seeber, M., Scherer, R., Wagner, J., Solis-Escalante, T., and Müller-Putz, G. R. (2015). High and low gamma EEG oscillations in central sensorimotor areas are conversely modulated during the human gait cycle. *Neuroimage* 112, 318–326. doi: 10.1016/j.neuroimage.2015.03.045

Severens, M., Nienhuis, B., Desain, P., and Duysens, J. (2012). Feasibility of measuring event Related Desynchronization with electroencephalography during walking. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2764–2767. doi: 10.1109/EMBC.2012.6346537

Singh, A., Plate, A., Kammermeier, S., Mehrkens, J. H., Ilmberger, J., and Bötzel, K. (2013). Freezing of gait-related oscillatory activity in the human subthalamic nucleus. *Basal Ganglia* 3, 25–32. doi: 10.1016/j.baga.2012.10.002

Snijders, A. H., Leunissen, I., Bakker, M., Overeem, S., Helmich, R. C., Bloem, B. R., et al. (2011a). Gait-related cerebral alterations in patients with Parkinson's disease with freezing of gait. *Brain* 134, 59–72. doi: 10.1093/brain/awq324

Snijders, A. H., Toni, I., Ružička, E., and Bloem, B. R. (2011b). Bicycling breaks the ice for freezers of gait. *Mov. Disord.* 26, 367–371. doi: 10.1002/mds.23530

Snijders, A. H., van Kesteren, M., and Bloem, B. R. (2012). Cycling is less affected than walking in freezers of gait. *J. Neurol. Neurosurg. Psychiatry* 83, 575–576. doi: 10.1136/jnnp-2011-300375

Solis-Escalante, T., Müller-Putz, G. R., Pfurtscheller, G., and Neuper, C. (2012). Cue-induced beta rebound during withholding of overt and covert foot movement. *Clin. Neurophysiol.* 123, 1182–1190. doi: 10.1016/j.clinph.2012.01.013

Stančák, A., Jr., and Pfurtscheller, G. (1996). Event-related desynchronisation of central beta-rhythms during brisk and slow self-paced finger movements of dominant and nondominant hand. *Brain Res. Cogn. Brain Res.* 4, 171–183. doi: 10.1016/s0926-6410(96)00031-6

Stančák, A., Jr., Riml, A., and Pfurtscheller, G. (1997). The effects of external load on movement-related changes of the sensorimotor EEG rhythms. *Electroencephalogr. Clin. Neurophysiol.* 102, 495–504. doi: 10.1016/s0013-4694(96)96623-0

Toledo, J. B., López-Azcárate, J., Garcia-Garcia, D., Guridi, J., Valencia, M., Artieda, J., et al. (2014). High beta activity in the subthalamic nucleus and freezing of gait in Parkinson's disease. *Neurobiol. Dis.* 64, 60–65. doi: 10.1016/j.nbd.2013.12.005

Trenado, C. (2015). Commentary: EEG beta suppression and low gamma modulation are different elements of human upright walking. *Front. Hum. Neurosci.* 9:380. doi: 10.3389/fnhum.2015.00380

van Boxtel, A. (2001). Optimal signal bandwidth for the recording of surface EMG activity of facial, jaw, oral and neck muscles. *Psychophysiology* 38, 22–34. doi: 10.1111/1469-8986.3810022

van Ede, F., and Maris, E. (2013). Somatosensory demands modulate muscular beta oscillations, independent of motor demands. *J. Neurosci.* 33, 10849–10857. doi: 10.1523/JNEUROSCI.5629-12.2013

Wagner, J., Solis-Escalante, T., Grieshofer, P., Neuper, C., Müller-Putz, G., and Scherer, R. (2012). Level of participation in robotic-assisted treadmill walking modulates midline sensorimotor EEG rhythms in able-bodied subjects. *Neuroimage* 63, 1203–1211. doi: 10.1016/j.neuroimage.2012.08.019

Wagner, J., Solis-Escalante, T., Scherer, R., Neuper, C., and Müller-Putz, G. (2014). It's how you get there: walking down a virtual alley activates premotor and parietal areas. *Front. Hum. Neurosci.* 8:93. doi: 10.3389/fnhum.2014.00093

Wieser, M., Haefeli, J., Bütler, L., Jäncke, L., Riener, R., and Koeneke, S. (2010). Temporal and spatial patterns of cortical activation during assisted lower limb movement. *Exp. Brain Res.* 203, 181–191. doi: 10.1007/s00221-010-2223-5

Williamson, J. W., Nobrega, A. C. L., McColl, R., Mathews, D., Winchester, P., Friberg, L., et al. (1997). Activation of the insular cortex during dynamic exercise in humans. *J. Physiol.* 503, 277–283. doi: 10.1111/j.1469-7793.1997.277bh.x

Wu, T., Wang, L., Hallett, M., Li, K., and Chan, P. (2010). Neural correlates of bimanual anti-phase and in-phase movements in Parkinson's disease. *Brain* 133, 2394–2409. doi: 10.1093/brain/awq151

Yogev-Seligmann, G., Giladi, N., Gruendlinger, L., and Hausdorff, J. M. (2013). The contribution of postural control and bilateral coordination to the impact of dual tasking on gait. *Exp. Brain Res.* 226, 81–93. doi: 10.1007/s00221-013-3412-9

Zar, J. H. (1999). *Biostatistical Analysis.* Upper Saddle River, New Jersy: Prentice Hall.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Stronger subthalamic beta power suppression in bicycling relative to walking in Parkinson's disease

Lena Storzer[1], Markus Butz[1*], Jan Hirschmann[1,2], Omid Abbasi[1,3], Maciej Gratkowski[4], Dietmar Saupe[4], Jan Vesper[5], Sarang S. Dalal[6,7,9], Alfons Schnitzler[1,8,9]

[1]Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany

[2]Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands

[3]Department of Medical Engineering, Ruhr-University Bochum, Bochum, Germany

[4]Department of Computer and Information Science, University of Konstanz, Konstanz, Germany

[5]Department of Functional Neurosurgery and Stereotaxy, Medical Faculty, University Hospital Düsseldorf, Germany

[6]Center of Functionally Integrative Neuroscience, Aarhus University, Aarhus, Denmark

[7]Zukunftskolleg and Department of Psychology, University of Konstanz, Konstanz, Germany

[8]Center for Movement Disorders and Neuromodulation, University Hospital Düsseldorf, Düsseldorf, Germany

[9]These authors contributed equally to this work

*** Correspondence:** Markus Butz, Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich Heine University Düsseldorf, Universitätsstraße 1, 40225 Düsseldorf, Germany.

Markus.Butz@hhu.de

Total number of words: 4648

Abstract

Freezing of gait is a poorly understood symptom in Parkinson's disease, a neurodegenerative disease compromising oscillatory activity in the basal ganglia. Surprisingly, bicycling ability remains preserved in patients suffering from freezing of gait. Local field potential recordings from the basal ganglia have demonstrated that walking modulates beta band oscillations. Here, we present the first local field potential recordings directly comparing bicycling and walking in Parkinsonian patients with electrodes implanted in the subthalamic nucleus for therapeutic stimulation. The specific beta band modulations for each condition were studied during rest, bicycling on a stationary bicycle, and walking.

Contrasting beta power (13-35 Hz) changes in 16 subthalamic nuclei of 10 Parkinson's disease patients (56.5 +/- 6.2 years, one female) revealed stronger beta power suppression in bicycling as compared to walking. Notably, patients with freezing of gait exhibited an abnormal ~18 Hz oscillation that intensified during walking but not during bicycling and was anti-correlated with the remaining beta band.

This study provides important first insight into basal ganglia oscillatory dynamics underlying bicycling and walking. Our results indicate that bicycling may facilitate suppression of ~18 Hz and overall beta power, while walking is prone to exaggerated synchronization within the basal ganglia. As beta band activity is suggested to be of antikinetic nature, these findings provide a promising starting point for elucidating the mechanism that preserves bicycling ability in Parkinson's disease. We speculate this may be due to the more continuous nature of bicycling, which is more predictable, computationally less demanding and less susceptible to interruptions than the alternating stance and swing phases in walking. This may prevent exaggerated synchronization within the basal ganglia which has been related to freezing of gait. These findings suggest a critical role of abnormal ~18 Hz oscillations in the pathophysiology of freezing of gait and may lead to promising new therapeutic stimulation strategies.

Keywords: freezing of gait, motor control, oscillatory activity, Parkinson's disease, subthalamic nucleus

Abbreviations

BDI	Becks Depression Inventory
DBS	deep brain stimulation
FAB	Frontal Assessment Battery
FOG-Q	Freezing of Gait Questionnaire
LFP	local field potential
MDRS	Mattis Dementia Rating Scale
MNI	Montreal Neurological Institute
PPN	pedunculopontine nucleus
rpm	revolutions per minute
spm	strides per minute
STN	subthalamic nucleus
UPDRS	Unified Parkinson's Disease Rating Scale

1 Introduction

The basal ganglia are a key player in the locomotor network interacting with cortical motor, cerebellar, and brainstem structures and consequently, gait impairments are a main problem in Parkinson's disease (Peterson and Horak, 2016). It is well-known that oscillatory activity in the cortico-basal ganglia loop is altered in Parkinson's disease (Schnitzler and Gross, 2005; Hammond *et al.*, 2007). In particular, research has focused on abnormally increased synchronization in the beta band (13-35 Hz) that is a hallmark of Parkinson's disease (Oswal *et al.*, 2013). It has been proposed that beta oscillations promote the maintenance of the motor state at the expense of voluntary movement (Engel and Fries, 2010).

Walking abilities are especially affected in patients suffering from freezing of gait, a common phenomenon in advanced Parkinson's disease. It is defined by the episodic inability of forward progression despite the intention to walk (Nutt *et al.*, 2011). Patients with freezing of gait also show an abnormal spatiotemporal gait pattern in between freezing episodes including smaller steps at higher cadence (Nieuwboer *et al.*, 2001; Hausdorff *et al.*, 2003; Chee *et al.*, 2009). Strikingly, most Parkinson's disease patients, with and without freezing of gait, were found to maintain the ability to bicycle (Snijders and Bloem, 2010; Snijders *et al.*, 2011; Snijders *et al.*, 2012b). Moreover, bicycling has been shown to be effective in ameliorating motor and cognitive deficits in Parkinsonian patients (Ridgel *et al.*, 2009, 2011, 2012). This is puzzling with respect to our understanding of the human motor system and strongly suggests that, despite the similarity in their rhythm and involved muscle groups (Raasch and Zajac, 1999), bicycling and walking may involve cerebral structures including the basal ganglia in different ways.

There is evidence linking freezing of gait to excessive synchronization in the basal ganglia caused by reduced levels of dopamine in combination with temporarily increased motor, cognitive, or limbic load (Lewis and Barker, 2009; Lewis and Shine, 2016). In line with this, abnormally synchronized basal ganglia oscillations, especially in the beta band, have been found in patients with freezing of gait both during rest (Toledo *et al.*, 2014) and during walking (Singh *et al.*, 2013). While non-freezers displayed the characteristic power reduction across the entire beta band in the subthalamic nucleus (STN) during walking, oscillatory activity specifically in the low beta band (12-22 Hz) was increased in freezers (Singh *et al.*, 2013). These findings are consistent with the assumed antikinetic nature of oscillatory activity in the beta band. Yet, the question remains how exactly this difference in movement-related beta power changes is related to freezing of gait. Is this difference specific to gait or is it rather a general signature of altered basal ganglia activity that distinguishes freezers from non-freezers?

As no study to date has examined basal ganglia activity during bicycling, or how it may differ from walking, potential mechanisms concerning how bicycling abilities are preserved in Parkinson's

disease have remained speculative. Thus, it is still not entirely clear if the basal ganglia are critically involved in the control of bicycling at all, and if so, how the underlying oscillatory activity may be modulated. Recently, our group demonstrated that healthy adults exhibit stronger sensorimotor high beta power (23-35 Hz) suppression in bicycling than in walking (Storzer *et al.*, 2016). We hypothesized that bicycling attenuates pathological oscillations also within the basal ganglia of Parkinson's disease patients as compared to walking. To test this hypothesis, we recruited Parkinson's patients with and without freezing of gait who had undergone implantation of electrodes for deep brain stimulation (DBS) therapy. This approach provides the rare opportunity to record local field potentials (LFPs) directly from the STNs while initiating, sustaining, and terminating pedaling on a stationary bicycle or walking, respectively. Comparing beta oscillatory activity in the STN between both conditions, we found stronger beta power suppression in bicycling relative to walking. Conversely, patients with freezing of gait exhibited a narrow band low beta power increase specifically during walking, reflecting the susceptibility to freezing.

2 Methods

2.1 Patients and surgery

13 Parkinson's disease patients clinically selected for bilateral DBS therapy participated in this study. One patient terminated the recording after the bicycling task due to fatigue and hence, did not perform the walking task. Data of two patients had to be excluded because of severe movement artifact contamination of all STN channels. Thus, data are presented from the remaining 10 patients (56.5 ± 6.2 years, one female, **Table 1**). The study was approved by the local ethics committee of the Medical Faculty of the Heinrich Heine University Düsseldorf (study number: 4294) in accordance with the Declaration of Helsinki. All patients gave their prior written informed consent. Motor state and history of freezing of gait were assessed preoperatively with part III of the Unified Parkinson's Disease Rating Scale (UPDRS), and the Freezing of Gait Questionnaire (FOG-Q; Giladi *et al.*, 2000). Cognitive and emotional states were assessed with the Mattis Dementia Rating Scale (MDRS), the Frontal Assessment Battery (FAB), and the Becks Depression Inventory (BDI). Four patients were classified as freezers because of a score >1 regarding the FOG-Q question #3: "Do you feel that your feet get glued to the floor while walking, turning or when trying to initiate walking?" Additionally, we observed freezing episodes in two out of these four patients during the experiment. These episodes were excluded from the analysis.

Surgery was performed at the Department of Stereotaxy and Functional Neurosurgery of the University Hospital Düsseldorf as described earlier (Özkurt *et al.*, 2011). Seven patients (#3-9) were bilaterally implanted with a rechargeable Vercise™ DBS system by Boston Scientific (model 2201, Boston Scientific, Marlborough, USA). Patient #11 was implanted with a Boston Scientific Vercise PC stimulator and had segmented directional leads with eight contacts arranged in two ring contacts and two 3-segment contacts (1-3-3-1, model 2202-DL). The remaining two patients (#13-14) were implanted with the Infinity™ DBS system by St. Jude Medical (model 6170, St. Jude Medical Inc., St. Paul, MN, USA), which is also equipped with segmented directional leads (1-3-3-1).

2.2 Experimental design and procedure

Recordings took place 1-5 days after electrode implantation using externalized leads. Patients were off oral dopaminergic medication for ≥ 12h and off subcutaneous apomorphin administration for ≥ 2h. Data of patient #4 was obtained in the medication ON state. As movement-related beta power changes were shown to be similar in the medication OFF and ON states (Alegre *et al.*, 2005), the data of this patient were included in the analyses.

Patients engaged in bicycling on a stationary bicycle simulator, overground walking, and the respective baseline conditions, i.e., sitting and standing (**Fig. 1**). Patients started with a 120 s

baseline rest period. This was followed by repeatedly alternating 10 s rest and 10 s movement. This way, 30 episodes of acoustically cued movement initiation and termination were captured. At last, patients engaged in 120 s continuous movement. Patients started either in the bicycling or in the walking condition with the order of conditions being pseudorandomized and counterbalanced across patients. For a more detailed description of the paradigm and the bicycle simulator see Storzer *et al.* (2016). Patients were instructed to bicycle and to walk at their own comfortable cadence as physical fitness was heterogeneous in the patients under study. Cadence was assessed in bicycling and walking as revolutions per minute (rpm) and strides per minute (spm), respectively. Patients were asked to keep cadence constant across conditions.

2.3 Data acquisition and analysis

LFPs from the STNs were recorded with a portable EEG amplifier at a sampling rate of 2048 Hz (Porti amplifier, TMSi, Enschede, The Netherlands) using the open source software packages OpenBCI and Svarog (Durka *et al.*, 2012). In addition, EEG from a few cortical Ag/AgCl electrodes, positioned over sensorimotor and parietal areas, and EMG of bilateral leg muscles (*tibialis anterior*, *biceps femoris*, and *rectus femoris*) were assessed simultaneously. The water-based ground electrode was integrated in a wristband and LFP and EEG data were recorded with an average reference. LFP and EEG data were re-referenced offline with a bipolar montage consisting of adjacent contacts in the vertical plane. This yielded seven and nine (in case of directional leads) bipolar channels per STN, respectively. Data were obtained from 20 STNs. Two STNs were excluded due to a malfunctional extension or connector. Two further STNs had to be excluded because of severe movement artifact contamination affecting all channels. Consequently, 16 STNs were included in the analysis.

Data were analyzed with the Matlab-based FieldTrip toolbox (Oostenveld *et al.*, 2011) using Matlab R2015b (The Mathworks, Natick, MA, USA). Analysis was focused on LFPs. First, data were band-pass filtered offline (1-1000 Hz). Next, data were visually inspected for movement artifacts and respective segments excluded from further analysis.

Spectral analysis

Power spectra were calculated for the baseline rest and continuous movement conditions. Data were divided into 1 s segments with an overlap of 50 % and the fast Fourier transform was calculated for each segment using a single Hanning taper. Afterwards, spectra were averaged over segments. Furthermore, changes of spectral power during movement were expressed as relative power change in dB to the baseline rest condition i.e., sitting or standing. Event-related modulations of LFP power were analyzed by performing time-frequency decomposition locked to movement initiation and

termination with a sliding Hanning window of 1 s length and a step size of 0.05 s. Likewise, power changes were expressed as the relative power change in dB to the baseline rest condition. The goniometer signal was used to define movement initiation and termination in line with Storzer and colleagues (2016). Based on visual inspection, 2.0 % of the selected initiations and 4.1 % of the selected terminations had to be adapted.

Channel selection

We selected one bipolar channel per STN for the analysis. Based on Litvak and colleagues (2012), the channel with the strongest change of spectral power in the 13-35 Hz range (pooled over conditions) was selected. We made sure that no spurious channels were detected by verifying that the corresponding channels also showed a baseline beta peak. The selected channel was the same for all movement conditions in order to prevent channel selection affecting the comparison between bicycling and walking. Due to non-functional contacts in patient #13, the contact pair 2C-4 had to be selected. Two bipolar channels had to be adapted due to movement artifact contamination in two patients (#4 and #5). In these cases, the next possible channel with strong beta suppression was selected instead.

Table 1 lists the selected channels for each STN together with the Montreal Neurological Institute (MNI) coordinates and the probability *p* to be within the STN (Forstmann *et al.*, 2012). Coordinates were determined by registering the postoperative CT to the preoperative MRI using FSL (Jenkinson *et al.*, 2012). The most ventral and the most dorsal contact of each electrode were visually identified (Hemm *et al.*, 2009). The remaining contact coordinates were obtained by linear interpolation and a mask image created containing the electrode contacts. MNI coordinates were estimated by transforming the preoperative MRI and mask image into MNI space using ANTs (Avants *et al.*, 2008). Electrode localization was not possible for one patient due to movement artifacts contaminating the CT.

2.4 Statistics

In line with the channel selection, the effect of movement and posture on beta power was evaluated consistently at the frequency (±1 Hz) showing the strongest individual beta power suppression during continuous movement relative to the baseline rest period (pooled over conditions). A two-way repeated measures ANOVA was conducted with the within-subject factors movement (‘rest’ vs. ‘move’) and posture (‘on bike’ vs. ‘on foot’) as implemented in IBM SPSS statistics, version 23 (IBM Deutschland GmbH, Ehningen, Germany). We ensured that data were normally distributed based on the Kolmogorov-Smirnov test and corrected for multiple testing using the adaptive Bonferroni correction (Holm, 1979). Further comparisons were made using two-sided

paired-samples t-tests or Wilcoxon signed-rank tests depending on the data distribution. The non-parametric Mann-Whitney-U-test was used to compare cadence during bicycling and walking between freezers and non-freezers because of the small sample sizes. For all tests, the significance level was set to 0.05. Differences in time-frequency and baseline spectra were evaluated by non-parametric cluster-based permutation testing implemented in the FieldTrip toolbox (Maris and Oostenveld, 2007).

3 Results

The average cadence across patients was 39.7 rpm (*SD* = 5.6) for bicycling and 47.0 spm (*SD* = 8.1) for walking and differed between conditions ($t_{(9)}$ = -3.1, p = 0.01). This difference was mainly driven by the high walking cadence of the four patients with freezing of gait. Walking cadence was significantly different between freezers and non-freezers (Non-freezers: *M* = 42.9, *SD* = 3.5; Freezers: *M* = 53.3, *SD* = 9.5; *U* = 0, p = 0.02). In contrast, bicycling cadence was similar between groups (Non-freezers: *M* = 38.5, *SD* = 6.9; Freezers: *M* = 41.6, *SD* = 2.8; *U* = 5, p = 0.17).

3.1 Effect of movement and posture on beta power

Bicycling and walking led to a power decrease relative to the baseline rest conditions, i.e., sitting and standing, that was maximal at 22.5 Hz (*SD* = 6.1 Hz). Using a repeated measures analysis of variance (ANOVA) to evaluate the effect of movement ('rest' vs. 'move') and posture ('on bike' vs. 'on foot') on power at the individual beta frequency resulted in a significant main effect of movement on power ($F_{(1,15)}$ = 44.9, p < 0.01). Beta power was significantly decreased during movement irrespective of posture. Furthermore, the ANOVA revealed a significant interaction between movement and posture ($F_{(1,15)}$ = 8.7, p < 0.01). **Fig. 2A** illustrates that this was due to a stronger power decrease from sitting to pedaling as compared to the power decrease from standing to walking. Individual power changes and group data are depicted for bicycling in **Fig. 2B** and for walking in **Fig. 2C**. Beta power suppression for bicycling and walking was consistently observed across the patients under study.

3.2 Beta power changes locked to movement initiation and termination

Relative power changes locked to movement initiation were evident in the beta band both in bicycling and in walking (**Fig. 3**, upper panel). For bicycling relative to the baseline rest condition, power decreased in the low (13-20 Hz) and high (21-35 Hz) beta band starting around movement initiation. These power changes could also be observed for the walking condition, however, to a smaller extent. Further, these were accompanied by a power increase in a narrow frequency range (17-20 Hz). Contrasting relative power between bicycling and walking revealed a significant cluster in the beta band (10-32 Hz, p < 0.01).

Time-frequency representations of LFP power locked to movement termination showed a high beta power increase relative to the baseline rest condition for both bicycling and walking (**Fig. 3**, lower panel). The magnitude of this beta rebound did not significantly differ between the movement conditions (p = 0.42).

Further testing for a baseline difference between sitting and standing revealed a higher beta power during sitting relative to standing (cluster 19-28 Hz, p < 0.01).

Movement-related beta power changes in patients with freezing of gait

Looking at individual time-frequency representations of movement-related power changes revealed that the narrow band (17-20 Hz) beta power increase locked to movement initiation in walking was mainly driven by the four patients (7 STNs) with freezing of gait (**Fig. 4,** upper panel). While bicycling was accompanied by a power reduction in the whole beta band or solely a slight power increase around movement initiation, walking was accompanied by a distinctive and sustained narrow band beta power increase at ~18 Hz. Contrasting relative power between bicycling and walking in freezers revealed a significant cluster in the beta band (17-30 Hz, $p = 0.02$).

This abnormal ~18 Hz oscillation was not observable in non-freezers, apart from a soupçon of power increase during walking (**Fig. 4,** lower panel). However, this power increase was not as distinct and narrow-band as in freezers. Instead, beta power suppression was observed in both conditions. The suppression was stronger in bicycling than in walking resulting in a significant cluster in the beta band (10-30 Hz, $p < 0.01$).

In order to further evaluate this abnormal oscillatory signature in patients with freezing of gait, LFP data of each STN were bandpass filtered around the frequency (±2 Hz) showing the strongest movement-related power increase. Next, envelopes of the filtered data were computed by taking the Hilbert transform. Envelopes were filtered by a moving average filter of length 2500 samples and correlated with the envelope of the remaining beta band. The ~18 Hz oscillation was found to be anti-correlated with the remaining beta band specifically during walking but not during cycling, and it was particularly enhanced at initiation and termination of walking (**Fig. 5,** upper panel). This resulted in a significant difference in the correlation between the envelopes of the ~18 Hz oscillation and the remaining beta band between bicycling and walking in freezers ($t_{(6)} = 4.1$, $p < 0.01$).

4 Discussion

We demonstrate for the first time that beta band activity in the Parkinsonian STN is modulated substantially differently by bicycling compared to walking. We found greater beta power suppression in bicycling relative to walking, while the beta rebound upon movement termination was equally strong. Importantly, patients with freezing of gait exhibited a characteristic ~18 Hz oscillation only during walking, a potential signature indicating the risk of freezing that has never been described before.

4.1 Stronger beta power suppression in bicycling

We found bicycling and walking to be associated with a decrease of oscillatory activity in the beta band relative to the respective baseline rest condition. This effect is not unexpected as activity in the beta band is known to be suppressed during movement execution in the STN of Parkinsonian patients (Cassidy *et al.*, 2002; Litvak *et al.*, 2012). Current knowledge about neural activity related to bicycling was primarily based on non-invasive imaging techniques, i.e., functional MRI (Mehta *et al.*, 2009) and PET (Christensen *et al.*, 2000) studies, which reported no basal ganglia involvement. Therefore, the current study provides important first evidence of a direct involvement of the basal ganglia in bicycling.

Interestingly, bicycling resulted in a stronger suppression of beta oscillations relative to walking, in line with previous observations in the sensorimotor cortex of healthy participants (Storzer *et al.*, 2016). The effect was evident both at movement initiation and during continuous movement. Beta rebound after movement termination was, however, of similar magnitude. Thus, the difference in beta power modulation between bicycling and walking was specific to beta power suppression during movement. These findings indicate that movement-related suppression of beta oscillations in the basal ganglia is stronger in bicycling relative to walking. It is not unlikely that this is a crucial part of the physiological mechanism explaining why bicycling ability is preserved in Parkinson's disease and more importantly, why bicycling has a therapeutic effect.

Some functional differences in the cerebral networks underlying bicycling and walking would be expected as they differ in some aspects such as sensorimotor input, postural control, and coordination. It remains to be clarified which of these differences may be associated with the stronger beta power suppression. Postural control during standing is impaired in Parkinson's disease patients, with impairment and decline being more pronounced in freezers (Schlenstedt *et al.*, 2016; Vervoort *et al.*, 2016). However, comparing beta power between the different movement conditions, we did find a difference between sitting and standing, but found no main effect of posture due to the stronger power decrease from sitting to pedaling exceeding the level of walking.

Consequently, stronger beta power suppression during bicycling cannot be due to the reduced need for postural control.

A key difference could be the more continuous nature of bicycling, which is associated with persistent tactile feedback to both feet and lacks the stationary phases that are part of walking. Thus, the likelihood of the subsequent movement is higher in bicycling which has been related to beta power suppression (Jenkinson and Brown, 2011). Furthermore, leg movements in bicycling have fewer degrees of freedom due to the circular pedal trajectory, regardless of the exact foot placement. In consequence, the limb movements required for bicycling are less complex than for walking and could impose a lower computational load on the motor system. In line with this interpretation, a previous study of our group found stronger gait phase-dependent power modulations in walking compared to bicycling in the sensorimotor cortex of healthy participants (Storzer *et al.*, 2016), which could be indicative of a reduced demand for cortical monitoring of ongoing movement.

4.2 Low beta power increase in patients with freezing of gait during walking

Patients with freezing of gait displayed an abnormal ~18 Hz oscillation in the STN that was intensified during walking. It was not present in Parkinson's disease patients without freezing of gait. Notably, this is perfectly in line with a previous report about increased low beta STN power (12-22 Hz) in freezers during walking (Singh *et al.*, 2013). Furthermore, akinetic-rigid patients exhibited a pattern of beta modulation during walking that appears related, with walking resulting in a decrease in power over approximately 5-16 Hz and 20-30 Hz, leaving a peak of about 18 Hz (Quinn *et al.*, 2015). Crucially, the abnormal ~18 Hz oscillation was anti-correlated with the remaining beta band specifically during walking but not during cycling in the study at hand.

From where might this oscillation originate and what are its implications? Due to its predominance in the OFF medication state and its corresponding reduction by both medication and DBS (Priori *et al.*, 2004; López-Azcárate *et al.*, 2010; Litvak *et al.*, 2011; Quinn *et al.*, 2015; Oswal *et al.*, 2016), the lower beta range is assumed to be particularly associated with antikinetic symptoms. Thus, the ~18 Hz oscillation might reflect a movement-inhibiting signal throughout the motor network. As the low beta power increase was seen irrespective of actual freezing episodes, it likely reflects a predisposition to freeze during walking. It might be boosted by interference in the cortico-basal ganglia loops due to additional response conflict or motor, cognitive or limbic load, thereby triggering a freezing episode (Lewis and Barker, 2009; Lewis and Shine, 2016).

Interestingly, phase synchronization in the beta band over the left prefrontal area was found to be associated with increased susceptibility to upper limb freezing (Scholten *et al.*, 2016). The STN receives direct cortical projections from frontal areas via the hyperdirect pathway (Nambu *et al.*, 1996), which is assumed to mediate a top-down stopping signal (Aron and Poldrack, 2006; Frank,

2006; Cavanagh and Frank, 2013). Thus, an excessive cortically driven inhibitory signal might manifest as an abnormal ~18 Hz oscillation in the STN of freezing patients. Alternatively, the ~18 Hz oscillation might emerge from the interaction between STN and GPe (Holgado *et al.*, 2010) or originate in the striatum due to increased levels of cholinergic drive as a consequence of dopamine depletion (McCarthy *et al.*, 2011). Results of a recent study analyzing functional interactions between the STN, motor cortex, and PPN during walking in hemiparkinsonian rats suggest the STN as the potential source of increased beta oscillations at around 18 Hz (Li *et al.*, 2016).

Why are freezers able to bicycle?

Our present results add substantially to the clarification of this question by providing electrophysiological correlates of the risk of freezing. We found that bicycling suppresses broadband beta power and narrowband beta oscillations that appear specifically in freezers. Hence, the effect of bicycling is reminiscent of the therapeutic effects of DBS and medication (Kühn *et al.*, 2006, 2008, 2009; Quinn *et al.*, 2015; Oswal *et al.*, 2016). We explain the comparably low level of beta power during bicycling by a comparably low computational load on the motor system. This low load may decrease the risk of interference between the parallel but separated cortico-basal ganglia loops, and thus the risk of freezing (Lewis and Barker, 2009; Lewis and Shine, 2016). If the movement sequence is made more complex, e.g., by uncoupling the pedals of the bike, the load is increased and patients with freezing of gait are identifiable by irregular pedaling patterns with the return of intermittent cessations (Abe *et al.*, 2003). Likewise, freezing was found to be partially alleviated by using a "walk-bicycle", i.e., a bicycle without pedals and a low seat (Stummer *et al.*, 2015). Locomotion with the walk-bicycle still requires alternating stepping movements of the legs but reduces the need for postural control and lateral weight shifts that were shown to be abnormally coupled in patients with freezing of gait (Jacobs *et al.*, 2009). In summary, we suggest that bicycling ability remains unaffected in most patients because it has a lower computational load on motor networks (Snijders *et al.*, 2011; Snijders *et al.*, 2012b).

4.3 Methodological considerations

A methodological challenge in EEG studies on different types of movements lies in movement-related artifacts. We carefully inspected our data and excluded contaminated data. Nevertheless, movement artifacts were still present in our data to some extent and in particular in the walking condition. These artifacts were found to be restricted to lower frequencies only up to 10 Hz, and so could not influence the presented results in the higher beta frequency band.

Furthermore, bicycling and walking differed in movement cadence and might have differed in other movement kinematics, such as movement amplitude and velocity, as well. Previous research has shown that STN beta power suppression is not directly related to movement kinematics (Anzak *et al.*, 2012; Joundi *et al.*, 2012). Hence, it is unlikely that these factors have caused the observed difference in beta power suppression between bicycling and walking. Furthermore, higher cadence has been shown to be associated with stronger cortical activity (Christensen *et al.*, 2000). Nonetheless, we found cycling to be accompanied by stronger beta suppression while cadence was higher during walking.

Due to the small sample sizes of the present study we did not test for differences between freezers and non-freezers. Nevertheless, our data are in line with previous research (Singh *et al.*, 2013) and provide a promising starting point for future studies. Such work should include a representative number of patients with and without freezing of gait allowing adequate statistical testing. Finally, patients were identified as freezers according to the FOG-Q. Future studies should include an objective examination of freezing of gait and include only patients with definite acute freezing of gait (Snijders *et al.*, 2012*a*).

5 Conclusion

Our study provides important first evidence for differences between bicycling and walking in the oscillatory activity of the STN in Parkinson's disease patients. Our results indicate that bicycling is accompanied by a stronger movement-related suppression of pathological beta oscillations compared to walking, with an influence on STN beta rhythms reminiscent of the effects of DBS. Furthermore, freezers exhibited a selective and prolonged distinct and narrowband beta oscillation locked to the initiation of walking at ~18 Hz. This oscillation was seen in walking irrespective of actual freezing episodes, and was furthermore weaker and rather brief in duration upon initiation of cycling, signifying that it likely reflects susceptibility to freezing. Bicycling not only facilitates suppression of this oscillation along with overall beta power, but we speculate that due to its continuous nature, it is also computationally less demanding than walking and thus less prone to 'overloading' the networks involved in locomotion.

6 Acknowledgments

We would like to express our sincere thanks to the patients who participated in this study. Furthermore, we thank Nitin Sharma (University of Konstanz) for assistance with constructing and programming the bicycle simulator and the neurologists and neurosurgeons of the University Hospital Düsseldorf for their support.

7 Funding

This work was generously supported by a grant from the Jacques and Gloria Gossweiler Foundation. Further support was received from the Zukunftskolleg of the University of Konstanz [SSD], Heinrich Heine University Strategic Research Funds [MB], and the research commission of the medical faculty of the Heinrich Heine University [9772562 to MB]. JH is supported by the German Academic Exchange Service (P.R.I.M.E. 2015). LS was supported by travel grants from the Boehringer Ingelheim Foundation and the DAAD. The authors declare no competing financial interests.

8 References

Abe K, Asai Y, Matsuo Y, Nomura T, Sato S, Inoue S, et al. Classifying lower limb dynamics in Parkinson's disease. Brain Res. Bull. 2003; 61: 219–226.

Alegre M, Alonso-Frech F, Rodríguez-Oroz MC, Guridi J, Zamarbide I, Valencia M, et al. Movement-related changes in oscillatory activity in the human subthalamic nucleus: ipsilateral vs. contralateral movements. Eur. J. Neurosci. 2005; 22: 2315–2324.

Anzak A, Tan H, Pogosyan A, Foltynie T, Limousin P, Zrinzo L, et al. Subthalamic nucleus activity optimizes maximal effort motor responses in Parkinson's disease.
Brain 2012; 135: 2766–2778.

Aron AR, Poldrack RA. Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. J. Neurosci. 2006; 26: 2424–2433.

Avants BB, Epstein CL, Grossman M, Gee JC. Symmetric diffeomorphic image registration with cross-correlation: Evaluating automated labeling of elderly and neurodegenerative brain.
Med. Image Anal. 2008; 12: 26–41.

Cassidy M, Mazzone P, Oliviero A, Insola A, Tonali P, Di Lazzaro V, et al. Movement-related changes in synchronization in the human basal ganglia. Brain 2002; 125: 1235–1246.

Cavanagh JF, Frank MJ. Stop! Stay tuned for more information.
Exp. Neurol. 2013; 247: 289–291.

Chee R, Murphy A, Danoudis M, Georgiou-Karistianis N, Iansek R. Gait freezing in Parkinson's disease and the stride length sequence effect interaction. Brain 2009; 132: 2151–2160.

Christensen LOD, Johannsen P, Sinkjaer T, Petersen N, Pyndt HS, Nielsen JB. Cerebral activation during bicycle movements in man. Exp. Brain Res. 2000; 135: 66–72.

Durka PJ, Kuś R, Żygierewicz J, Michalska M, Milanowski P, Łabęcki M, et al. User-centered design of brain-computer interfaces: OpenBCI.pl and BCI Appliance.
Bull. Polish Acad. Sci. Tech. Sci. 2012; 60: 427–431.

Engel AK, Fries P. Beta-band oscillations—signalling the status quo?
Curr. Opin. Neurobiol. 2010; 20: 156–165.

Forstmann BU, Keuken MC, Jahfari S, Bazin P-L, Neumann J, Schäfer A, et al. Cortico-subthalamic white matter tract strength predicts interindividual efficacy in stopping a motor response. Neuroimage 2012; 60: 370–375.

Frank MJ. Hold your horses: a dynamic computational role for the subthalamic nucleus in decision making. Neural Netw. 2006; 19: 1120–1136.

Giladi N, Shabtai H, Simon E, Biran S, Tal J, Korczyn A. Construction of freezing of gait questionnaire for patients with Parkinsonism. Parkinsonism Relat. Disord. 2000; 6: 165–170.

Hammond C, Bergman H, Brown P. Pathological synchronization in Parkinson's disease: networks, models and treatments. Trends Neurosci. 2007; 30: 357–364.

Hausdorff JM, Schaafsma JD, Balash Y, Bartels AL, Gurevich T, Giladi N. Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait.
Exp. Brain Res. 2003; 149: 187–194.

Hemm S, Coste J, Gabrillargues J, Ouchchane L, Sarry L, Caire F, et al. Contact position analysis of deep brain stimulation electrodes on post-operative CT images.
Acta Neurochir. (Wien). 2009; 151: 823–829.

Holgado AJN, Terry JR, Bogacz R. Conditions for the Generation of Beta Oscillations in the Subthalamic Nucleus-Globus Pallidus Network. J. Neurosci. 2010; 30: 12340–12352.

Holm S. A simple sequentially rejective multiple test procedure. Scand. J. Stat. 1979; 6: 65–70.

Jacobs J V, Nutt JG, Carlson-Kuhta P, Stephens M, Horak FB. Knee trembling during freezing of gait represents multiple anticipatory postural adjustments. Exp. Neurol. 2009; 215: 334–341.

Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. Fsl.
Neuroimage 2012; 62: 782–790.

Jenkinson N, Brown P. New insights into the relationship between dopamine, beta oscillations and motor function. Trends Neurosci. 2011; 34: 611–618.

Joundi RA, Brittain J-S, Green AL, Aziz TZ, Brown P, Jenkinson N. Oscillatory activity in the subthalamic nucleus during arm reaching in Parkinson's disease.
Exp. Neurol. 2012; 236: 319–326.

Kühn AA, Kempf F, Brucke C, Gaynor Doyle L, Martinez-Torres I, Pogosyan A, et al. High-Frequency Stimulation of the Subthalamic Nucleus Suppresses Oscillatory Activity in Patients with Parkinson's Disease in Parallel with Improvement in Motor Performance.
J. Neurosci. 2008; 28: 6165–6173.

Kühn AA, Kupsch A, Schneider G-H, Brown P. Reduction in subthalamic 8-35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease.
Eur. J. Neurosci. 2006; 23: 1956–1960.

Kühn AA, Tsui A, Aziz T, Ray N, Brücke C, Kupsch A, et al. Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity.
Exp. Neurol. 2009; 215: 380–387.

Lewis SJG, Barker RA. A pathophysiological model of freezing of gait in Parkinson's disease.
Parkinsonism Relat. Disord. 2009; 15: 333–338.

Lewis SJG, Shine JM. The Next Step: A Common Neural Mechanism for Freezing of Gait.
Neuroscientist 2016; 22: 72–82.

Li M, Zhou M, Wen P, Wang Q, Yang Y, Xiao H, et al. The network of causal interactions for beta oscillations in the pedunculopontine nucleus, primary motor cortex, and subthalamic nucleus of walking parkinsonian rats. Exp. Neurol. 2016; 282: 27–36.

Litvak V, Eusebio A, Jha A, Oostenveld R, Barnes G, Foltynie T, et al. Movement-Related Changes in Local and Long-Range Synchronization in Parkinson's Disease Revealed by Simultaneous Magnetoencephalography and Intracranial Recordings.
J. Neurosci. 2012; 32: 10541–10553.

Litvak V, Jha A, Eusebio A, Oostenveld R, Foltynie T, Limousin P, et al. Resting oscillatory cortico-subthalamic connectivity in patients with Parkinson's disease. Brain 2011; 134: 359–374.

López-Azcárate J, Tainta M, Rodríguez-Oroz MC, Valencia M, González R, Guridi J, et al. Coupling between beta and high-frequency activity in the human subthalamic nucleus may be a pathophysiological mechanism in Parkinson's disease. J. Neurosci. 2010; 30: 6667–6677.

Maris E, Oostenveld R. Nonparametric statistical testing of EEG- and MEG-data.
J. Neurosci. Methods 2007; 164: 177–190.

McCarthy MM, Moore-Kochlacs C, Gu X, Boyden ES, Han X, Kopell N. Striatal origin of the pathologic beta oscillations in Parkinson's disease.
Proc. Natl. Acad. Sci. U. S. A. 2011; 108: 11620–11625.

Mehta JP, Verber MD, Wieser JA, Schmit BD, Schindler-Ivens SM. A novel technique for examining human brain activity associated with pedaling using fMRI.
J. Neurosci. Methods 2009; 179: 230–239.

Nambu A, Takada M, Inase M, Tokuno H. Dual somatotopical representations in the primate subthalamic nucleus: evidence for ordered but reversed body-map transformations from the primary motor cortex and the supplementary motor area. J. Neurosci. 1996; 16: 2671–2683.

Nieuwboer A, Dom R, De Weerdt W, Desloovere K, Fieuws S, Broens-Kaucsik E. Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. Mov. Disord. 2001; 16: 1066–1075.

Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A. Freezing of gait: moving forward on a mysterious clinical phenomenon. Lancet Neurol. 2011; 10: 7347–7344.

Oostenveld R, Fries P, Maris E, Schoffelen J-M. FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. Comput. Intell. Neurosci. 2011; 2011: 156869.

Oswal A, Beudel M, Zrinzo L, Limousin P, Hariz M, Foltynie T, et al. Deep brain stimulation modulates synchrony within spatially and spectrally distinct resting state networks in Parkinson's disease. Brain 2016; 139: 1482–1496.

Oswal A, Brown P, Litvak V. Synchronized neural oscillations and the pathophysiology of Parkinson's disease. Curr. Opin. Neurol. 2013; 26: 662–670.

Özkurt TE, Butz M, Homburger M, Elben S, Vesper J, Wojtecki L, et al. High frequency oscillations in the subthalamic nucleus: a neurophysiological marker of the motor state in Parkinson's disease. Exp. Neurol. 2011; 229: 324–331.

Peterson DS, Horak FB. Neural Control of Walking in People with Parkinsonism. Physiology 2016; 31: 95–107.

Priori A, Foffani G, Pesenti A, Tamma F, Bianchi AM, Pellegrini M, et al. Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. Exp. Neurol. 2004; 189: 369–379.

Quinn EJ, Blumenfeld Z, Velisar A, Koop MM, Shreve LA, Trager MH, et al. Beta oscillations in freely moving Parkinson's subjects are attenuated during deep brain stimulation. Mov. Disord. 2015; 30: 1750–1758.

Raasch CC, Zajac FE. Locomotor strategy for pedaling: muscle groups and biomechanical functions. J. Neurophysiol. 1999; 82: 515–525.

Ridgel AL, Kim C, Fickes EJ, Muller MD, Alberts JL. Changes in Executive Function After Acute Bouts of Passive Cycling in Parkinson ' s Disease. J. Aging Phys. Act. 2011; 19: 87–98.

Ridgel AL, Peacock CA, Fickes EJ, Kim C-H. Active-Assisted Cycling Improves Tremor and Bradykinesia in Parkinson's Disease. Arch. Phys. Med. Rehabil. 2012; 93: 2049–2054.

Ridgel AL, Vitek JL, Alberts JL. Forced, not voluntary, exercise improves motor function in Parkinson's disease patients. Neurorehabil. Neural Repair 2009; 23: 600–608.

Schlenstedt C, Muthuraman M, Witt K, Weisser B, Fasano A, Deuschl G. Postural control and freezing of gait in Parkinson's disease. Parkinsonism Relat. Disord. 2016; 24: 107–112.

Schnitzler A, Gross J. Normal and pathological oscillatory communication in the brain. Nat. Rev. Neurosci. 2005; 6: 285–296.

Scholten M, Govindan RB, Braun C, Bloem BR, Plewnia C, Krüger R, et al. Cortical correlates of susceptibility to upper limb freezing in Parkinson's disease. Clin. Neurophysiol. 2016; 127: 2386–2393.

Singh A, Plate A, Kammermeier S, Mehrkens JH, Ilmberger J, Bötzel K. Freezing of gait-related oscillatory activity in the human subthalamic nucleus. Basal Ganglia 2013; 3: 25–32.

Snijders AH, Bloem BR. Cycling for Freezing of Gait. N. Engl. J. Med. 2010; 362: e46.

Snijders AH, Haaxma CA, Hagen YJ, Munneke M, Bloem BR. Freezer or non-freezer: clinical assessment of freezing of gait. Parkinsonism Relat. Disord. 2012a; 18: 149–154.

Snijders AH, van Kesteren M, Bloem BR. Cycling is less affected than walking in freezers of gait. J. Neurol. Neurosurg. Psychiatry 2012b; 83: 575–576.

Snijders AH, Toni I, Ružička E, Bloem BR. Bicycling breaks the ice for freezers of gait. Mov. Disord. 2011; 26: 367–371.

Storzer L, Butz M, Hirschmann J, Abbasi O, Gratkowski M, Saupe D, et al. Bicycling and Walking are Associated with Different Cortical Oscillatory Dynamics. Front. Hum. Neurosci. 2016; 10: 61.

Stummer C, Dibilio V, Overeem S, Weerdesteyn V, Bloem BR, Nonnekes J. The walk-bicycle: A new assistive device for Parkinson's patients with freezing of gait? Parkinsonism Relat. Disord. 2015; 21: 755–757.

Toledo JB, López-Azcárate J, Garcia-Garcia D, Guridi J, Valencia M, Artieda J, et al. High beta activity in the subthalamic nucleus and freezing of gait in Parkinson's disease. Neurobiol. Dis. 2014; 64: 60–65.

Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov. Disord. 2010; 25: 2649–2653.

Vervoort G, Bengevoord A, Strouwen C, Bekkers EMJ, Heremans E, Vandenberghe W, et al. Progression of postural control and gait deficits in Parkinson's disease and freezing of gait: A longitudinal study. Parkinsonism Relat. Disord. 2016; 28: 73–79.

9 Figures

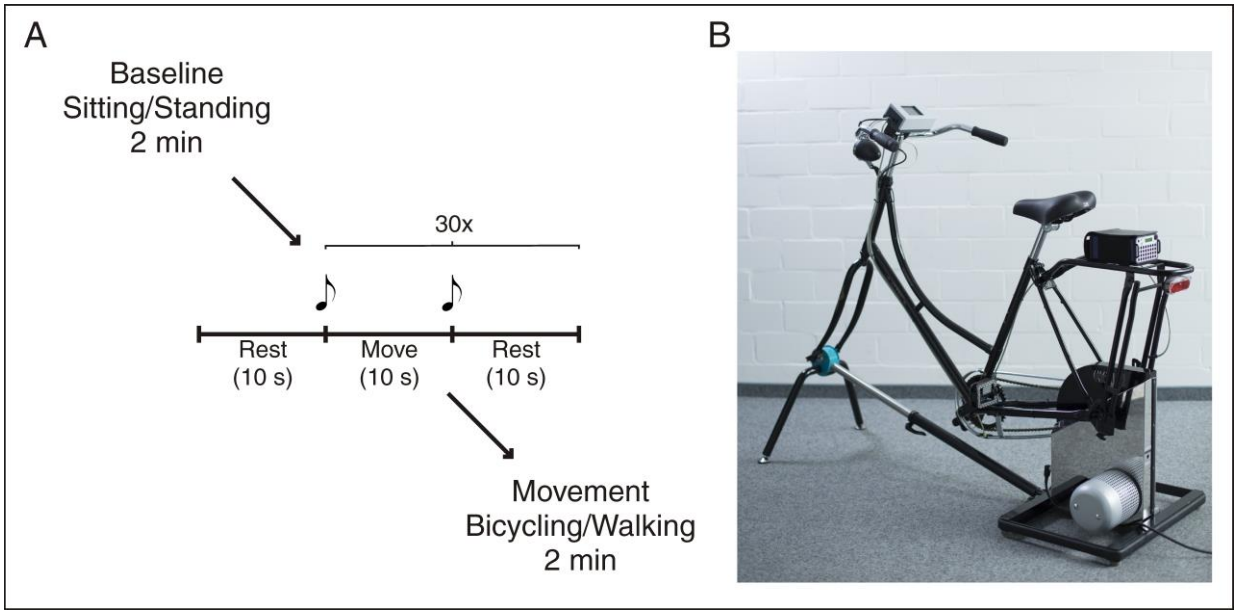

Figure 1: Experimental setup. (A) Schematic illustration of the experimental paradigm adapted from Storzer *et al.* (2016). Patients started with a 2 min baseline rest period, i.e., sitting on the bicycle or standing, respectively. This was followed by repeatedly alternating 10 s movement and 10 s rest with further 10 s of rest at the beginning. This way, 30 instances of acoustically cued movement initiation and termination were captured. Subsequently, patients walked or pedaled continuously for 2 min. **(B)** The bicycle simulator consisted of a Dutch-style bicycle frame mounted on an ergometer. Pedal position was recorded simultaneously with all electrophysiological signals.

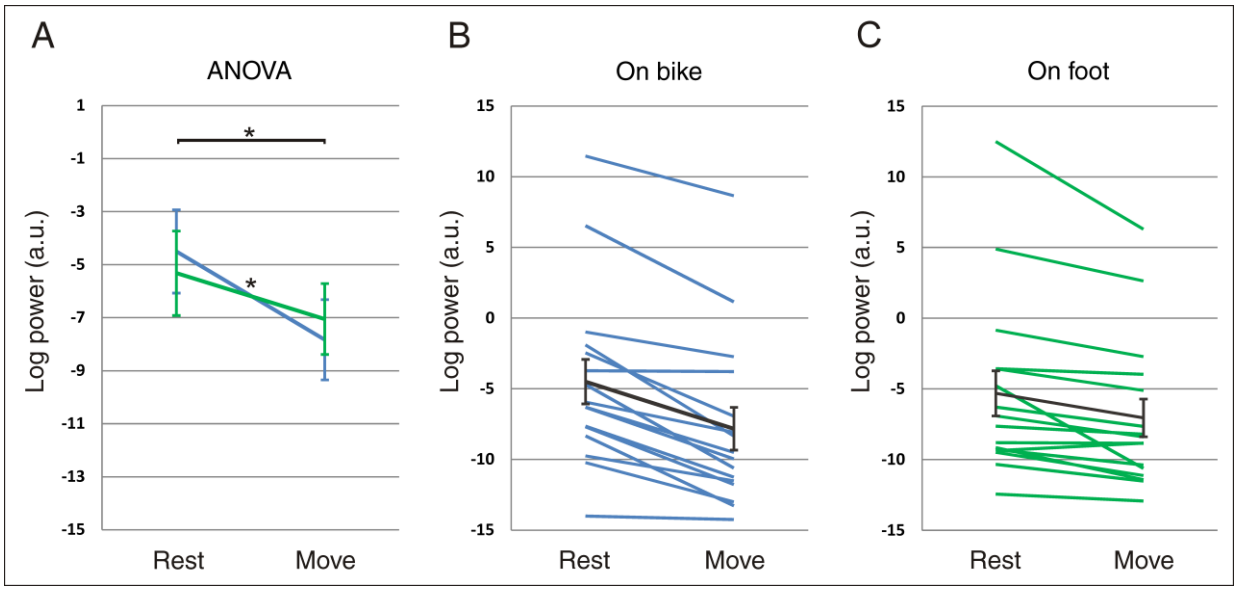

Figure 2: Effect of movement and posture on beta power. (A) Grand average plot showing the modulation of STN beta power by movement ('rest' vs. 'move') and posture ('on bike' vs. 'on foot'). Results for 'on bike' are depicted in blue, results for 'on foot' are depicted in green. A repeated-measures ANOVA showed a significant beta power decrease from rest to move irrespective of posture. The beta power decrease from sitting to pedaling was stronger compared to the beta decrease from standing to walking. Significant effects are indicated by asterisks. Error bars are mean ± standard error. Changes of beta power from sitting to pedaling **(B)** and standing to walking **(C)** are depicted for the individual 16 STNs. Mean and standard error are indicated by black lines.

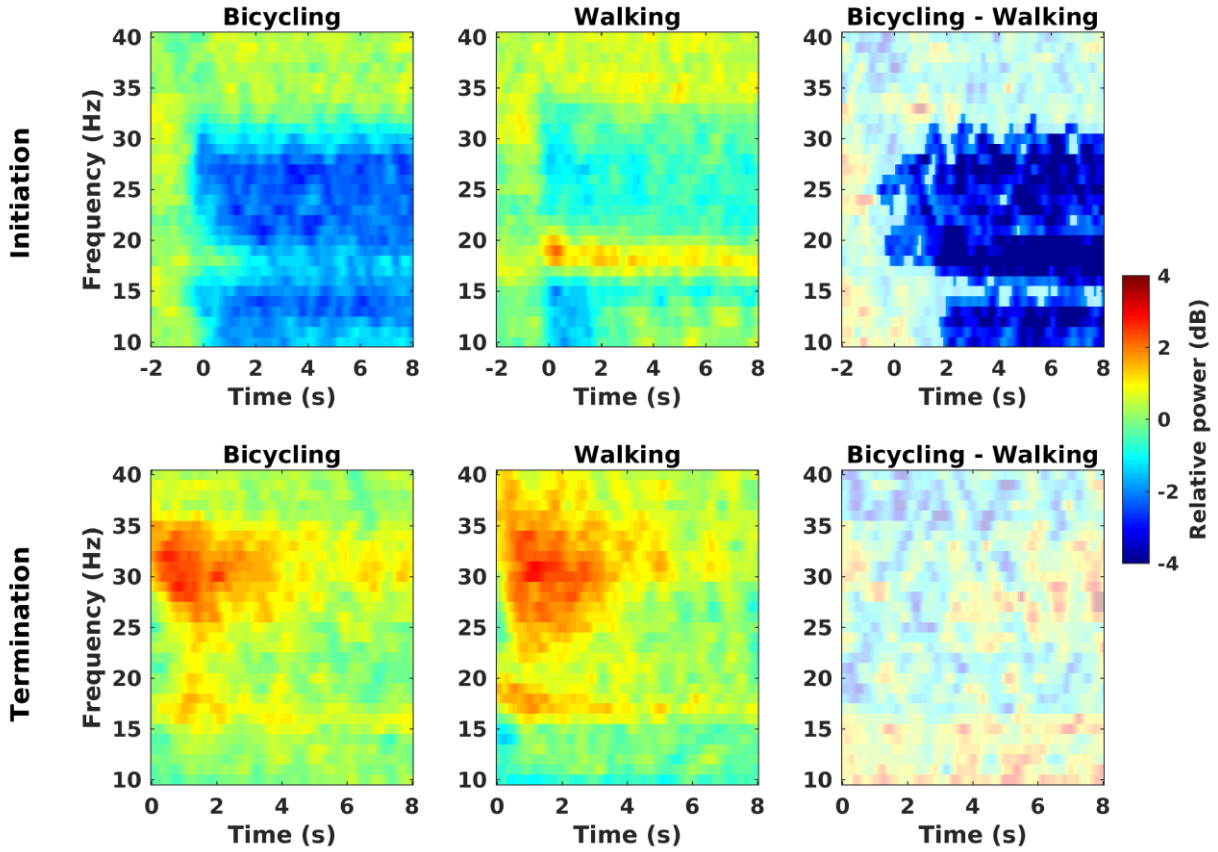

Figure 3: Time-frequency representation of movement initiation and termination. Grand average time-frequency plots of normalized STN power, locked to a change of the movement state for bicycling, walking, and the difference between both (non-significant differences are masked). **Upper row:** Movement initiation is at $t = 0$. Beta power decreases (blue) in both conditions, but with a stronger beta power decrease in bicycling. Beta power increases (red) in a narrow frequency range in the low beta band only in walking. **Lower row:** Movement termination is at $t = 0$. Beta power rebound upon movement termination is observable in both conditions and is of similar magnitude.

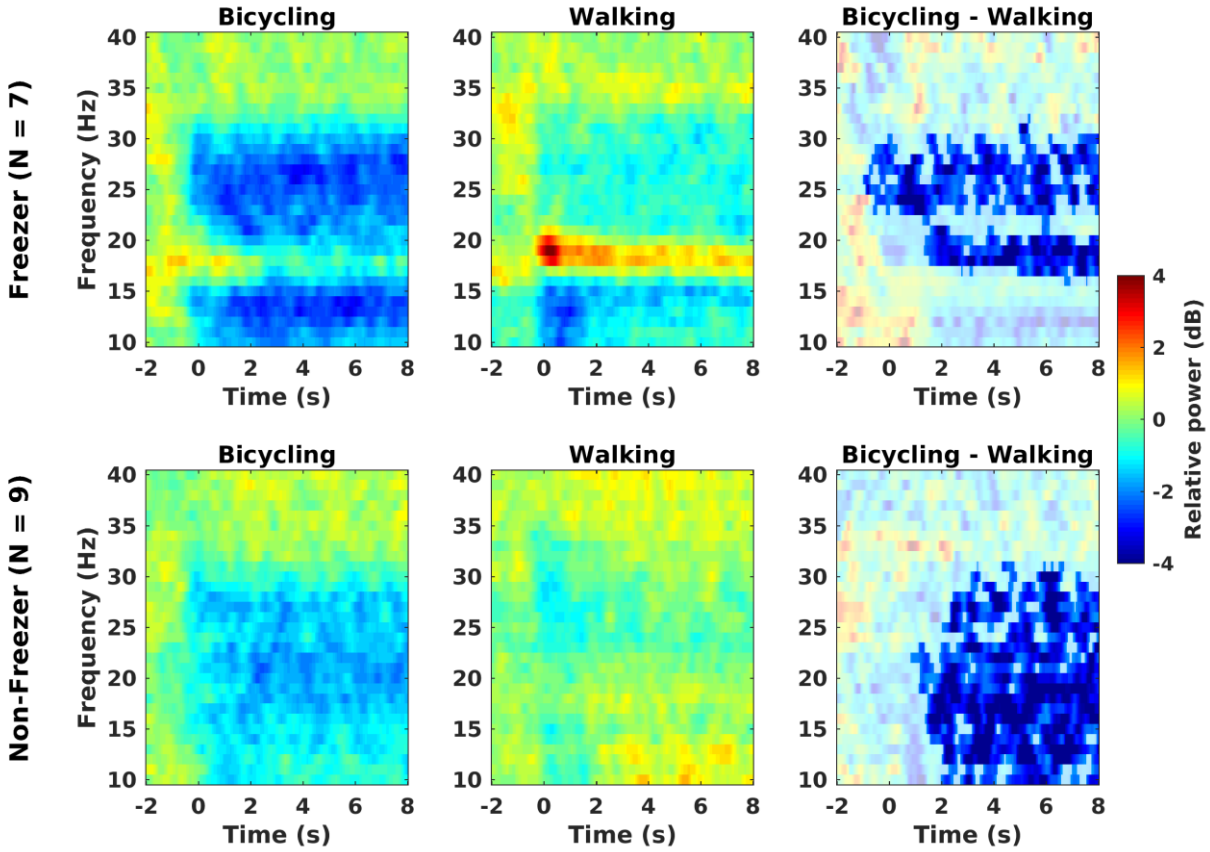

Figure 4: Beta power changes in freezers and non-freezers. Grand average time-frequency plots showing power changes locked to movement initiation ($t = 0$) in freezers (7 STNs) and non-freezers (9 STNs) for bicycling and walking, and the difference between both (non-significant differences are masked). **Upper row:** Beta power decreases (blue) in both conditions in non-freezers, but with a stronger beta power decrease in bicycling. **Lower row:** In freezers, bicycling is accompanied by a broad-band beta power decrease and briefly by a slight power increase (red) in a narrow band around 18 Hz, following movement initiation. Opposed to this, walking is accompanied by a distinctive and sustained power increase in this band.

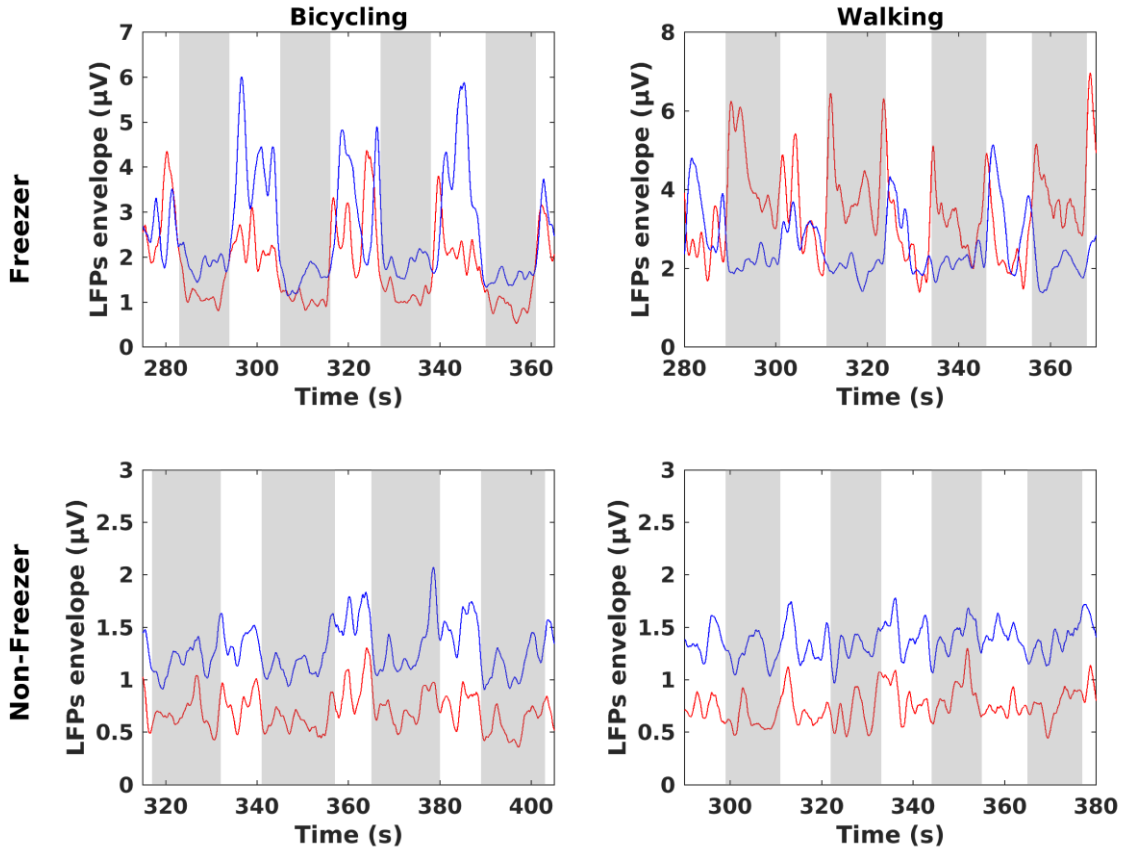

Figure 5: Modulation of the ~18 Hz oscillation and the remaining beta band. Two examples of one patient with FOG **(upper row)** and one patient without FOG **(lower row)** illustrating the envelopes of the filtered LFPs around 18 Hz (red) and the remaining beta band (blue). The grey boxes represent periods of movement, i.e., bicycling and walking. Narrow- and broadband beta envelopes are anti-correlated during walking but not during cycling in the patient with FOG. Modulation of the ~18 Hz oscillation is increased at start and end of the movement phases. Conversely, the two beta bands show the same rhythmic pattern in the patient without FOG.

Table 1: Patient Demographics

Patient	Age/ Sex	Disease duration (years)	Subtype	UPDRS III OFF scores	Levodopa equivalent dose (mg/day)	Most affected Side	Selected contacts	MNI coordinates of selected contact, X, Y, Z	*P*	Individual beta frequency (Hz)	MDRS	FAB	BDI	FOG-Q
3	61M	7	Hypokinetic-rigid	15	980	R	L 5 vs 6 R 4 vs 5	-12.5,-14.5,3 15.5,-14,-2	0% 0%	15 16	138	17	7	3
4	61M	11	Hypokinetic-rigid	40	1940	L	L 2 vs 3	-12,-17,-8.5	8%	27	134	16	5	5
5	46M	8	Hypokinetic-rigid	20	930	R	L 2 vs 3 R 2 vs 3	Not available		34 16	144	18	4	4
6*	62F	14	Hypokinetic-rigid	15	1080	R	L 3 vs 4 R 3 vs 4	-9.5,-15.5,-7 12,-14.5,-7.5	38% 25%	27 20	142	17	4	7
7	52M	8	Equivalent	24	600	R	L 3 vs 4	-10.5,-15.5,-6	29%	24	140	18	3	4
8	56M	4	Tremor-dominant	Not available	0	R	L 2 vs 3 R 1 vs 2	-10,-14.5,-7.5 12,-15,-7,5	29% 25%	27 25	143	17	5	2
9	50M	2	Equivalent	30	960	L	R 2 vs 3	12,-15,-7	25%	29	142	17	3	5
11*	61M	9	Equivalent	36	1270	R	L 2 vs 5 R 1 vs 2	-11,-14.5,-8 12.5,-12.5,-9	29% 21%	14 15	143	18	6	13
12*	64M	25	Hypokinetic-rigid	46	1410	L	L 2A vs 3A	-11,-16,-7	17%	19	141	17	0	16
13*	52M	5	Hypokinetic-rigid	33	850 + Safinamide 50**	L	L 2B vs 3B R 2C vs 4	-11.5,-16.5,-7 13.5,-16,-6	12% 8%	27 25	142	15	14	11

P, STN probability map entries for selected contacts. The atlas maximum is 0.46.

* Patient with freezing of gait according to score >1 at item 3 of the FOG-Q.

** Safinamide 50 mg is not included in the Levodopa equivalent dose as it is currently not included in the calculation based on Tomlinson *et al.* (2010).

Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Are Beta Phase-Coupled High-Frequency Oscillations and Beta Phase-Locked Spiking Two Sides of the Same Coin?

Lena Storzer, Steffen Bürgers, and Jan Hirschmann

Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich-Heine-University Düsseldorf, D-40225 Düsseldorf, Germany

Review of Yang et al.

Changes of oscillatory patterns in the basal ganglia and in subcortico-cortical motor loops are a hallmark of Parkinson's disease (PD; Hammond et al., 2007). However, the neuronal mechanisms underlying these spectral dynamics and how they contribute to motor symptoms remain to be clarified. A popular hypothesis is that beta oscillations (13–30 Hz) in the subthalamic nucleus (STN) are associated with impaired motor performance, whereas gamma (60–90 Hz) and high-frequency oscillations (HFOs; 200–500 Hz) are associated with normal movement (Oswal et al., 2013). Notably, there are cross-frequency interactions in the parkinsonian STN. The amplitude of HFOs is modulated by the phase of beta oscillations, and this phase–amplitude coupling is increased when patients are in an unmedicated (OFF) state (Lopéz-Azcárate et al., 2010; Özkurt et al., 2011). Furthermore, it was observed that beta–HFO phase–amplitude coupling correlates positively with motor symptom severity, whereas baseline HFO power and modulation of HFO power during movement are strongest in patients with relatively good motor performance (Lopéz-Azcárate et al., 2010; Wang et al., 2014). Thus, it seems plausible that beta oscillations exert an adverse effect on HFOs, which would otherwise facilitate movement.

Despite its potential importance for motor control, the mechanisms generating beta–HFO phase–amplitude coupling remain elusive. A recent study by Yang et al. (2014) in *The Journal of Neuroscience* is an important first step toward understanding phase–amplitude coupling in PD. The authors investigated whether beta–HFO phase–amplitude coupling might emerge as a consequence of beta spike-phase locking, i.e., a tendency for spikes to occur at a specific phase within the beta cycle. Thus, this interesting paper links neuronal oscillations to spiking in the STN, which has been shown to encode diverse aspects of motor state, such as the type of movement (active or passive) or the muscles involved (extensor or flexor; Magariños-Ascone et al., 2000).

The data were recorded in PD patients undergoing surgery for deep brain stimulation (DBS). A combination of micro- and macro-electrodes was gradually inserted along the trajectory of the DBS electrode so that recordings of both local field potentials and spiking activity in and around the STN could be obtained. The authors then analyzed the spectral and spatiotemporal characteristics of phase–amplitude coupling and spike-phase locking.

Yang and colleagues (2014) found both the amplitude of HFOs and spiking to be significantly coupled to the phase of beta oscillations, and both couplings showed a similar spatial distribution. Phase–amplitude coupling and spike-phase locking were most pronounced near the dorsal border of the STN. This was also the site most frequently selected for DBS based on the therapeutic window, i.e., the span between the minimum voltage producing clinical improvement (window entry voltage) and the minimum voltage producing side effects. In addition, the authors found a negative correlation between phase–amplitude coupling strength for each electrode contact and its therapeutic window entry voltage. This finding suggests that phase–amplitude coupling is strongest at the most efficient stimulation targets. These findings are remarkable because they point to beta–HFO phase–amplitude coupling as a spatial biomarker in DBS target localization, emphasizing its clinical relevance. Unfortunately, the direct importance of beta–HFO phase–amplitude coupling for PD symptoms remains unclear, because the authors did not assess correlations between phase–amplitude coupling and clinical ratings of symptom severity.

Intriguingly, the authors could not find any spatiotemporal association between phase–amplitude coupling and spike-phase locking, even though both spikes and HFOs were locked to beta band oscillations and had a similar topography. Phase–amplitude coupling and spike-phase locking were uncorrelated across recording sites with respect to the percentage of occurrence and coupling strength. Moreover, HFOs and spikes significantly differed in their preferred beta phase. HFOs tended to occur near beta peaks, whereas spikes were more frequent

Received Nov. 11, 2014; revised Dec. 11, 2014; accepted Dec. 15, 2014.

L.S. is supported by the Jacques and Gloria Gossweiler Foundation. J.H. is supported by the Heinrich Heine University Strategic Research Fund. We thank Markus Butz for his helpful comments on this manuscript.

Correspondence should be addressed to Jan Hirschmann, Institute of Clinical Neuroscience and Medical Psychology, Heinrich-Heine-University Düsseldorf, Universitätsstrasse 1, D-40225 Düsseldorf, Germany. E-mail: Jan.Hirschmann@med.uni-duesseldorf.de.

DOI:10.1523/JNEUROSCI.4647-14.2015

 0270-6474/15/351819-02$15.00/0

near the troughs. Importantly, Yang and colleagues (2014) further tested for a temporal relationship between phase–amplitude coupling and spike-phase locking. HFO power did not increase around spike times, and HFO activity did not systematically precede or follow spikes. Of course, one has to keep in mind that absence of proof is not proof of absence. Nevertheless, the experimental design and the sound data analysis are compelling and indicate that spike-phase locking and phase–amplitude coupling might be unrelated phenomena in the parkinsonian STN.

The finding that spike-phase locking and beta–HFO phase–amplitude coupling are uncorrelated is particularly interesting with regard to the unknown origins of HFOs. In fact, most researchers intuitively suspect hypersynchronized spiking to be the cause of HFOs. What other process is both fast and strong enough to produce a high-frequency, extracellular potential that can be detected by the comparably large contacts of a DBS electrode? Theoretically, hypersynchronized spiking could be locked to a specific phase within the beta cycle and thereby produce beta–HFO phase–amplitude coupling. The results by Yang and colleagues (2014), however, suggest that phase–amplitude coupling and spiking may not be two sides of the same coin. Notably, this idea is supported by recent data from other labs. Wang et al. (2014) investigated subthalamic HFOs recorded during DBS surgery and found no qualitative change in HFO characteristics after removing spikes from the raw data traces. Thus, local spiking does not seem to contribute significantly to HFOs and their coupling to beta oscillations.

Importantly, these observations do not exclude the possibility that spiking is important for HFO generation on a larger spatial scale. Because microelectrodes sample only a limited anatomical area, it is conceivable that they miss multiunit activity related to HFOs and beta–HFO phase–amplitude coupling. Ultimately, this issue can only be resolved by recording more cells, which is currently not feasible in DBS surgery. High-density probes used in animal recordings might be able to provide an answer (Nicolelis et al., 2003), but currently it is not even known whether subthalamic HFOs and beta–HFO phase–amplitude coupling exist in either rodent or primate models of PD.

Despite these limitations, the lack of association between spikes and subthalamic HFOs remains striking, particularly given recent literature on HFOs in epilepsy. In the dentate gyrus of epileptic mice, there seems to be a strong relationship between synchronized discharge of principal cells and pathological fast ripples (Bragin et al., 2002). It is important to note, however, that hippocampal fast ripples hardly resemble subthalamic HFOs in terms of stability, frequency content, or coupling to slower oscillations. Hence, it seems reasonable to assume that subthalamic and epilepsy-related HFOs reflect different neuronal processes.

Another important issue related to the origins of HFOs is the distribution of HFO peak frequencies. Given the results of previous studies, this distribution might be bimodal. Two recent studies demonstrated the existence of two distinct high-frequency rhythms: a slow rhythm of ~260 Hz and a fast rhythm of ~340 Hz (López-Azcárate et al., 2010; Özkurt et al., 2011). A similar distinction has been suggested for the beta band (Priori et al., 2004). The slow HFO rhythm dominates under dopamine depletion while the fast rhythm is enhanced under medication. Since the relative strengths of these two rhythms reflect the medication state very reliably, they could turn out to be powerful biomarkers (Özkurt et al., 2011). Currently, it remains unclear whether slow and fast HFOs are produced by different neuronal populations or by two different processes co-occurring within the same population of neurons.

In conclusion, the study by Yang et al. (2014) provides valuable new information for comprehending the complex dynamics of oscillatory activity in the parkinsonian STN. To date, research concerning the pathophysiology of PD has concentrated on beta and gamma oscillations, whereas the role of HFOs has only recently been put into focus. The findings of Yang and colleagues (2014) give further support to the importance of HFOs and provide a starting point for further investigation of their origin and functional relevance.

References

Bragin A, Mody I, Wilson CL, Engel J Jr (2002) Local generation of fast ripples in epileptic brain. J Neurosci 22:2012–2021. Medline

Hammond C, Bergman H, Brown P (2007) Pathological synchronization in Parkinson's disease: networks, models and treatments. Trends Neurosci 30:357–364. CrossRef Medline

López-Azcárate J, Tainta M, Rodríguez-Oroz MC, Valencia M, González R, Guridi J, Iriarte J, Obeso JA, Artieda J, Alegre M (2010) Coupling between beta and high-frequency activity in the human subthalamic nucleus may be a pathophysiological mechanism in Parkinson's disease. J Neurosci 30:6667–6677. CrossRef Medline

Magariños-Ascone CM, Figueiras-Mendez R, Riva-Meana C, Córdoba-Fernández A (2000) Subthalamic neuron activity related to tremor and movement in Parkinson's disease. Eur J Neurosci 12:2597–2607. CrossRef Medline

Nicolelis MA, Dimitrov D, Carmena JM, Crist R, Lehew G, Kralik JD, Wise SP (2003) Chronic, multisite, multielectrode recordings in macaque monkeys. P Natl Aacd Sci U S A 100:11041–11046. CrossRef

Oswal A, Brown P, Litvak V (2013) Synchronized neural oscillations and the pathophysiology of Parkinson's disease. Curr Opin Neurol 26:662–670. CrossRef Medline

Özkurt TE, Butz M, Homburger M, Elben S, Vesper J, Wojtecki L, Schnitzler A (2011) High frequency oscillations in the subthalamic nucleus: a neurophysiological marker of the motor state in Parkinson's disease. Exp Neurol 229:324–331. CrossRef Medline

Priori A, Foffani G, Pesenti A, Tamma F, Bianchi AM, Pellegrini M, Locatelli M, Moxon KA, Villani RM (2004) Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. Exp Neurol 189:369–379. CrossRef Medline

Wang J, Hirschmann J, Elben S, Hartmann CJ, Vesper J, Wojtecki L, Schnitzler A (2014) High-frequency oscillations in Parkinson's disease: spatial distribution and clinical relevance. Mov Disord 29:1265–1272. CrossRef Medline

Yang AI, Vanegas N, Lungu C, Zaghloul KA (2014) Beta-coupled high-frequency activity and beta-locked neuronal spiking in the subthalamic nucleus of Parkinson's disease. J Neurosci 34:12816–12827. CrossRef Medline

Cognition and Behavior

No Effect of Subthalamic Deep Brain Stimulation on Intertemporal Decision-Making in Parkinson Patients[1,2,3]

Maayke Seinstra,[1] Lars Wojtecki,[2] Lena Storzer,[2] Alfons Schnitzler,[2] and Tobias Kalenscher[1]

DOI:http://dx.doi.org/10.1523/ENEURO.0019-16.2016

[1]Comparative Psychology, Institute of Experimental Psychology, Heinrich-Heine University Düsseldorf, 40225 Düsseldorf, Germany, [2]Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich-Heine University Düsseldorf, 40225 Düsseldorf, Germany

Abstract

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a widely used treatment for the motor symptoms of Parkinson's disease (PD). DBS or pharmacological treatment is believed to modulate the tendency to, or reverse, impulse control disorders. Several brain areas involved in impulsivity and reward valuation, such as the prefrontal cortex and striatum, are linked to the STN, and activity in these areas might be affected by STN-DBS. To investigate the effect of STN-DBS on one type of impulsive decision-making—delay discounting (i.e., the devaluation of reward with increasing delay until its receipt)—we tested 40 human PD patients receiving STN-DBS treatment and medication for at least 3 months. Patients were pseudo-randomly assigned to one of four groups to test the effects of DBS on/off states as well as medication on/off states on delay discounting. The delay-discounting task consisted of a series of choices among a smaller. sooner or a larger, later monetary reward. Despite considerable effects of DBS on motor performance, patients receiving STN-DBS did not choose more or less impulsively compared with those in the off-DBS group, as well as when controlling for risk attitude. Although null results have to be interpreted with caution, our findings are of significance to other researchers studying the effects of PD treatment on impulsive decision-making, and they are of clinical relevance for determining the therapeutic benefits of using STN-DBS.

Key words: deep brain stimulation; intertemporal choice; Parkinson's disease

Significance Statement

To improve the quality of life of patients with Parkinson's disease, it is important to uncover the cognitive side effects of deep brain stimulation of subthalamic nucleus. In this study, we show no effect of deep brain stimulation on altered impulsive decision-making, measured with a financial delay-discounting paradigm. Our study adds an important piece of information on the cognitive side effects of deep brain stimulation, although further studies are needed to verify our results.

Introduction

Parkinson's disease (PD) is characterized by a cell loss in substantia nigra and ventral tegmental area, leading to a reduced level of the neurotransmitter dopamine and abnormal functionality of the basal ganglia. The progressive loss of dopamine results in impaired motor functioning, such as bradykinesia, muscle rigor, and/or resting tremor, as well as in characteristic nonmotor symptoms, including depression and memory deficits. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a widely used treatment for the motor symptoms of PD. STN-DBS is usually applied when conventional medication starts to become increasingly ineffective (Deuschl et al., 2006). Although STN-DBS has major benefits in reducing motor symptoms (Deuschl et al., 2006; Wichmann and DeLong, 2006), the side effects of STN-DBS on cognition are often less clear (Demetriades et al., 2011).

Several studies indicate that DBS affects neural activity in surrounding areas, thereby altering the activity of a whole network of brain structures (Chang et al., 2007; Li et al., 2007; McCracken and Grace, 2007; Montgomery and Gale, 2007; Li et al., 2012). Since the STN is connected to a number of basal ganglia nuclei as well as cortical areas, STN-DBS can have widespread effects that are not just limited to motor behavior. Not only motor areas are found to be projecting to the STN, but also brain areas involved in the valuation of choice options, such as the medial/orbital cortex in rats (Maurice et al., 1998) and monkeys (Haynes and Haber, 2013) via the so-called hyperdirect pathway (Nambu et al., 2002), which links the cortex with the basal ganglia via the STN. In addition, the STN can be subdivided into several functional zones that can, according to their structural connectivity, be identified as motor, associative, and limbic regions (Lambert et al., 2012), which are part of corticobasal ganglia-thalamo-cortical loops involved in emotion, movement, and cognition (Parent and Hazrati, 1995a,b).

Patients have often undergone a long period of dopaminergic medical treatment before DBS is considered as the therapy of choice. Dopaminergic treatment usually consists of the intake of levodopa (L-dopa), a dopamine precursor, and/or dopamine agonists. An increased tendency for impulse control disorders (ICDs), which include pathological gambling, compulsive shopping, hypersexuality, and hyperphagia (Weintraub, 2008), can develop in PD patients. These ICDs are associated with dopaminergic treatment, in particular with the use of dopamine agonists (Voon and Fox, 2007; Voon et al., 2011a,b; Raja and Bentivoglio, 2012) as well as L-dopa treatment (Zurowski and O'Brien, 2015).

How STN-DBS affects impulsive behavior is unclear, with reports of increases in both the severity of even the new development of ICDs (Hälbig et al., 2009; Lim et al., 2009; Broen et al., 2011; Moum et al., 2012), as well as the attenuation or disappearance of ICD symptoms after the start of STN-DBS treatment (Witjas et al., 2005; Ardouin et al., 2006; Bandini et al., 2007; Lim et al., 2009; Broen et al., 2011). As the dopaminergic medication intake can usually be decreased after the onset of STN-DBS treatment, the reduction in ICD severity might be due to a decrease in the medication dosage, but other factors, such as electrode placement, stimulation parameters, or patient history may underlie changes in ICD severity too (Zurowski and O'Brien, 2015). Several brain areas connected with the STN are involved in impulsive behavior, including the orbitofrontal cortex and the nucleus accumbens (Cardinal et al., 2001; Kheramin et al., 2002; Kalenscher and Pennartz, 2008). Stimulation of the STN can therefore affect impulsive choice in the following two ways: either by directly altering STN functioning, and/or via indirect moderation of activity in connected areas known to be involved in impulsive decision-making.

Since (case study) reports concerning the effects of therapeutic STN-DBS on ICDs are ambiguous, it is important to uncover exactly how STN-DBS affects impulsive behavior, and in particular impulsive choice. The study presented here focuses on delay discounting (i.e., the devaluation of a reward when its receipt is delayed to a future point in time), which can be seen as a measure of impulsive economic decision-making, and is often used to assess impulsive decision-making (Bickel et al., 2012). Although delay discounting captures only one of the many facets of ICDs, reduced delay sensitivity lies at the heart of most concepts of impulsive choice. To dissociate the putative effects of STN-DBS from the effects of dopaminergic medication on delay discounting, we used a 2×2 design for DBS (on/off) and medication state (L-dopa on/off).

Materials and Methods

Participants

Fifty-four patients with bilaterally implanted stimulation electrodes in the STN were recruited for a screening session at the University Clinic Düsseldorf (Center for Movement Disorders and Neuromodulation, Department of Neurology, Institute of Clinical Neuroscience and Medical Psychology, Heinrich-Heine University Düsseldorf), with the aim of identifying patients with no current severe depression [Beck Depression Inventory (BDI), <20], no indication of dementia [Mattis Dementia Rating Scale (MDRS), >130], and inconspicuous performance in a range of other cognitive and mnemonic tests (see below) for inclusion in the experiment. Forty patients (16 female)

Received January 28, 2016; accepted April 7, 2016; First published May 02, 2016.

[1]The authors declare no competing financial interests.

[2]Author Contributions: M.S., L.W., A.S. and T.K. designed research; M.S. and L.S. performed research; M.S. analyzed data; M.S. and T.K. wrote the paper.

[3]The project was funded by internal budgets of T.K.

Acknowledgments: We thank Sonja Ascheid, Nina Kessler, Kerstin Frie, and Marika Biernat, as well as the doctors at the Parkinson Ward at the University Clinic Düsseldorf for their aid and help during data collection.

Correspondence should be addressed to Maayke Seinstra, Institute of Experimental Psychology, Heinrich-Heine University Düsseldorf, Universitaetsstrasse 1, 40225 Düsseldorf, Germany. E-mail: maayke.seinstra@hhu.de.

DOI:http://dx.doi.org/10.1523/ENEURO.0019-16.2016

between 42 and 78 years of age (mean, 62.7 years of age; SD, 7.4 years of age) met the inclusion criteria. Further inclusion criteria were bilateral DBS of the STN for a period of at least 3 months and no preimplant history of major depression.

DBS treatment consisted of bilateral 130 Hz stimulation, except for two patients who received 174 Hz stimulation in the right hemisphere and 130 Hz stimulation in the left hemisphere, two patients who received bilateral 150 Hz stimulation, and one patient who received unilateral (right) 130 Hz stimulation. Stimulation intensity was either fixed on voltage ($N = 26$) or amperage ($N = 14$), with voltages ranging between 1.2 and 4.0 V and amperage ranging between 1.1 and 3.4 mA. Pulse width was set at 60 μs, with the exception of three patients receiving 62 μs pulses and one patient receiving 65 μs pulses. One patient received 60 μs in the left hemisphere and 90 μs in the right hemisphere. The average time since DBS implantation was 30.0 months (SD, 23.7 months), with a minimum of 3 months and a maximum of 85 months. All but one patient received dopamine replacement therapy, with an L-dopa equivalent dose (LED) ranging from 120 to 1975 (mean, 675; SD, 390). All participants were recruited within a time period of 16 months, during their periodic inpatient visits that lasted at least 2 nights. The year of diagnosis ranged from 1989 until 2012. All participants were instructed in detail about the experimental procedure as well as the payment procedure before they provided written informed consent. The study was approved by the local ethics committee of the Medical Faculty of the Heinrich-Heine University Düsseldorf.

Materials

During screening, patients performed a range of tests designed to measure mood as well as cognitive and mnemonic traits [MDRS, BDI-II, Quick Delay Questionnaire (QDQ), Baratt Impulsiveness Scale (BIS), South Oaks Gambling Screen (SOGS), and Ardouin Behavior Scale (ABS); see below], along with a delay-discounting task [intertemporal choice task (ICT)], risk attitude measurements (Holt-Laury task), and motor skills assessment [Unified Parkinson's Disease Rating Scale (UPDRS)] during testing sessions. We used the following tests.

Mattis Dementia Rating Scale

The MDRS was used to test for cognitive deficits (Mattis, 1988). This test is commonly used in clinical settings for older patients and can detect dementia disorders such as Alzheimer's disease. It is subdivided into the following five categories: attention, verbal and motor initiation and preservation, construction, conceptualization, and memory (Lucas et al., 1998). Patients with scores of $<$130 points (of a total of 144 points) were excluded from further testing (Schmidt et al., 1994).

Beck Depression Inventory II

The German version of the BDI-II (Beck et al., 1996) was used to assess depressive symptoms reported for the previous 2 weeks. It consists of 21 items, and each item is ranked from 0 to 3. The exclusion criterion was a count of $\geq$20 points, which is indicative of severe depression.

Quick Delay Questionnaire

The QDQ was administered to assess subjective delay aversion and delay discounting (Clare et al., 2010). The subjects have to rate five items on delay aversion and five items on delay discounting on a 5-point Likert scale. This questionnaire was added to obtain a baseline self-reported measure of delay discounting/delay aversion.

Barratt Impulsiveness Scale

The BIS is often used as a measure of impulsivity, and its short German version (BIS-15; Spinella, 2007) has been used in the current study. Fifteen items assess nonplanning, motor, or attention impulsivity (Spinella, 2007). Each item is rated on a 4-point Likert scale. This questionnaire was added to obtain a baseline self-reported measure of impulsiveness.

South Oaks Gambling Screen

The SOGS (Lesieur and Blume, 1987) consists of 20 items and is commonly used to screen for pathological gambling. In this test, a score of $\geq$5 is considered as probable pathological gambling. This questionnaire was added to identify and control for problem gambling or gambling tendencies, respectively.

Ardouin Behavior Scale

This scale was designed to detect changes in mood and behavior in PD patients (Ardouin et al., 2009). This semi-structured interview entails 18 items and is rated in 5 points, from 0 (absent) to 4 (severe). The ABS was used to identify potential addictive tendencies (regarding food or medication intake) that might hint at an ICD.

Unified Parkinson's Disease Rating Scale

Part III of the Movement Disorder Society-sponsored revision of the UPDRS (MDS-UPDRS-III) was used to assess the severity of motor impairment, as well as the efficacy of the different treatment states. Patients had to perform specific movements and were rated from 0 to 4 on each of 18 items covering tremor, rigidity, posture, agility, and general movement (Goetz et al., 2008). The MDS-UPDRS-III was used to assess differences in motor symptoms between the respective on/off states during sessions.

Intertemporal Choice Task

The ICT used in this study is a common and well validated task with which to elicit time preferences and measure delay discounting (Kirby and Maraković, 1996; Hardisty et al., 2013). The task consisted of a series of binary choices between a smaller, sooner, and a larger, later monetary reward. Choice items were arranged in six blocks with 11 trials each, with an instruction screen after each block to provide the opportunity to take a short break. Within each block, the amount of the smaller, sooner option varied over trials, while the larger, later option remained constant across trials within a given block. The delays used within each block were specified in the instruction screen before each block. In three blocks, the larger, later reward was fixed at €20, with the smaller, sooner option ranging from €0 to €20 in steps of €2, presented in randomized order. In the other three blocks, the larger, later reward was fixed at €30, with the

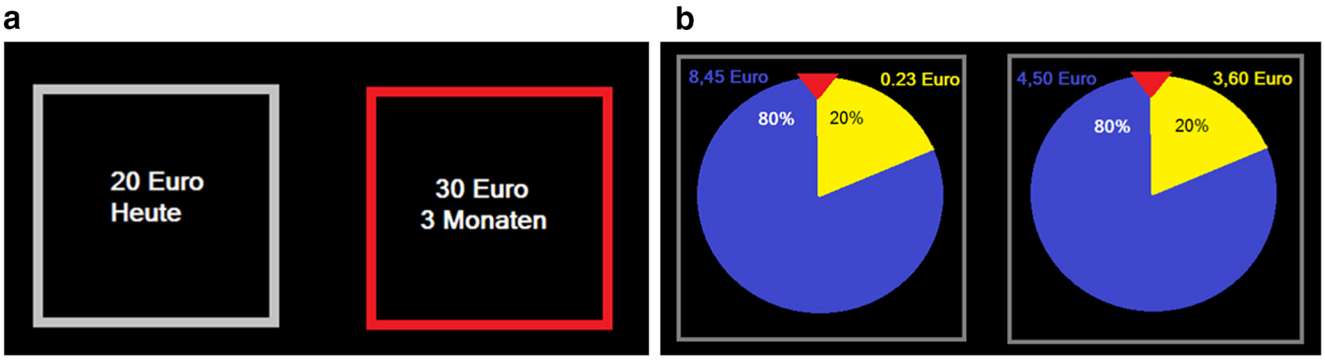

Figure 1. Screenshot of tasks. ***a***, Intertemporal choice task. Participants chose between a smaller reward now or a larger reward later by pressing the E or I key. When the choice was made, the chosen option was highlighted by a red frame. ***b***, Holt-Laury task: participants chose one of two gambles, one considered risky and one considered safer. Lotteries were depicted as wheels of fortune.

smaller, sooner option ranging from €0 to €30 in steps of €3, presented in randomized order. The smaller, sooner option was always immediate. For each of the two large reward amounts, the delay was 3, 6, or 9 months, and the order was randomized across blocks. The options were presented simultaneously on the left and right sides of the screen, and the side of presentation of each choice option was randomized (Fig. 1*a*). Participants pressed the "E" key to choose the left option and the "I" key to choose the right option. There was no time limit for each choice. The trials with either €0 "now" or €20/€30 now were considered catch trials, as the choices in these trials indicate whether the participant paid attention or chose rationally. The task was programmed and conducted using the MATLAB (MathWorks) toolbox *Cogent*. One of the 66 trials was randomly chosen for payment after task performance. Participants received the amount they had selected with the corresponding delay. Both immediate and delayed payment was accomplished by a check that was given either right after the session (immediate payment) or was sent by mail (delayed payment).

Holt-Laury task

The Holt-Laury task (Holt and Laury, 2002) is a short, thoroughly validated 10-trial task to measure risk attitude (Filippin and Crosetto, 2014). Here, we elicited risk attitude as a control variable as time preference measures may potentially be confounded with risk preference. In each trial, participants chose between two lotteries. In one of the lotteries, the payout was either €8.45 or €0.23 with variable probability (riskier lottery); in the other lottery, the payout was either €4.50 or €3.60 with the same variable probability (safer lottery). The probability of winning the large reward of each lottery varied from 10% to 100% in steps of 10% across trials in randomized order. Correspondingly, the probability of winning the small reward was 100% − *p*(large reward). The probabilities of large and small rewards were identical for both lotteries in a given trial (Fig. 1*b*). After task performance, the computer randomly picked one trial and played the lottery that was chosen. The outcome was paid by check at the end of the session.

Procedure

PD patients were recruited and tested during their regular visit to the clinic, which lasted at least 2 nights. After patients were informed about the procedure of our experiment and provided written informed consent, they underwent the screening session in the afternoon on the day of their arrival, or 1 d after, at the clinic. The screening session involved the mood, memory, and cognition tests outlined above, and lasted ~1 h. During screening, patients were always in their most optimal treatment state (i.e., on-stimulation and on-medication).

To test the effect of DBS and L-dopa on delay discounting, we used a between-subject 2 × 2 design with the factors medication (medication on vs off) and STN-DBS (on vs off). Forty patients were randomly assigned to one of the four treatment groups (10 patients/group). The testing procedures were as follows.

A regular visit included an ~16 h period in which patients refrained from taking medication on either the first or the second night of their stay, starting at about 8:00 P.M. If the test session took place in the on-medication state, patients received 1.5× their regular dose of L-dopa (but never more than the maximum dosage of 200 mg), and/or other medication (dopamine agonists; see Table 4), on the morning of the test session, 1 h before the start of the session, to ensure a robust on-state during the whole procedure. Off-medication testing was always performed in the morning after spending a night without medication.

A test session (for overview, see Fig. 2) took place between 9:00 A.M. and noon, and was conducted by two experimenters, of whom only one knew the current DBS state of the patient (passive experimenter), and the other exclusively interacted with and guided the patient through the session (active experimenter). The test sessions started with switching the DBS state of the patient. To ensure double blindness regarding the DBS state, the stimulator was either turned off or left on by a nurse or doctor who was informed by the passive experimenter, without informing the patient about what was done. The patient was aware that the stimulator would be either turned off or remain on and was informed beforehand about the necessity of the double-blind procedure. At least 50 min after the switch, the MDS-UPDRS-III was

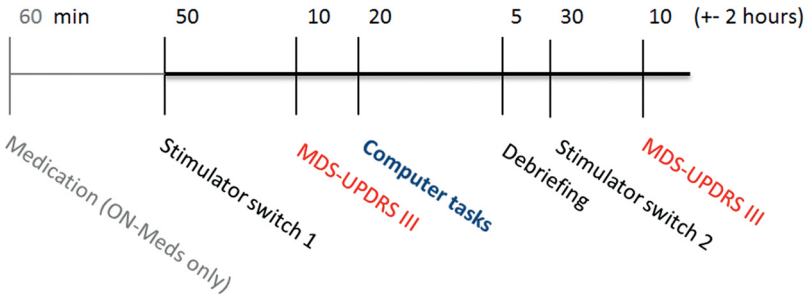

Figure 2. Schematic overview of a session. If patients were tested in the on-medication condition, they received medication (1.5× their regular L-dopa dose) 60 min before DBS was switched off or left on. Patients in the off-medication condition had not ingested dopaminergic medication since the previous evening. At the end of a session, a second MDS-UPDRS-III assessment was conducted in the opposite DBS state to confirm DBS effects within subjects.

conducted, followed by the delay-discounting task (ICT) and subsequently the Holt-Laury risk attitude task. Each patient received oral instructions before each task, and was asked control questions to ensure that they understood the tasks. The MDS-UPDRS-III, ICT, and Holt-Laury tasks were completed in ~30–40 min. Several trials in the tasks were randomly selected for payout (see above). The patient received feedback about the trials chosen for payment immediately after completing the two tasks and was paid accordingly by means of a check. Directly after, the patient was asked about his/her strategy during the choice tasks and was informed about the goal of the experiment. Thirty minutes after changing the stimulation state, a second motor assessment using the MDS-UPDRS-III was conducted as a within-subjects control of the DBS state. A within-subjects repetition of the ICT and Holt-Laury task was not conducted because both tasks were deemed to be unsuitable for repeated measures within the short timeframe of one or two mornings.

Data analysis

We used a 2 × 2 between-subjects factorial design with medication (on vs off) and DBS state (on vs off) as independent factors, and choice parameters (see below) as a dependent variable. To estimate discounting parameters in the ICT, we used the following two different, well established models: the hyperbolic discounting model (Mazur, 1984); and the Laibson (1997) quasi-hyperbolic discounting model (see below). In addition, we also used the total number of choices of the smaller, sooner option as a model-free measure of discounting (yielding a value between 0 and 66), as well as a model-free measure of present bias (i.e., the overweighting of immediate outcomes, see below for details). For the Holt-Laury task, we used the switching point [i.e., the probability at which the participant was indifferent between the two gambles (Holt-Laury task indifference points [HL-IPs])]. This measure was obtained using logistic regression. A higher switching point indicated more risk aversion.

Fitting of discounting models

All mathematical procedures to determine the participants' discount parameters were performed using MATLAB (MathWorks). We first identified the individual IPs (the magnitude of the smaller, sooner reward that renders it equally valuable to the larger, later reward) for each of the six blocks, using logistic regression. This resulted in three values between 0 and 20 for the three blocks with €20 as maximum reward, and three values between 0 and 30 for the three blocks with €30 as the maximum reward.

We first fitted the standard hyperbolic model separately to the IPs of blocks 1–3 and blocks 4–6, using the following equation (Mazur, 1984):

$$SV_T = A/(1 + kT),$$

where SV is the subjective value of the reward at delay T (in months), A is the monetary amount of the reward, and k is the hyperbolic discount parameter describing the steepness of the discount function. The amount was set to $A = 1$ as the values were expressed as proportions of the later reward. Larger k-values indicate a greater impact of delay on value and therefore steeper discounting. The resulting k-values for the €20 and €30 blocks were subsequently log transformed and averaged to obtain one k-value per individual (note that the correlation between the two k-values for the €20 and €30 blocks was very high; $r = 0.96$, $p < 0.000$).

Further, the Laibson quasi-hyperbolic β-δ model was separately fitted to the indifference points of blocks 1–3 and 4–6 to obtain measures of present bias and patience, as follows:

$$SV_{T=0} = 1$$

$$SV_{T>0} = \beta \times \delta^T.$$

SV_t is the subjective value of a reward at time T. This equation models the often observed initial rapid decline in subjective value with small delays (present bias) separately, represented by the parameter β (with $0 \leq \beta \leq 1$). The inverse of β can be interpreted as the extra weight added to immediacy, thus smaller β values can be construed as stronger present bias. The discount rate of the discount function is $\log(1/\delta)$. Thus, the parameter δ (with $0 \leq \delta \leq 1$) can be interpreted as a measure of patience, with higher δ values indicating higher patience. The resulting β and δ parameters for the €20 and €30 blocks were subsequently averaged to obtain one β and δ value for each participant [note that there was a strong correlation

Table 1. Demographic, screening and questionnaire results per DBS/Med state

	State (MED/DBS)				Statistics	
	(1) On/On (N = 8)	(2) On/Off (N = 7)	(3) Off/On (N = 10)	(4) Off/Off (N = 7)	F (p value)	*Post hoc* test (Gabriel)
Age (years)	66.5 (1.4)	57.1 (1.4)	63.5 (2.6)	64.7 (2.9)	3.00 (0.047)*	Group 1 vs 2: p = 0.045*
Year diagnosis	2001 (2.3)	2001 (2.0)	2000 (2.2)	2000 (2.0)	0.09 (0.963)	
Months receiving DBS	30 (8.6)	20 (5.1)	30 (8,6)	39 (10.0)	0.75 (0.534)	
LED	594 (209.4)	671 (118.0)	623 (120.3)	642 (125.0)	0.04 (0.988)	
MDRS	139 (1.2)	138 (1.6)	138 (1.1)	138 (1.3)	0.19 (0.902)	
BDI	6.1 (1.4)	8.4 (1.5)	7.9 (1.2)	7.0 (1.0)	0.60 (0.620)	
BIS-total	25.8 (1.7)	32.3 (1.9)	32.5 (1.7)	25.0 (2.5)	4.34 (0.012)*	Group 3 vs 4: p = 0.055
BIS-nonplanning	9.3 (1.0)	11.9 (0.5)	11.5 (1.2)	8.1 (1.1)	2.74 (0.062)	
BIS-motor	8.9 (1.1)	10.0 (1.3)	11.1 (0.6)	8.4 (0.8)	1.66 (0.197)	
BIS-attention	7.6 (0.9)	10.4 (1.0)	9.9 (0.6)	8.4 (0.8)	2.54 (0.076)	
QDQ-total	22.9 (2.5)	24.9 (2.0)	26.0 (1.8)	20.3 (2.1)	1.40 (0.264)	
QDQ-discounting	11.1 (1.4)	12.0 (1.1)	12.5 (1.0)	10.6 (1.5)	0.48 (0.698)	
QDQ-Aversion	11.8 (1.3)	12.9 (1.5)	13.5 (1.6)	9.7 (1.3)	1.30 (0.294)	

*$p < 0.05$.

between the β values of the €20 and €30 blocks (r = 0.83, $p < 0.000$) and the δ values (r = 0.59, $p < 0.000$)].

The model fits were performed for each participant individually, using a least-squares algorithm implemented in MATLAB R2013a (MathWorks). The fitting parameters k, β, and δ were allowed to vary freely. We calculated the Akaike Information Criterion (AIC) for each model per participant to check the goodness of fit of each model. We then averaged the scores across all participants, resulting in one average AIC value for the hyperbolic model and another AIC value for the Laibson quasi-hyperbolic model. These AIC scores showed that, in general, the data were better described by the quasi-hyperbolic model (mean, −17.5) than the standard hyperbolic model (mean, −10.1). However, when comparing individual AIC values, the quasi-hyperbolic model had higher AIC values compared with the hyperbolic model in 10 participants, indicating a better fit of the hyperbolic model in these participants.

To obtain an additional, model-free measure of present bias, we used the following formula:

Present bias (PB) = (large reward − 3 months IP)/(6 months IP − 9 months IP). To obtain an overall measure, we averaged the model-free present bias measure for the €20 and €30 blocks (PB). A higher score indicated more present bias.

Statistical analysis

The statistical analyses reported below were performed using the IBM software package SPSS Statistics 20. We mainly used standard ANOVAs and ANCOVAs to investigate the main effects of DBS and medication state, as well as their interaction on the dependent variables described above. When necessary, we selected the Gabriel pairwise comparisons test as the *post hoc* test, which is robust against differences in group sample size. Furthermore, we used Bayesian statistics (Wagenmakers, 2007; Masson, 2011) to calculate the evidence in favor of the null hypothesis.

Results

Subject demographics and trait variables

Data from eight participants were excluded as they chose the dominated alternative on >6 of the 12 catch trials in the ICT (i.e., they selected €0 now over €20/€30 later; or they selected €20/€30 later over the same reward now; see above). In addition, two of these participants scored ≥5 points on the SOGS, indicating potential pathological gambling behavior. Our results do not change when these subjects are included in our analysis, except when explicitly mentioned below. Table 1 shows the general descriptive statistics of the remaining 32 patients. The DBS-on group consisted of 18 participants, of whom 8 were tested in the on-medication state. The DBS-off group consisted of 14 participants, of whom 7 were tested in the on-medication state. There was no significant difference in any of the demographic parameters between DBS and medication groups, except for age ($F_{(3,28)}$ = 3.00, p = 0.047, η^2 = 0.24; Table 1).

Table 1 shows the descriptive statistics of the screening tasks and questionnaires. A one-way ANOVA showed a significant difference between the groups in the self-reported impulsiveness (BIS-total), $F_{(3,28)}$ = 4.34, p = 0.012, η^2 = 0.317. However, Gabriel *post hoc* tests showed no significant differences between groups: group 1 versus 2: mean difference = −6.54, p = 0.157; group 1 vs 3: mean difference = −6.75, p = 0.084; group 1 vs 4: mean difference = 0.75, $p > 0.999$; group 2 vs 3: mean difference = −0.21, $p > 0.999$; group 2 vs 4: mean difference = 7.50, p = 0.107; group 3 vs 4: mean difference = 7.50, p = 0.055. Nevertheless, we included BIS-total scores as a covariate in all subsequent analyses to account for potential group differences in impulsiveness. Note that all participants filled out the questionnaires in their optimal (on-medication, on-stimulation) state, so this difference in BIS-total scores reflects a trait difference between groups, not the effect of DBS on impulsiveness.

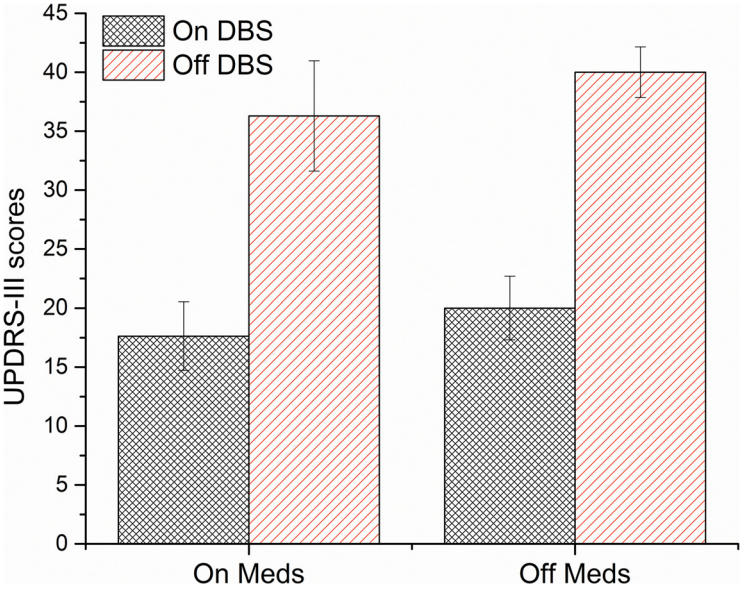

Figure 3. MDS-UPDRS-III scores for each DBS and medication state. Higher scores indicate greater motor impairments. Error bars show SEs.

Differential treatment effects on motor scores, but not delay discounting

As expected, MDS-UPDRS-III scores were significantly different between DBS/medication states, $F_{(3,28)} = 11.96$, $p < 0.001$, $\eta^2 = 0.56$ (Fig. 3). *Post hoc* tests revealed a significant difference between DBS states (group 1 vs 2, 0.002; group 3 vs 4, $p \leq 0.001$), whereas no significant difference was observed between medication states (group 1 vs 3, $p = 0.993$; group 2 vs 4, $p = 0.990$). This is likely due to relatively high interindividual differences in motor scores obscuring the relatively small but often beneficial effect of medication treatment within subjects. Comparing the MDS-UPDRS-III scores within patients (DBS on vs off only) also showed a significant improvement of motor symptoms with stimulation, time × DBS interaction ($F_{(1,31)} = 138.84$, $p < 0.001$, $\eta^2 = 0.82$). Overall, this indicates that DBS significantly improved motor symptoms in our sample, while medication did not.

Table 2 shows the discounting parameters k, β, and δ, the number of impulsive choices (NImp), the model-free measure of PB, as well as the HL-IPs within each group. We used a two-way ANOVA to test for the effects of DBS and medication on discounting and risk parameters, as well as on their interaction. We found no significant main or interaction effects of DBS or medication on any of the discounting parameters (Table 2). Figure 4, *A* and *B*, shows the discounting curves for each medication/DBS state for €20 and €30 blocks, respectively. Figure 4, *C* and *D*, shows the median fits of the hyperbolic and quasi-hyperbolic models, respectively, as well as the 25th and 75th percentile borders, for each DBS state. Figure 5 shows the total number of impulsive choices for each

Table 2. Delay-discounting parameters and risk measure per DBS/Medication state

	DBS				Medication				Interaction	
	On	Off	ANOVA	ANCOVAa	On	Off	ANOVA	ANCOVAa	ANOVA	ANCOVAa
Ln(k)	−1.67 (0.38)	−2.17 (0.34)	0.90 (0.352)	0.23 (0.636)	−1.90 (0.33)	−1.88 (0.429)	0.003 (0.972)	0.09 (0.767)	0.18 (0.677)	0.13 (0.725)
NImp	33.2 (3.8)	27.1 (3.6)	1.31 (0.262)	0.41 (0.526)	31.6 (4.2)	29.5 (3.5)	0.17 (0.684)	0.46 (0.502)	0.053 (0.820)	0.24 (0.625)
βb	0.70 (0.08–1.0)	0.78 (0.35–0.98)	0.95 (0.338)	0.82 (0.374)c	0.62 (0.08–0.97)	0.80 (0.14–1.0)	1.25 (0.274)	1.55 (0.223)c	0.09 (0.765)	0.00 (0.999)c
δb	0.97 (0.83–1.0)	0.98 (0.78–1.0)	0.44 (0.511)	0.002 (0.967)c	0.99 (0.83–1.0)	0.97 (0.78–1.0)	1.19 (0.285)	1.21 (0.282)c	1.09 (0.306)	1.66 (0.208)c
PB	9.19 (1.60)	7.00 (1.34)	1.20 (0.283)	1.00 (0.325)	9.48 (1.86)	7.13 (1.19)	1.14 (0.295)	1.10 (0.303)	0.31 (0.580)	0.003 (0.956)
HL-IPs	41.5 (7.5)	46.5 (11.4)	0.22 (0.641)		49.3 (8.6)	38.7 (9.5)	1.24 (0.375)		5.29 (0.029)*	

Values are reported as the mean (SE), unless otherwise indicated.
[a]Age and BIS-total scores were added as covariates.
[b]Due to violation of normality, median (range) is shown instead of mean (SE). The rank transform procedure was used to test for main effects and interactions.
[c]A nonparametric equivalent of ANCOVA, as discussed in the study by Quade (1967), was used. Here the resulting F statistic and p value are shown.
*$p < 0.05$.

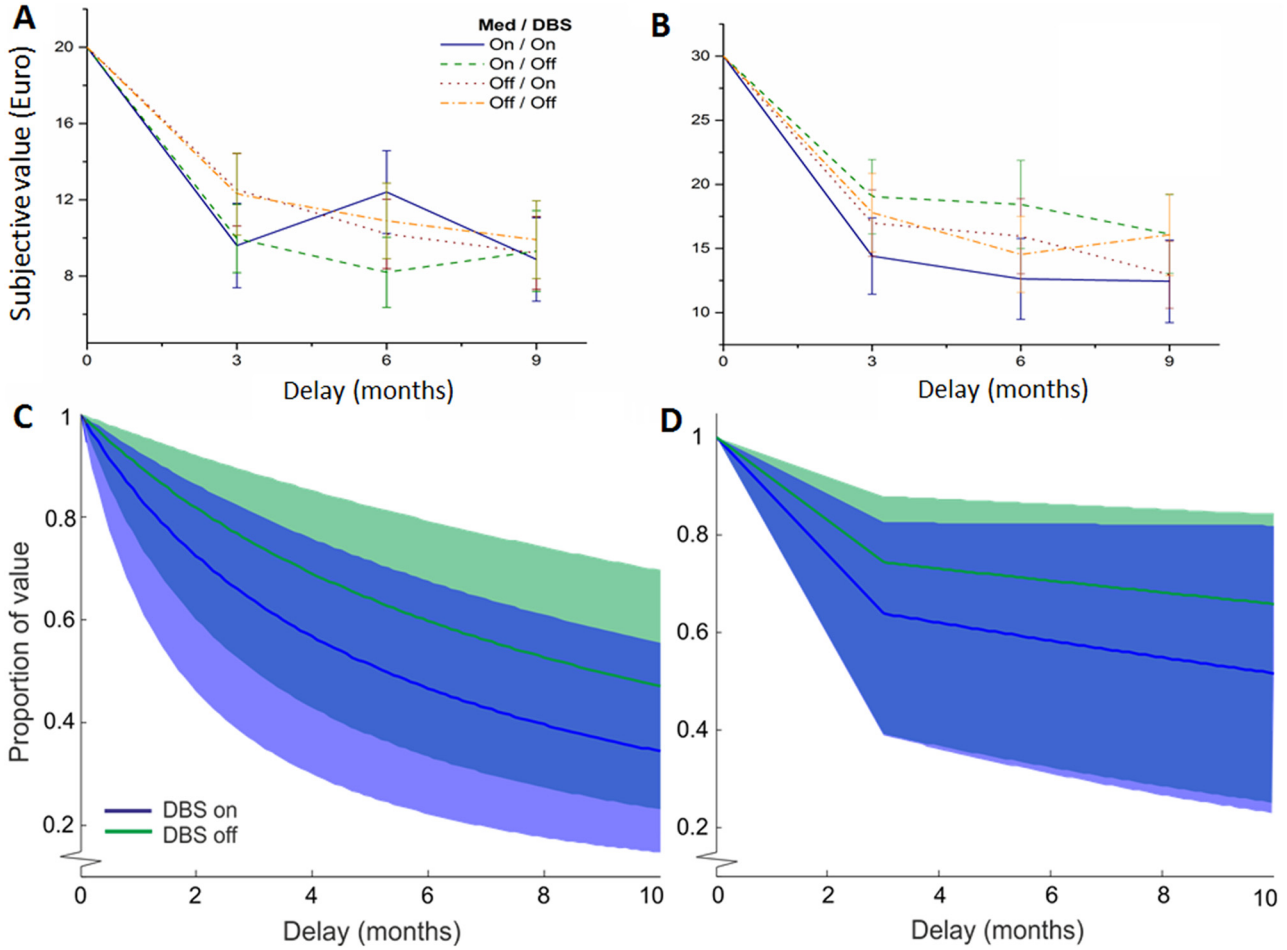

Figure 4. ***A***, ***B***, Discounting curves per medication/DBS state subgroup for €20 (***A***) and €30 (***B***), based on the indifference point at 3, 6, and 9 months. Error bars show SEs. ***C***, Plots of the hyperbolic model in the on-DBS and off-DBS states, based on the median *k*-value. Shaded areas show the 25th and 75th percentile range. ***D***, Plots of the quasi-hyperbolic model in the on-DBS and off-DBS state based on the median β and δ values. The initial linear decline represents present bias and is determined by the β parameter, whereas the subsequent exponential curve represents "patience" and is determined by the δ parameter. Shaded areas show the 25th to 75th percentile range.

medication/DBS state. When adding age and the BIS-total score as covariates in an additional ANCOVA, THE main and interaction effects of DBS and medication states on any of the discounting parameters remained nonsignificant (DBS state: ln(*k*): $F_{(1,28)} = 0.23$, $p = 0.636$, $\eta^2 = 0.009$; NImp: $F_{(1,28)} = 0.41$, $p = 0.526$, $\eta^2 = 0.018$; β: $F_{(1,28)} = 0.819$, $p = 0.37$, $\eta^2 = 0.029$; δ: $F_{(1,28)} = 0.002$, $p = 0.967$, $\eta^2 = <0.001$; PB: $F_{(1,28)} = 1.00$, $p = 0.325$, $\eta^2 = 0.037$; Table 2).

To calculate the probability that the null hypothesis (no effect of DBS on delay discounting) is true given our data ($p(H_0|D)$), we used a Bayesian approach developed by Wagenmakers (2007) and also described in detail in a tutorial by Masson (2011). We used the Bayesian information criterion to calculate the posterior probability $p(H_0|D)$, with the assumption that the null and alternative hypotheses are equally likely. The results are presented in Table 3. We found $p(H_0|D)$ values ranging between 0.73 and 0.81, indicating positive evidence in favor of the null hypothesis, as suggested by Raftery (1995).

Some patients were treated with dopamine agonists instead of, or in addition to, L-dopa. As dopamine agonists are associated with impulsive behavior (Zurowski and O'Brien, 2015), we checked for differences between the DBS groups in the LED when considering only patients who receive dopamine agonists (LED agonists; Table 4). In each of the DBS groups, five patients used dopamine agonists, with no significant difference in LED agonist levels between groups ($U = 110.50$, $p = 0.561$, $r = 0.13$).

The Holt-Laury task was added as a control for the fact that impulsive behavior sometimes correlates with altered risk preferences (Kalenscher and Pennartz, 2008). There were no significant main effects of DBS or medication on Holt-Laury task scores (DBS state: $F_{(1,28)} = 0.22$, $p = 0.641$, $\eta^2 = 0.01$; medication: $F_{(1,28)} = 1.24$, $p = 0.275$, $\eta^2 = 0.04$), suggesting no effect of DBS and/or medication on risk attitude. Note, though, that we found a significant interaction effect of DBS and medication state on HL-IPs ($F_{(1,28)} = 5.29$, $p = 0.029$, $\eta^2 = 0.16$). However,

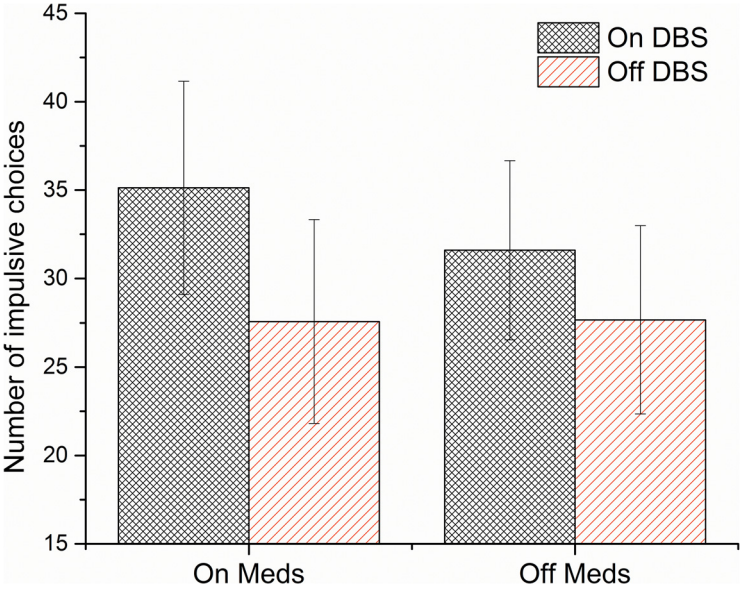

Figure 5. The total number of impulsive choices (smaller, sooner reward) for each DBS and medication state. Error bars show SDs.

when using the complete sample of 40 patients, the interaction effect of DBS and medication state on HL-IPs failed to reach significance ($F_{(1,39)} = 1.00$, $p = 0.325$, $\eta^2 = 0.027$). Note that a relatively large number of patients showed an inconsistent choice pattern (i.e., switching more than once between the risky and safe gamble), with 47,5% making at least one error (one more switch) and 30% having at least two errors, compared with the numbers mentioned in the original article on the Holt-Laury task (Holt and Laury, 2002), where only 13.2% of the participants made at least one error.

Discussion

In this study, we aimed to investigate the effect of STN-DBS on impulsive decision-making, using a delay-discounting paradigm. We found no evidence for an effect of either STN-DBS or medication on delay-discounting behavior, a commonly used measure of impulsive choice. Although we found a significant effect of the interaction of DBS and medication state on risk aversion, this effect did not hold when all participants were included in the analysis. In addition, due to the relatively large number of errors the participants made in this task, we refrain from further interpretation of this finding.

Our findings are in line with a study by Torta et al. (2012), who investigated the effects of STN-DBS on delay aversion. Twenty-one PD patients with STN-DBS turned on and off (patients were off medication) performed the Cambridge Gambling Task, which measured both risk behavior and delay aversion, and filled out questionnaires assessing self-reported delay aversion, delay discounting, and impulsivity. The authors found no effects of stimulation on delay aversion or task behavior, although patients self-reported a higher feeling of impulsivity in the off-stimulation state. Thus, while increased levels of delay discounting have been associated with several impulse control disorders, such as substance abuse, attention deficit hyperactivity disorder, as well as pathological gambling and overeating (Bickel et al., 2012)—behaviors often shown by PD patients in response to their treatment—there is no evidence so far that STN-DBS alters delay discounting.

Although the development of ICDs is often attributed to side effects of dopaminergic medication (Voon and Fox, 2007; Voon et al., 2011a,b; Poletti et al., 2013), several studies point toward a potential role of STN-DBS in the development of ICDs in PD patients (Hälbig et al., 2009; Lim et al., 2009; Moum et al., 2012). However, it has been argued that the development of ICDs after STN-DBS onset may be an indirect consequence of disease history and treatment, as they may result from long-term alterations of frontolimbic structures, which are presumed to be involved in ICDs (Brewer and Potenza, 2008), due to disease progress and long-term medication use (Moum et al., 2012). Because ICDs themselves are considered to be chronic disorders, a short change in DBS state, as

Table 3. Bayesian posterior probabilities for the hypothesis that there is an effect (H_1), or for the hypothesis that there is no effect (H_0), of DBS on discounting measures, given our data

	NImp	Ln(*k*)	β	δ
$p(H_0\|D)$	0.731	0.774	0.765	0.813
$p(H_1\|D)$	0.269	0.226	0.235	0.187

Table 4. Number of participants receiving dopamine agonists, and the LED agonists of the dopamine agonists used, per DBS group

	N	LED agonists	Average LED agonists
DBS on	5	595	119.0
DBS off	5	837	167.4

applied here, after several months of chronic stimulation might not be sufficient to uncover potential long-term effects leading to the development of ICDs. This would be in line with findings pointing at an increase in cognitive impulsivity reported by both patients and relatives 3 months after STN-DBS onset compared with a baseline taken before STN-DBS onset (Pham et al., 2015), but would be contradictory to the above-mentioned self-reported increase in impulsivity in a short-term off-state compared with scores in the DBS-on state (Torta et al., 2012). Although the motor effects of STN-DBS are often visible within minutes, cognitive effects of STN-DBS on impulsive decision-making might not be visible in the short term. For example, as reward learning seems to be affected by STN-DBS, perhaps experiences with rewards after STN-DBS onset influence subsequent choice behavior that could lead to the development of ICDs in a subgroup of patients. Future studies need to monitor long-term changes in delay discounting in particular, and impulsivity in general, after STN-DBS treatment onset.

Impulsivity itself is considered a multifaceted construct (Evenden, 1999; Kalenscher et al., 2006), with one subtype being defined as impulsive action (the inability to inhibit a prepotent response) and another subtype defined as impulsive choice (preferring a smaller, more immediate reward over a larger, more delayed reward; Winstanley et al., 2004; Kalenscher and Pennartz, 2008; Robinson et al., 2009). Motor impulsivity is commonly assessed with reaction time tasks, in which motor responses need to be inhibited either before ("waiting") or during ("stopping") execution, whereas choice impulsivity is often assessed with an intertemporal choice task, in which participants make repetitive choices between a smaller/sooner and larger/later (often monetary) reward. Several studies have dissociated the cognitive and neural bases of these two types of impulsivity (Winstanley et al., 2004; Van den Bergh et al., 2006; Broos et al., 2012). So far, studies have uncovered the effects of STN-DBS on motor impulsivity (Witt et al., 2004; Frank et al., 2007; Aleksandrova et al., 2013), which is in line with literature supporting the involvement of the STN in controlling the threshold for responding in situations with high conflict (i.e., when two choice options are relatively similar in value; Baunez and Robbins, 1997; Baunez et al., 2001; Desbonnet et al., 2004; Frank, 2006; Cavanagh et al., 2011). With regard to reward processing and decision-making, STN-DBS seems to mainly influence reward learning (Serranová et al., 2011; van Wouwe et al., 2011) and the evaluation of losses (Rogers et al., 2011), but, to the best of our knowledge, there is no evidence so far of an effect of STN-DBS on risky decision-making (Brandt et al., 2015).

One concern with our study is the small sample size, and, by consequence, the low statistical power. We cannot reject the possibility that we missed a small effect of STN-DBS on delay discounting because we lacked the statistical power to detect it. However, our Bayesian analysis showed positive evidence in favor of the null hypothesis. This suggests that the effect size is either very small or nonexistent. Therefore, we can conclude with some confidence that, if there were a short-term effect of STN-DBS on delay discounting, it would be miniscule and probably negligible.

Note that we started off with a small pilot experiment to check whether our task was suitable for repeated measures, as this would greatly increase power. However, we found that patients often made stereotypical, repetitive choices on subsequent repetitions of the task, which was supported by anecdotal remarks about their choice behavior and strategy (e.g., they would ask why they had to do the same task again; or they specifically commented on the fact that they would remember their choices in the previous task, and aimed to copy their own choices). For this reason, we opted against using a repeated-measures design.

Additionally, we would like to note that, although highly undesirable, underpowered statistics are frequently unavoidable in studies with clinical populations; due to the difficulty of finding a sufficient number of patients meeting the inclusion criteria, patient samples in medical studies are often smaller than desired. Nevertheless, despite the admittedly low power, we believe that our results are of significance to other scientists studying the effects of PD treatment on impulsive decision-making. To prevent the so-called "file drawer effect" (i.e., publication biases due to potentially informative studies ending up not being published due to nonsignificant findings; Sterling et al., 1995; Hopewell et al., 2009; Song et al., 2009), we would like to make our findings accessible to researchers interested in similar research problems.

In conclusion, we failed to demonstrate a significant effect of STN-DBS on delay discounting. Although an absence of evidence is not evidence of absence, calling for interpretative caution, this could potentially imply that STN-DBS effects on delay discounting do not exist. From a clinical perspective, this study provides evidence for a lack of negative cognitive side effects of STN-DBS in the form of altered intertemporal decision-making. Even if a small effect of STN-DBS on delay discounting existed, a risk of slightly altered decision-making likely does not weigh the same as the benefits of STN-DBS on motor functioning. Our findings, therefore, underscore the clinical safety of DBS-STN as a therapeutic treatment.

References

Aleksandrova LR, Creed MC, Fletcher PJ, Lobo DSS, Hamani C, Nobrega JN (2013) Deep brain stimulation of the subthalamic nucleus increases premature responding in a rat gambling task. Behav Brain Res 245:76-82. CrossRef

Ardouin C, Voon V, Worbe Y, Abouazar N, Czernecki V, Hosseini H, Pelissolo A, Moro E, Lhommée E, Lang AE, Agid Y, Benabid AL, Pollak P, Mallet L, Krack P (2006) Pathological gambling in Parkinson's disease improves on chronic subthalamic nucleus stimulation. Mov Disord 21:1941-1946. CrossRef

Ardouin, C, Chereau, I, Llorca, PM, Lhommee, E, Durif, F, Pollak, P, Krack, P & Mal, G.E.C. (2009) Assessment of hyper- and hypodopaminergic behaviors in Parkinson's disease. Rev Neurol-France 165, 845-856. Medline

Bandini F, Primavera A, Pizzorno M, Cocito L (2007) Using STN DBS and medication reduction as a strategy to treat pathological gambling in Parkinson's disease. Parkinsonism Relat Disord 13:369-371. CrossRef

Baunez C, Robbins TW (1997) Bilateral lesions of the subthalamic nucleus induce multiple deficits in an attentional task in rats. Eur J Neurosci 9:2086-2099. Medline

Baunez C, Humby T, Eagle DM, Ryan LJ, Dunnett SB, Robbins TW (2001) Effects of STN lesions on simple vs choice reaction time tasks in the rat: preserved motor readiness, but impaired response selection. Eur J Neurosci 13:1609-1616. CrossRef

Beck, AT, Steer, RA, Ball, R & Ranieri, WF (1996) Comparison of Beck Depression Inventories-IA and -II in psychiatric outpatients. J Pers Assess 67, 588-597.

Bickel WK, Jarmolowicz DP, Mueller ET, Koffarnus MN, Gatchalian KM (2012) Excessive discounting of delayed reinforcers as a trans-disease process contributing to addiction and other disease-related vulnerabilities: emerging evidence. Pharmacol Ther 134: 287-297. CrossRef

Brandt J, Rogerson M, Al-Joudi H, Reckess G, Shpritz B, Umeh CC, Aljehani N, Mills K, Mari Z (2015) Betting on DBS: effects of subthalamic nucleus deep brain stimulation on risk taking and decision making in patients with Parkinson's disease. Neuropsychology 29:622-631. CrossRef

Brewer JA, Potenza MN (2008) The neurobiology and genetics of impulse control disorders: relationships to drug addictions. Biochem Pharmacol 75:63-75. CrossRef

Broen M, Duits A, Visser-Vandewalle V, Temel Y, Winogrodzka A (2011) Impulse control and related disorders in Parkinson's disease patients treated with bilateral subthalamic nucleus stimulation: a review. Parkinsonism Relat Disord 17:413-417. CrossRef

Broos N, Schmaal L, Wiskerke J, Kostelijk L, Lam T, Stoop N, Weierink L, Ham J, de Geus EJC, Schoffelmeer ANM, van den Brink W, Veltman DJ, de Vries TJ, Pattij T, Goudriaan AE (2012) The relationship between impulsive choice and impulsive action: a cross-species translational study. PLoS One 7:e36781. CrossRef

Cardinal RN, Pennicott DR, Sugathapala CL, Robbins TW, Everitt BJ (2001) Impulsive choice induced in rats by lesions of the nucleus accumbens core. Science 292:2499-2501. CrossRef Medline

Cavanagh JF, Wiecki TV, Cohen MX, Figueroa CM, Samanta J, Sherman SJ, Frank MJ (2011) Subthalamic nucleus stimulation reverses mediofrontal influence over decision threshold. Nat Neurosci 14:1462-1467. CrossRef

Chang JY, Shi LH, Luo F, Zhang WM, Woodward DJ (2007) Studies of the neural mechanisms of deep brain stimulation in rodent models of Parkinson's disease. Neurosci Biobehav Rev 31:643-657. CrossRef

Clare, S, Helps, S & Sonuga-Barke, EJ (2010) The quick delay questionnaire: a measure of delay aversion and discounting in adults. Attention deficit and hyperactivity disorders 2, 43-48. Medline

Demetriades P, Rickards H, Cavanna AE (2011) Impulse control disorders following deep brain stimulation of the subthalamic nucleus in Parkinson's disease: clinical aspects. Parkinsons Dis 2011:658415. CrossRef

Desbonnet L, Temel Y, Visser-Vandewalle V, Blokland A, Hornikx V, Steinbusch HWM (2004) Premature responding following bilateral stimulation of the rat subthalamic nucleus is amplitude and frequency dependent. Brain Res 1008:198-204. CrossRef

Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, Daniels C, Deutschländer A, Dillmann U, Eisner W, Gruber D, Hamel W, Herzog J, Hilker R, Klebe S, Kloss M, Koy J, Krause M, Kupsch A, Lorenz D, et al. (2006) A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med 355:896-908. CrossRef

Evenden JL (1999) Varieties of impulsivity. Psychopharmacology 146:348-361. Medline

Filippin A, Crosetto P (2014) A reconsideration of gender differences in risk attitudes. Manage Sci. Advance online publication. Retrieved 1 May 2016. doi:10.1287/mnsc.2015.2294.

Frank MJ (2006) Hold your horses: a dynamic computational role for the subthalamic nucleus in decision making. Neural Netw 19:1120-1136. CrossRef Medline

Frank MJ, Samanta J, Moustafa AA, Sherman SJ (2007) Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. Science 318:1309-1312. CrossRef Medline

Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, et al. (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 23:2129-2170. CrossRef

Hälbig TD, Tse W, Frisina PG, Baker BR, Hollander E, Shapiro H, Tagliati M, Koller WC, Olanow CW (2009) Subthalamic deep brain stimulation and impulse control in Parkinson's disease. Eur J Neurol 16:493-497. CrossRef Medline

Hardisty DJ, Thompson KF, Krantz DH, Weber EU (2013) How to measure time preferences: an experimental comparison of three methods. Judgm Decis Mak 8:236-249.

Haynes WIA, Haber SN (2013) The organization of prefrontal-subthalamic inputs in primates provides an anatomical substrate for both functional specificity and integration: implications for basal ganglia models and deep brain stimulation. J Neurosci 33: 4804-4814. CrossRef

Holt CA, Laury SK (2002) Risk aversion and incentive effects. Am Econ Rev 92:1644-1655. CrossRef

Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K (2009) Publication bias in clinical trials due to statistical significance or direction of trial results. Cochrane Database Syst Rev (1): MR000006.

Kalenscher T, Pennartz CMA (2008) Is a bird in the hand worth two in the future? The neuroeconomics of intertemporal decision-making. Prog Neurobiol 84:284-315. CrossRef Medline

Kalenscher T, Ohmann T, Güntürkün O (2006) The neuroscience of impulsive and self-controlled decisions. Int J Psychophysiol 62: 203-211. CrossRef Medline

Kheramin S, Body S, Mobini S, Ho MY, Velazquez-Martinez DN, Bradshaw CM, Szabadi E, Deakin JFW, Anderson IM (2002) Effects of quinolinic acid-induced lesions of the orbital prefrontal cortex on inter-temporal choice: a quantitative analysis. Psychopharmacology 165:9-17.

Kirby KN, Maraković NN (1996) Delay-discounting probabilistic rewards: rates decrease as amounts increase. Psychon Bull Rev 3:100-104. CrossRef

Laibson D (1997) Golden eggs and hyperbolic discounting. Q J Econ 112:443-477. CrossRef

Lambert C, Zrinzo L, Nagy Z, Lutti A, Hariz M, Foltynie T, Draganski B, Ashburner J, Frackowiak R (2012) Confirmation of functional zones within the human subthalamic nucleus: patterns of connectivity and sub-parcellation using diffusion weighted imaging. Neuroimage 60:83-94. CrossRef

Lesieur, HR & Blume, S.B. (1987) The South Oaks Gambling Screen (SOGS): a new instrument for the identification of pathological gamblers. The American journal of psychiatry 144, 1184-1188. Medline

Li Q, Ke Y, Chan DCW, Qian ZM, Yung KKL, Ko H, Arbuthnott GW, Yung WH (2012) Therapeutic deep brain stimulation in Parkinsonian rats directly influences motor cortex. Neuron 76:1030-1041. CrossRef Medline

Li S, Arbuthnott GW, Jutras MJ, Goldberg JA, Jaeger D (2007) Resonant antidromic cortical circuit activation as a consequence of high-frequency subthalamic deep-brain stimulation. J Neurophysiol 98:3525-3537. CrossRef

Lim SY, O'Sullivan SS, Kotschet K, Gallagher DA, Lacey C, Lawrence AD, Lees AJ, O'Sullivan DJ, Peppard RF, Rodrigues JP, Schrag A, Silberstein P, Tisch S, Evans AH (2009) Dopamine dysregulation syndrome, impulse control disorders and punding after deep brain stimulation surgery for Parkinson's disease. J Clin Neurosci 16: 1148-1152. CrossRef

Lucas, JA, Ivnik, RJ, Smith, GE & Bohac, DL (1998) Normative data for the Mattis Dementia Rating Scale. Arch Clin Neuropsych, 13, 41-42. Medline

Masson ME (2011) A tutorial on a practical Bayesian alternative to null-hypothesis significance testing. Behav Res Methods 43:679-690. CrossRef Medline

Mattis S. Dementia Rating Scale: Professional Manual. Odessa, FL: Psychological Assessment Resources; 1988.

Maurice N, Deniau JM, Glowinski J, Thierry AM (1998) Relationships between the prefrontal cortex and the basal ganglia in the rat: physiology of the corticosubthalamic circuits. J Neurosci 18:9539-9546.

Mazur JE (1984) Tests of an equivalence rule for fixed and variable reinforcer delays. J Exp Psychol Anim Behav Process 10:426-436. CrossRef

McCracken CB, Grace AA (2007) High-frequency deep brain stimulation of the nucleus accumbens region suppresses neuronal activity and selectively modulates afferent drive in rat orbitofrontal cortex *in vivo*. J Neurosci 27:12601-12610. CrossRef

Montgomery EB Jr, Gale JT (2007) Mechanisms of action of deep brain stimulation (DBS). Neurosci Biobehav Rev 32:388-407. CrossRef Medline

Moum SJ, Price CC, Limotai N, Oyama G, Ward H, Jacobson C, Foote KD, Okun MS (2012) Effects of STN and GPi deep brain stimulation on impulse control disorders and dopamine dysregulation syndrome. PLoS One 7:e29768. CrossRef

Nambu A, Tokuno H, Takada M (2002) Functional significance of the cortico-subthalamo-pallidal "hyperdirect" pathway. Neurosci Res 43:111-117. Medline

Parent A, Hazrati LN (1995a) Functional-anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. Brain Res Rev 20:91-127. Medline

Parent A, Hazrati LN (1995b) Functional-anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Res Rev 20:128-154. Medline

Pham U, Solbakk AK, Skogseid IM, Toft M, Pripp AH, Konglund AE, Andersson S, Haraldsen IR, Aarsland D, Dietrichs E, Malt UF (2015) Personality changes after deep brain stimulation in Parkinson's disease. Parkinsons Dis 2015:490507 CrossRef

Poletti M, Logi C, Lucetti C, Del Dotto P, Baldacci F, Vergallo A, Ulivi M, Del Sarto S, Rossi G, Ceravolo R, Bonuccelli U (2013) A single-center, cross-sectional prevalence study of impulse control disorders in Parkinson disease: association with dopaminergic drugs. J Clin Psychopharmacol 33:691-694. CrossRef

Quade D (1967) Rank analysis of covariance. J Am Stat Assoc 62:1187-1200. CrossRef

Raftery AE (1995) Bayesian model selection in social research. Sociol Methodol 25:111-163. CrossRef

Raja M, Bentivoglio AR (2012) Impulsive and compulsive behaviors during dopamine replacement treatment in Parkinson's Disease and other disorders. Curr Drug Saf 7:63-75. CrossRef

Robinson ESJ, Eagle DM, Economidou D, Theobald DEH, Mar AC, Murphy ER, Robbins TW, Dalley JW (2009) Behavioural characterisation of high impulsivity on the 5-choice serial reaction time task: specific deficits in "waiting" versus "stopping." Behav Brain Res 196:310-316. CrossRef

Rogers RD, Wielenberg B, Wojtecki L, Elben S, Campbell-Meiklejohn D, Schnitzler A (2011) Deep brain stimulation of the subthalamic nucleus transiently enhances loss-chasing behaviour in patients with Parkinson's Disease. Exp Neurol 231:181-189. CrossRef

Schmidt, R, Freidl, W, Fazekas, F, Reinhart, B, Grieshofer, P, Koch, M, Eber, B, Schumacher, M, Polmin, K & Lechner, H (1994) The Mattis-Dementia-Rating-Scale - Normative Data from 1,001 Healthy-Volunteers. Neurology 44, 964-966. CrossRef

Serranová T, Jech R, Dušek P, Sieger T, Ruˇžička F, Urgošík D, Ruˇžička E (2011) Subthalamic nucleus stimulation affects incentive salience attribution in Parkinson's disease. Mov Disord 26: 2260-2266. CrossRef Medline

Song FJ, Parekh-Bhurke S, Hooper L, Loke YK, Ryder JJ, Sutton AJ, Hing CB, Harvey I (2009) Extent of publication bias in different categories of research cohorts: a meta-analysis of empirical studies. BMC Med Res Methodol 9:79. CrossRef

Spinella, M (2007) Normative data and a short form of the Barratt Impulsiveness Scale. The International journal of neuroscience 117, 359-368. Medline

Sterling TD, Rosenbaum WL, Weinkam JJ (1995) Publication decisions revisited: the effect of the outcome of statistical tests on the decision to publish and vice-versa. Am Stat 49:108-112. CrossRef

Torta DME, Vizzari V, Castelli L, Zibetti M, Lanotte M, Lopiano L, Geminiani G (2012) Impulsivities and Parkinson's disease: delay aversion is not worsened by deep brain stimulation of the subthalamic nucleus. PLoS One 7:e43261. CrossRef

Van den Bergh F, Spronk M, Ferreira L, Bloemarts E, Groenink L, Olivier B, Oosting R (2006) Relationship of delay aversion and response inhibition to extinction learning, aggression, and sexual behaviour. Behav Brain Res 175:75-81. CrossRef Medline

van Wouwe NC, Ridderinkhof KR, van den Wildenberg WPM, Band GPH, Abisogun A, Elias WJ, Frysinger R, Wylie SA (2011) Deep brain stimulation of the subthalamic nucleus improves reward-based decision-learning in Parkinson's disease. Front Hum Neurosci 5:30. CrossRef

Voon V, Fox SH (2007) Medication-related impulse control and repetitive behaviors in Parkinson Disease. Arch Neurol 64:1089-1096. CrossRef Medline

Voon V, Gao J, Brezing C, Symmonds M, Ekanayake V, Fernandez H, Dolan RJ, Hallett M (2011a) Dopamine agonists and risk: impulse control disorders in Parkinson's; disease. Brain 134:1438-1446. CrossRef Medline

Voon V, Mehta AR, Hallett M (2011b) Impulse control disorders in Parkinson's disease: recent advances. Curr Opin Neurol 24:324-330. CrossRef Medline

Wagenmakers EJ (2007) A practical solution to the pervasive problems of p values. Psychon Bull Rev 14:779-804. Medline

Weintraub D (2008) Dopamine and impulse control disorders in Parkinson's disease. Annal Neurol 64 [Suppl. 2]:S93–S100. CrossRef

Wichmann T, DeLong MR (2006) Deep brain stimulation for neurologic and neuropsychiatric disorders. Neuron 52:197-204. CrossRef Medline

Winstanley CA, Dalley JW, Theobald DEH, Robbins TW (2004) Fractionating impulsivity: contrasting effects of central 5-HT depletion on different measures of impulsive behavior. Neuropsychopharmacology 29:1331-1343. CrossRef

Witjas T, Baunez C, Henry JM, Delfini M, Regis J, Cherif AA, Peragut JC, Azulay JP (2005) Addiction in Parkinson's disease: impact of subthalamic nucleus deep brain stimulation. Mov Disord 20:1052-1055. CrossRef Medline

Witt K, Pulkowski U, Herzog J, Lorenz D, Hamel W, Deuschl G, Krack P (2004) Deep brain stimulation of the subthalamic nucleus improves cognitive flexibility but impairs response inhibition in Parkinson disease. Arch Neurol 61:697-700. CrossRef

Zurowski M, O'Brien JD (2015) Developments in impulse control behaviours of Parkinson's disease. Curr Opin Neurol 28:387-392. CrossRef Medline

BrainCycles: Experimental Setup for the Combined Measurement of Cortical and Subcortical Activity in Parkinson's Disease Patients During Cycling

Maciej Gratkowski [1,*], **Lena Storzer** [2], **Markus Butz** [2], **Alfons Schnitzler** [2], **Dietmar Saupe** [1] **and Sarang S. Dalal** [3,4]

[1] *Department of Computer and Information Science, University of Konstanz, Konstanz, Germany*
[2] *Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany*
[3] *Center of Functionally Integrative Neuroscience, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark*
[4] *Zukunftskolleg and Department of Psychology, University of Konstanz, Germany*

Correspondence*:
Maciej Gratkowski
Department of Computer and Information Science, University of Konstanz, Fach 697, 78457 Konstanz, Germany, maciej.gratkowski@gmail.com

ABSTRACT

Recently, it has been demonstrated that bicycling ability remains surprisingly preserved in Parkinson's disease (PD) patients who suffer from freezing of gait. Cycling has been also proposed as a therapeutic means of treating PD symptoms, with some preliminary success. The neural mechanisms behind these phenomena are however not yet understood. One of the reasons is that the investigations of neuronal activity during pedaling have been up to now limited to PET and fMRI studies, which restrict the temporal resolution of analysis, and to scalp EEG focused on cortical activation. However, deeper brain structures like the basal ganglia are also associated with control of voluntary motor movements like cycling and are affected by PD. Deep brain stimulation (DBS) electrodes implanted for therapy in PD patients provide rare and unique access to directly record basal ganglia activity with a very high temporal resolution. In this paper we present an experimental setup allowing combined investigation of basal ganglia local field potentials (LFPs) and scalp EEG underlying bicycling in PD patients. The main part of the setup is a bike simulator consisting of a real Dutch-style bicycle frame mounted on a commercially available ergometer. The pedal resistance is controllable in real-time by custom software and the pedal position is continuously tracked by custom Arduino-based electronics using optical and magnetic sensors. A portable bioamplifier records the pedal position signal, the angle of the knee, and the foot pressure together with EEG, EMG, and basal ganglia LFPs. A handlebar-mounted display provides additional information for patients riding the bike simulator, including the current and target pedalling rate. In order to demonstrate the utility of the setup, example data from pilot recordings are shown. The presented experimental setup provides means to directly record basal ganglia activity not only during cycling but also during other movement tasks in patients who have elected DBS treatment. Thus it can facilitate studies comparing bicycling and walking, to elucidate why PD patients often retain the ability to bicycle despite severe freezing of gait. Moreover it can help clarifying the mechanism through which cycling may have therapeutic benefits.

Keywords: DBS, LFPs, EEG, Cycling, Ergometer, Freezing of gait, Parkinson's disease

1 INTRODUCTION

Recently, it has been demonstrated that bicycling ability remains surprisingly preserved in Parkinson's disease (PD) patients. In the first report on this phenomenon (Snijders and Bloem, 2010), a video of a 58-year-old man with a 10-year history of idiopathic PD suffering from severe freezing of gait (FOG) is presented. The patient had difficulties initiating gait, which resulted in forward festination and eventually in a fall to the ground. He was able to perform only a few steps when provided with a visual cue and the axial turning was not possible at all. However, the patient had no apparent problems riding and controlling a bike. Immediately after hopping off the bike the FOG episode recurred. Follow-up reports by these investigators showed that most PD patients, with and without FOG, maintain the ability to bicycle despite severe walking deficits (Snijders et al., 2011, 2012). It has been also demonstrated that the loss of bicycling ability early in the progression of disease strongly supports a diagnosis of atypical parkinsonism rather than PD (Aerts et al., 2011).

It has long been established that PD patients have abnormal basal ganglia function. As the basal ganglia are thought to be heavily critical for all types of locomotion, the observation that bicycling and walking are so differentially impacted in FOG is surprising. Snijders et al. (2011) propose possible explanations for this phenomenon: The bicycle's rotating pedals may act as an external pacing cue for the legs. Alternatively, gait and other activities like cycling, which involve moving the legs, might be differentially affected in PD. One may also speculate that the special conditions of bicycling, e.g., continuous resistance and angular momentum of the pedals, may provide feedback that is substantially different from walking. Bicycling has also been recently promoted as a viable therapy for PD (Mohammadi-Abdar et al., 2016), with evidence emerging that it may stimulate improvements in motor control (Ridgel et al., 2009, 2015) and cognitive performance (Ridgel et al., 2011; Alberts et al., 2011), as well as reduce severity of tremor, bradykinesia (Ridgel et al., 2012) and of orthostatic hypotension (Ridgel et al., 2016).

The neural mechanisms behind these phenomena are however not yet understood. One of the reasons is that investigation of neuronal activity during pedaling has been limited up to now to functional imaging and scalp EEG studies. Functional imaging restricts the temporal resolution of analysis, and scalp EEG is focused on cortical activation. Christensen et al. (2000) examined bicycling movements with PET in healthy subjects, observing activation of many typical motor structures (primary motor cortex, supplementary motor area, cerebellum), but notably not basal ganglia. Fukuyama et al. (1997) used SPECT to determine involvement of the basal ganglia in walking in healthy subjects, along with primary motor cortex, supplementary motor area, and cerebellum. SPECT, however, reflects the summation of all brain activity over several minutes and can therefore not reveal oscillatory activity or connectivity patterns. A recent study in dystonia patients measured local field potentials (LFPs) from the basal ganglia while they walked on a treadmill, and found increases in theta (4–8 Hz), alpha (8–12 Hz), and gamma (60–90 Hz) power compared to rest, while beta (15–25 Hz) power was markedly reduced (Singh et al., 2011). Importantly, no power differences were noted between sitting and standing positions, reducing the likelihood that the seated configuration of bicycling could play a significant role in the context of the bicycling ability phenomena in PD patients.

The first scalp EEG study of cortical activity as a function of instantaneous pedaling (Jain et al., 2013) reported that beta power over the motor cortex was significantly reduced in active pedaling as opposed to passive pedaling. Furthermore, they demonstrated a relationship between EEG power and EMG power of various leg muscles as a function of pedal position. Recently, it has been shown using scalp EEG that bicycling relative to walking has a stronger sustained cortical activation and less demanding cortical motor control within the movement cycle (Storzer et al., 2016). This is probably due to the fact that walking

demands more phase-dependent sensory processing and motor planning, because each leg is independent in altering stance and swing movement phases. In bicycling, pedals are locked to each other, imposing continuous movement of both legs.

No study to date has recorded deep brain activity during bicycle pedaling. Thus, there is a need for further investigation of cortical and deep brain structures to understand both the mechanism through which cycling ability is preserved in PD patients and the mechanism through which cycling may have therapeutic benefits for them. Electrodes implanted for deep brain stimulation (DBS) therapy in PD patients provide the unique chance to directly record basal ganglia activity.

DBS is an established therapeutic strategy that, for PD patients, involves neurosurgical implantation of electrodes directly in the basal ganglia to allow stimulation with electric current, somewhat analogous to a cardiac pacemaker. If externalized, the same electrodes can be used to also record LFPs, providing an opportunity to measure basal ganglia activity during motor and cognitive behavior.

In this paper, we present an experimental setup that we call *BrainCycles*. It allows combined investigation of basal ganglia LFPs and scalp EEG in conjunction with physiological and performance parameters during bicycling tasks in patients with implanted DBS electrodes. Furthermore, example data from pilot recordings with PD patients are presented.

2 MATERIAL & METHODS

2.1 Experimental setup overview

The BrainCycles setup is a modified version of the Powerbike simulator, which was developed for data acquisition, analysis, and visualization of performance parameters in endurance cycling (Dahmen et al., 2011). The full Powerbike software suite incorporates cyclist and bicycle management, synchronized videos of cycling routes, an electronic gear shifter, and the recording and visualization of various performance parameters during a ride like speed, cadence, power, heart rate, and height profile. For the present experimental setup, the Powerbike's capabilities to record bicycling performance parameters as well as to actively control pedal resistance are used. Additionally, the setup was extended with a device for real-time measurement of pedal position. Custom software was developed for the control of the acquisition of the EEG, EMG and other physiological parameters important for experiment protocols involving PD patients. The main hardware component of the setup is a Cyclus2 ergometer (RBM elektronik-automation GmbH, Germany) with an eddy current brake. The brake force can be controlled through a serial port with a sampling rate of 20 Hz using a custom-made software interface. A classic Dutch-style bike frame is mounted on the ergometer brake. The frame, saddle and handlebar were chosen taking the special needs of PD patients into consideration. They ensure that the patients are able to easily get on and get off the bike simulator and have a comfortable sitting position (see Figure 1).

An Arduino Due board (Arduino LLC, USA) controls the sensors that assess the crank phase angle and a TFT-display mounted on the handlebar. The Due board includes an Atmel SAM3X8E ARM Cortex-M3 microcontroller and features 54 digital input/output pins, 12 analog inputs, 4 hardware serial ports, an 84 MHz clock and 2 digital-to-analog converters (DACs). A vast number of extension boards (shields) and libraries for interfacing to a wide range of hardware is available for Arduino platform. Thus, the board is especially suitable for easy and fast prototyping.

In this setup a TFT/SD shield (SainSmart, USA) is used to interface with a 3.2 TFT LCD touch-display (SainSmart, USA). The display is mounted on the handlebar and is used to present information and feedback

for participants during experiments. For example, the display can show current and desired target cadence in revolutions per minute (rpm). If the target cadence is not being met, a colored arrow is shown, signaling the patient to pedal faster or slower. The color (red or yellow) of the arrow indicates the magnitude of deviation from the target cadence, with the thresholds adjustable by the experimenter.

The data acquisition in the BrainCycles setup is managed with the help of the OpenBCI software framework (Durka et al., 2012). OpenBCI is a complete open source software modular framework for brain-computer interfaces. The architecture of the framework is based on a centralized modular approach, where different modules communicate through a central multiplexer. The framework includes a module for online communication with signal acquisition hardware and a graphical module for signal review. Thus, OpenBCI can be used as a complete software EEG recording suite. The OpenBCI's tags manager module can be used to annotate the electrophysiological data with events like FOG episodes or start/stop signals, which are used to instruct participants to start or stop pedaling. The open source character of the framework enables the integration of cycling performance measures within the data stream. For example, twice per pedal revolution, data such as current brake force and cadence are saved as tags in the data stream. The analysis module enables the realization of feedback loops, e.g., in order to control pedal brake force depending on the parameters of electrophysiological signals like EEG or EMG.

2.2 Data Acquisition

All electrophysiological data is acquired by a 32-channel TMSi Porti amplifier (TMSi, Enschede, The Netherlands). This lightweight, compact amplifier is battery-powered and can therefore be worn by the patient on a belt and used for recording signals "untethered" for comparison of walking and pedaling conditions. It has a maximum sampling rate of 2048 Hz, and, unlike most other portable devices, is therefore capable of capturing high frequency oscillations (100–500 Hz) particularly relevant for basal ganglia pathology in PD (Özkurt et al., 2011; Hirschmann et al., 2016). Additionally, it has several auxiliary channels, which can be used for the recording of performance data from the ergometer and other physical measurements. The amplifier provides 24 unipolar, 4 bipolar as well as 4 auxiliary channels. The 32-channels can be used to record from basal ganglia implants, which have 4-8 electrode contacts each, typically placed bilaterally for a total of 8-16 intracerebral channels. Scalp EEG can be recorded with an electrode montage optimized for capturing sensorimotor cortex activity (e.g. Fp1, Fz, Cz, C3, C4, and reference), along with bilateral EMG of the tibialis anterior (TA), rectus femoris (RF), and biceps femoris (BF) leg muscles. EMG and scalp EEG are recorded with actively shielded cables, which reduce sensitivity to motion artifacts and are therefore particularly suitable for recording during locomotion tasks. Furthermore, respiration rate, ECG, knee flexion and foot pressure can also be monitored. TMSi electronic goniometers and footswitches (TMSi, Enschede, The Netherlands) were successfully tested with the setup.

2.3 Measurement of LFPs

DBS treatment of PD involves the implantation of stimulating electrodes in the subthalamic nucleus (STN) or the globus pallidus interna (GPi). At many DBS clinics, the electrodes are implanted in a first step, and the stimulator device a few days later in a second step, allowing the chance to record LFPs from the externalized electrodes. Light physical activity is usually manageable for PD patients shortly after the implantation of electrodes. Thus, it is possible to record LFPs while the PD patient is pedaling a stationary bicycle in a laboratory environment. The LFPs can be recorded unipolarly or bipolarly using selected pairs of DBS electrode contacts. Bipolar measurements or bipolar digital rereferencing should be used in order to reduce contamination from distant sources as well as movement artifacts. Those could degrade true local LFPs, bias power spectral estimates, or influence coherence and correlation estimations between different

brain regions (Whitmore and Lin, 2016). We have successfully tested Boston Scientific Vercise and St. Jude Medical Infinity DBS systems with the BrainCycles experimental setup. Both of them offer 8 contacts per electrode. Using directional leads they allow for stimulation and measurement in directions orthogonal to the lead trajectory.

2.4 Measurement of Pedal Position

One of the requirements of the BrainCycles setup is to provide a means to investigate possible relationships between EEG power and EMG power of various leg muscles as a function of pedal position. A custom made electronic circuit encodes the current crank position as an analog signal proportional to the angular position of the pedals. This analog signal is acquired together with electrophysiological signals using the auxiliary input of the EEG amplifier. An important advantage of this approach is that this eliminates the need to coregister data prior to analysis. Furthermore, the knowledge of the real-time pedal position opens new possibilities for experimental protocols with tasks or control parameters depending on the instantaneous position of the pedals. For example, the pedaling resistance at the push-down phase of the pedal motion could be independently set for each leg.

The main part of the rotary encoder are two forked light barriers consisting of infrared LEDs and phototransistors. The barriers are mounted next to the front chainring so that the teeth of the chainring pass through the light barriers, and the distance between the light axes of the barriers is smaller than the width of the teeth. The first light barrier acts as a key that changes the state when a tooth first breaks and then releases the light barrier. Thus, an inversed impulse is created every time a tooth passes through the barrier and temporarily interrupts the light. The falling edge of the impulse invokes a hardware interrupt in the microcontroller. The microcontroller counts each such event. The increase of the angular position of the cranks can be derived from this count and the number of teeth on the chainring. The orientation of the crank rotation can be determined with the help of the second barrier. If the pedalling is forward, the second barrier will be open at the time the tooth is entering the first barrier. If the pedalling is backwards, the second barrier will be closed.

The angular resolution of such encoder is directly proportional to the number of teeth on the chainring, because the teeth on the sprocket are equidistantly distributed. In our particular setup, the chainring has 42 teeth and thus the angular resolution is 360° / 42 = 8.57°. In order to know the absolute position of the pedals a reset signal at position 0° is needed. The reset signal is provided by mounting a magnet on the crank and a magnetically actuated reed switch at position 0°, which in our case is the top position of the right pedal. The absolute position of the pedals is then converted to an analog signal by the DAC integrated on the Arduino Due board and connected to the auxiliary input of the EEG amplifier. The DAC output and the auxiliary input of the Porti amplifier are galvanically separated with an optocoupler for an additional layer of patient safety and to prevent ground loop interference.

2.5 Example Data

In order to demonstrate the utility of the setup, sample data from pilot recordings is presented. The shown data were recorded from a 56-year-old patient, who was diagnosed with PD in 2011 with motor symptoms predominantly on the right side. The patient had opted for bilateral DBS therapy (Boston Scientific Vercise system with 8 contacts per STN), and was recorded one day after the implantation of DBS electrodes while off any dopaminergic medication. Custom-made connectors were used to connect the DBS electrodes with the EEG amplifier.

The recording protocol consisted of 30 intermittent rest and pedaling periods guided by acoustic signals. The patient was provided with start and stop signals in form of a tone of 500 ms duration and frequency 1000 Hz in case of the start signal and 1500 Hz for the end signal. The duration of the rest and pedaling phases were around 10 seconds. The patient was instructed to pedal at a relaxed pace of his own preferred cadence. The brake force of the ergometer was constantly kept at a low level of 30 N. Individual gel-based electrodes were placed at Pz, Oz and P3 to capture signals from somatomotor areas. The bandage left after the implantation of electrodes did not allow placement of electrodes more anterior. Subsequently, the recorded signals were digitally rereferenced to a bipolar montage of Pz-P3 and Pz-Oz. A water-based ground electrode (TMSi, Netherlands) integrated in a wristband was used. Bipolar surface EMG activity of TA, BF, and RF was recorded bilaterally using disposable Ag/AgCl electrodes. Electrodes were placed 2 cm apart on the belly of each muscle. EMG, scalp EEG and LFPs were recorded with actively shielded cables compensating for movement artifacts.

In previous studies, modulation of cortical oscillatory activity in the beta band during transitions between rest and pedaling conditions was observed (Storzer et al., 2016). Thus, we hypothesized that this modulation should also be seen in deeper brain regions. The recorded data were processed in Matlab (Mathworks, Inc., Natick, MA) using the FieldTrip open source Toolbox (Oostenveld et al., 2011). The bipolar LFP channel with the highest resting beta activity was chosen for further analysis. LFPs and EEG data were bandpass filtered with cutoff frequencies of 13 Hz and 33 Hz. Next, the filtered data were Hilbert-transformed in order to compute their envelopes. The envelope signals were then averaged taking 5 seconds of data before and 10 seconds of data after each movement initiation. Both ongoing and averaged envelope signals were filtered by a moving average filter of length 2500 samples, which represents around 1.2 seconds of data.

3 RESULTS

Beta band activity in the STN sharply decreased upon initiation of pedaling and rebounded after termination. This can be clearly seen even in continuous time series (see Figure 2 C). The beta increase is visible upon return to resting, when muscle activity is minimal. Thus, it is unlikely that the increase in the beta band is due to movement artifacts. The beta modulation can also be observed from the scalp EEG data (Pz-Oz) when averaged relative to movement initiation (see Figure 3).

4 DISCUSSION

In this paper we presented an experimental setup for combined recording of cortical and deep brain oscillations during pedaling. We showed that direct recordings from the STN during bicycling are possible in a laboratory environment. Visual inspection suggests that the recorded signals have a very high SNR. The reduction of the beta power in the STN during bicycling is visible even in the raw data. A similar effect

could be observed in the surface EEG. However, for the later the change of the amplitude is much smaller and only visible after averaging the EEG locked to the movement initiation.

The presented experimental setup provides means to directly record basal ganglia activity not only during cycling but also during other movement tasks in patients who have elected DBS treatment. Thus it can facilitate studies comparing bicycling and walking, to elucidate why PD patients often retain the ability to bicycle despite severe FOG. Moreover, it can help to clarify the mechanism through which cycling may have therapeutic benefits.

At present, the experiments can be performed between 1 and 6 days after electrode implantation, while the electrode cable is externalized and therefore allows recording of LFPs from the implanted structures. The next generation of DBS systems will additionally allow LFPs recording by the same unit that performs stimulation and storing the data internally for subsequent retrieval via wireless data transfer. This will allow recording of data after electrode cables have been internalized, greatly expanding opportunities to record LFPs, and eventually allowing recordings after patients have recovered from the surgical procedure and have become accustomed to the implant. Thus, task-related modulations of oscillatory activity and coupling could be monitored during a cycling training regimen and correlated to therapeutic outcomes. Importantly, several months after implantation, the patients would be able to participate in more strenuous activity, such as the forced pedaling regimens described in Alberts et al. (2011) and Ridgel et al. (2012).

The BrainCycles setup could also be used to investigate visuomotor processing in PD patients. It has been hypothesized that PD is associated with a visuomotor disturbance and PD patients produce exaggerated responses to visual information (Cowie et al., 2010). For example, many patients slow down dramatically or even freeze when attempting to approach narrow doorways. Similarly, FOG episodes can be elicited by unexpectedly appearing obstacles (Delval et al., 2010). The Powerbike's ability to play videos synchronized to pedaling could be used to investigate how such sudden visual cues and obstacles are processed during cycling. Visuomotor processing during walking on a treadmill and cycling on an ergometer could be also compared in a lab environment.

DISCLOSURE/CONFLICT-OF-INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the design of the experiment setup and revised the manuscript. MG constructed and programmed the BrainCycles setup. LS acquired the data. MG, SSD and LS were involved in data analysis and interpretation. All authors approved the final version of the manuscript, agreed to be accountable for all aspects of the work and qualify for authorship.

ACKNOWLEDGMENTS

We thank Nitin Sharma (University of Konstanz) for assistance with constructing and programming the experimental setup.

Funding: This work was generously supported by a grant from the Jacques and Gloria Gossweiler Foundation. Further support was received from the Zukunftskolleg of the University of Konstanz [SSD],

Heinrich Heine University Strategic Research Funds [MB], the Open Access Publication Fund of the University of Konstanz, and the research commission of the medical faculty of the Heinrich Heine University [9772562 to MB]. LS was supported by a travel grant from the Boehringer Ingelheim Foundation (BIF).

REFERENCES

Aerts, M., Abdo, W., and Bloem, B. (2011). The "bicycle sign" for atypical parkinsonism. *The Lancet* 377, 125–126

Alberts, J. L., Linder, S. M., Penko, A. L., Lowe, M. J., and Phillips, M. (2011). It is not about the bike, it is about the pedaling: forced exercise and parkinson's disease. *Exercise and Sport Sciences Reviews* 39, 177–186

Christensen, L. O., Johannsen, P., Sinkjær, T., Petersen, N., Pyndt, H., and Nielsen, J. B. (2000). Cerebral activation during bicycle movements in man. *Experimental Brain Research* 135, 66–72

Cowie, D., Limousin, P., Peters, A., and Day, B. L. (2010). Insights into the neural control of locomotion from walking through doorways in parkinson's disease. *Neuropsychologia* 48, 2750–2757

Dahmen, T., Byshko, R., Saupe, D., Röder, M., and Mantler, S. (2011). Validation of a model and a simulator for road cycling on real tracks. *Sports Engineering* 14, 95–110

Delval, A., Snijders, A. H., Weerdesteyn, V., Duysens, J. E., Defebvre, L., Giladi, N., et al. (2010). Objective detection of subtle freezing of gait episodes in parkinson's disease. *Movement Disorders* 25, 1684–1693

Durka, P., Kuś, R., Żygierewicz, J., Michalska, M., Milanowski, P., Łabęcki, M., et al. (2012). User-centered design of brain-computer interfaces: Openbci.pl and bci appliance. *Bulletin of the Polish Academy of Sciences: Technical Sciences* 60, 427–431

Fukuyama, H., Ouchi, Y., Matsuzaki, S., Nagahama, Y., Yamauchi, H., Ogawa, M., et al. (1997). Brain functional activity during gait in normal subjects: a spect study. *Neuroscience Letters* 228, 183–186

Hirschmann, J., Butz, M., Hartmann, C. J., Hoogenboom, N., Özkurt, T. E., Vesper, J., et al. (2016). Parkinsonian rest tremor is associated with modulations of subthalamic high-frequency oscillations. *Movement Disorders* doi:10.1002/mds.26663

Jain, S., Gourab, K., Schindler-Ivens, S., and Schmit, B. D. (2013). Eeg during pedaling: evidence for cortical control of locomotor tasks. *Clinical Neurophysiology* 124, 379–390

Mohammadi-Abdar, H., Ridgel, A. L., Discenzo, F. M., and Loparo, K. A. (2016). Design and development of a smart exercise bike for motor rehabilitation in individuals with parkinson's disease. *IEEE-ASME Transactions on Mechatronics* 21, 1650–1658. doi:10.1109/TMECH.2015.2508030

Oostenveld, R., Fries, P., Maris, E., and Schoffelen, J.-M. (2011). Fieldtrip: Open source software for advanced analysis of meg, eeg, and invasive electrophysiological data. *Computational Intelligence and Neuroscience* doi:10.1155/2011/156869

Özkurt, T. E., Butz, M., Homburger, M., Elben, S., Vesper, J., Wojtecki, L., et al. (2011). High frequency oscillations in the subthalamic nucleus: A neurophysiological marker of the motor state in parkinson's disease. *Experimental Neurology* 229, 324–331. doi:10.1016/j.expneurol.2011.02.015

Ridgel, A. L., Kim, C.-H., Fickes, E. J., Muller, M. D., and Alberts, J. L. (2011). Changes in executive function after acute bouts of passive cycling in parkinson's disease. *Journal Of Aging And Physical Activity* 19, 87–98

Ridgel, A. L., Peacock, C. A., Fickes, E. J., and Kim, C.-H. (2012). Active-assisted cycling improves tremor and bradykinesia in parkinson's disease. *Archives of Physical Medicine and Rehabilitation* 93, 2049–2054

Ridgel, A. L., Phillips, R. S., Walter, B. L., Discenzo, F. M., and Loparo, K. A. (2015). Dynamic high-cadence cycling improves motor symptoms in parkinson's disease. *Frontiers in Neurology* 6. doi:10.3389/fneur.2015.00194

Ridgel, A. L., Vitek, J. L., and Alberts, J. L. (2009). Forced, not voluntary, exercise improves motor function in parkinson's disease patients. *Neurorehabilitation and Neural Repair* 23, 600–608

Ridgel, A. L., Walter, B. L., Tatsuoka, C., Walter, E. M., Colon-Zimmermann, K., Welter, E., et al. (2016). Enhanced exercise therapy in parkinson's disease: A comparative effectiveness trial. *Journal of Science and Medicine in Sport* 19, 12–17. doi:10.1016/j.jsams.2015.01.005

Singh, A., Kammermeier, S., Plate, A., Mehrkens, J. H., Ilmberger, J., and Bötzel, K. (2011). Pattern of local field potential activity in the globus pallidus internum of dystonic patients during walking on a treadmill. *Experimental Neurology* 232, 162–167

Snijders, A. H. and Bloem, B. R. (2010). Cycling for freezing of gait. *New England Journal of Medicine* 362, e46

Snijders, A. H., Toni, I., Ružička, E., and Bloem, B. R. (2011). Bicycling breaks the ice for freezers of gait. *Movement Disorders* 26, 367–371

Snijders, A. H., van Kesteren, M., and Bloem, B. R. (2012). Cycling is less affected than walking in freezers of gait. *Journal of Neurology, Neurosurgery & Psychiatry* 83, 578–581

Storzer, L., Butz, M., Hirschmann, J., Abbasi, O., Gratkowski, M., Saupe, D., et al. (2016). Bicycling and walking are associated with different cortical oscillatory dynamics. *Frontiers in Human Neuroscience* 10

Whitmore, N. W. and Lin, S.-C. (2016). Unmasking local activity within local field potentials (lfps) by removing distal electrical signals using independent component analysis. *Neuroimage* 132, 79–92. doi:10.1016/j.neuroimage.2016.02.032

FIGURES

Figure 1. The BrainCycles experimental setup; left - classic Dutch frame and EEG amplifier mounted on the Cyclus2 ergometer; right - handlebar display presenting information about the current and the desired trarget cadence in rpm

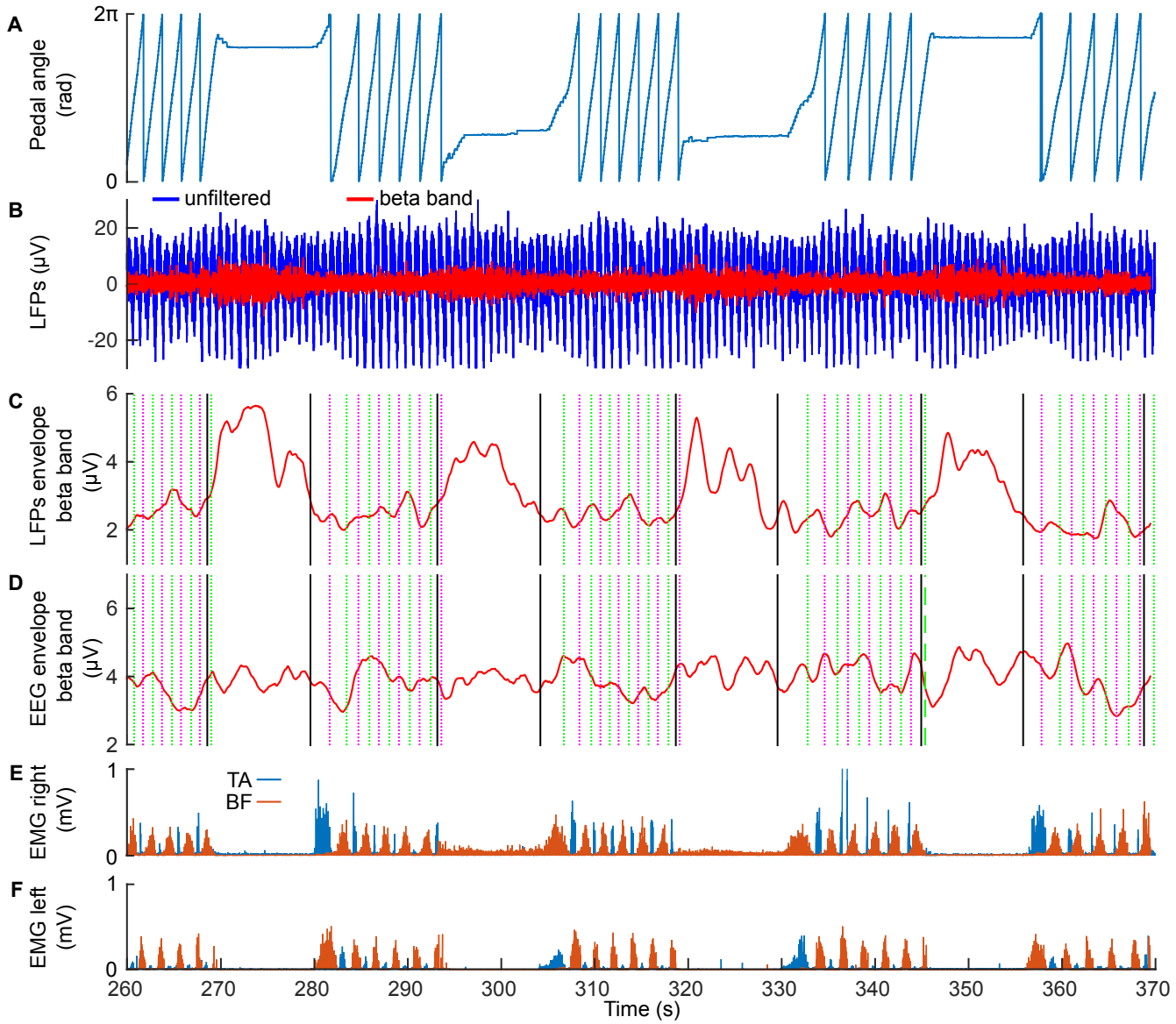

Figure 2. Modulation of the beta band in the LFPs (left STN) and EEG data (Pz-Oz); A - the recorded pedal angle; B - the unfiltered (blue curve) and filtered (red curve) data recorded from the left STN; C and D - the envelopes of filtered LFPs and EEG data. The solid and dashed black lines represent start and stop signals, respectively. The magenta and green dotted lines represent the events of the right pedal crossing the top and bottom positions, respectively; E and F - EMG signals recorded from TA and BF in the right and left legs.

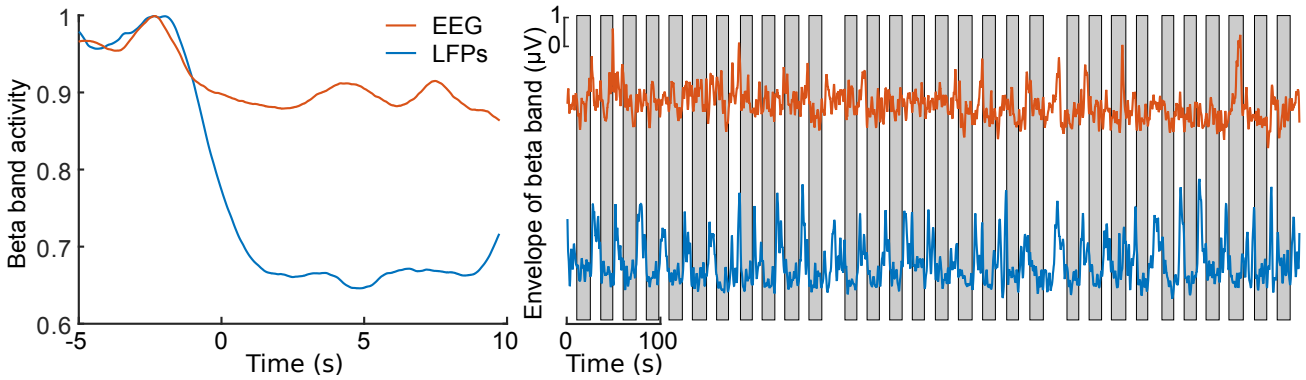

Figure 3. Envelopes of the beta band of the EEG signal (red) and LFPs (blue). At left, the averaged and normalized envelopes are presented. The averaging was locked to the movement initiation at t=0 seconds and the curves are normalized to their maximum value. At right, ongoing envelopes are presented. The gray boxes represent periods of pedaling. All the envelopes were filtered with a moving average filter of length 2500 samples (1.2 seconds).