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Cortical Oscillations underlying Bicycling and Walking in Patients with Parkinson's Disease and Freezing of Gait

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Summary

In Parkinson's disease (PD) a degenerative process in the basal ganglia (BG) leads to an impaired interaction between subcortical and cortical brain areas resulting in rigor, tremor, and akinesia. An akinetic symptom appearing in advanced stages of PD is Freezing of Gait (FOG), which is characterized by a sudden inability of movement initiation. The underlying pathophysiology, however, remains unknown, but FOG is thought to be associated with synchronized cortical and subcortical oscillatory activity. Interestingly, the ability to ride a bicycle is often preserved in patients with FOG. A recent study demonstrated that the oscillatory activity within the subthalamic nucleus differs between patients with and without FOG, as patients with FOG present an increase of oscillatory activity at 18 Hz.

The aim of the present thesis was to compare cortical oscillatory activity of PD patients with and without FOG using electroencephalogram (EEG). In particular, it was tried to elucidate the role of the motor cortices in the generation of the symptom. Of special interest was to investigate, if a movement related oscillatory signal, comparable to the reported subcortical signal at 18 Hz, exists.

Brain activity of 20 PD patients with FOG, 13 patients without FOG and 16 healthy controls was recorded during bicycling and walking initiation and termination. The bicycling condition was assessed on a Dutch-style bicycle on an ergometer. The main focus of the analyses lied on the *beta* band comprising oscillatory activity between 13 and 35 Hz.

Bicycling and walking were both associated with a suppression of oscillatory activity in the *beta* band, which was stronger for bicycling than for walking. This might result from the continuity of the movement. Walking requires a higher cognitive load than bicycling, which leads to excessive activity in the BG, and therefore might result in freezing episodes. Interestingly, there were no cortical differences between patients with and without FOG observable. This was even true for periods of active freezing.

These findings suggest that the pathological signal causing FOG does not evolve from the primary motor cortices.

Zusammenfassung

Beim *Morbus Parkinson* kommt es aufgrund degenerativer Prozesse in den Basalganglien zu einer gestörten Interaktion kortikaler und subkortikaler Areale. Dies führt zu den Kardinalsymptomen Rigor, Tremor und Akinese. Zu den akinetischen Symptomen zählt zudem auch das sog. „*Freezing of Gait*“ (FOG), welches durch ein plötzliches Einfrieren von Bewegungen charakterisiert ist. Dieses wenig verstandene Phänomen ist mit pathologischer oszillatorischer Aktivität assoziiert. So zeigten sehr aktuelle Ergebnisse eine für *Freezing* spezifische oszillatorische Aktivität um 18 Hz im *Nucleus subthalamicus* von Patienten mit FOG. Daneben können Patienten, die bereits erheblich gangbeeinträchtigt sind, interessanterweise oft noch problemlos Fahrrad fahren. Ziel dieser Dissertation war es, die kortikale oszillatorische Aktivität bei Patienten mit und ohne FOG beim Fahrradfahren bzw. Gehen zu untersuchen.

Mit Hilfe der Elektroenzephalographie (EEG) wurde die Gehirnaktivität bei 20 Parkinsonpatienten mit FOG, 13 Patienten ohne FOG und 16 gesunden Kontrollen während Bewegungsinitiierung, während Drehbewegungen auf der Stelle sowie bei Bewegungsende aufgezeichnet. Kortikale Aktivität beim Fahrradfahren wurde dabei auf einem befestigten Ergometer gemessen. Der Fokus der Analyse lag auf dem motorischen Kortex und dem sog. *Beta* Band, welches die oszillatorische Aktivität zwischen 13 – 35 Hz umfasst.

Es konnte gezeigt werden, dass sowohl Fahrradfahren als auch Gehen mit einer Unterdrückung oszillatorischer Aktivität im *Beta* Band einhergehen, die beim Fahrradfahren stärker ausgeprägt ist. Dies könnte durch die Kontinuität der Bewegung erklärt sein. Darüber hinaus konnten keine Unterschiede kortikaler oszillatorischer Aktivität zwischen Patienten mit und ohne FOG gefunden werden.

Diese Befunde legen den Schluss nahe, dass die pathologischen Oszillationen bei FOG nicht im motorischen Kortex generiert werden, sondern ein subkortikales Störsignal darstellen. Demnach resultiert eine erhöhte kognitive Belastung beim Gehen in einer erhöhten Aktivität in den Basalganglien, welche dann in einer Überbelastung und einem plötzlichen Einfrieren in der Bewegung endet. Dennoch kann davon ausgegangen werden, dass FOG eine Dysfunktion im Zusammenspiel verschiedener kortikaler und subkortikaler Areale darstellt.

Glossary

APA	Anticipatory postural adjustments
aDBS	Adaptive deep brain stimulation
BG	Basal ganglia
CBT	Cortico-basal-ganglia-thalamic-circuitry
CNS	Central nervous system
CPG	Central pattern generator
dB	Decibel
DBS	Deep brain stimulation
EEG	Electroencephalogram
EMG	Electromyography
FAB	Frontal Assessment Battery
FFT	Fast Fourier transform
fMRI	Functional magnetic resonance imaging
FOG	Freezing of Gait
GPe	External segment of the *Globus pallidus*
GPi	Internal segment of the *Globus pallidus*
ICA	Independent component analysis
IEEG	Intracranial electroencephalogram
LFP	Local Field Potentials
MEG	Magnetoencephalography
MDS	Movement Disorders
MDRS	Mattis Dementia Rating Scale
MLR	Mesencephalic locomotor region
PD	Parkinson’s disease
PIGD	Postural instability and gait difficulty
PMC	Primary motor cortex
PMRF	Pontomedullary reticular formation
PPN	*Pedunculopontine nucleus*
Rpm	Revolution per minute
SNc	*Substantia nigra pars compacta*

SNCA	α synuclein encoding gene
SNr	*Substantia nigra pars reticularis*
SMA	Supplementary motor area
SMC	Supplementary motor complex
Spm	Strides per minute
STN	Subthalamic nucleus
TUG	Timed up and go task
UPDRS	Unified Parkinson's Disease Rating Scale
VR	Virtual reality

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1. Introduction

1.1. Parkinson's disease

Parkinson's disease (PD) is a common neurodegenerative disorder, which was initially described by James Parkinson in 1817 in his *"Essay on the shaking palsy"* (Parkinson, 1817).

Since it is a progressive and age-related disabling disease, management and treatment of PD becomes a growing challenge in our ageing population. After Alzheimer's disease, PD is the most common neurodegenerative disorder (reviewed by Lau and Breteler, 2006) with a lifetime risk estimated to be 2 % for men and 1 - 3 % for women for individuals aged 40 (Ascherio and Schwarzschild, 2016).

1.1.1. Clinical characteristics

Clinical features of PD can be recognized with the acronym *TRAP*: Resting tremor, rigor, akinesia and postural instability (Jankovic, 2008; Moustafa *et al.*, 2016). Furthermore, flexed posture and motor blocks (in the following referred to as Freezing) were introduced in addition to the classical, cardinal symptoms. Initial symptoms are often misinterpreted and attributed to age or orthopedic problems.

PD presents itself as a rather heterogeneous disease with variable clinicopathologic phenotypes, as for example tremor-dominant and akinetic-rigid or postural instability and gait difficulty (PIGD) subtypes (for a review see Thenganatt and Jankovic, 2014). The tremor dominant group suffers especially from rest tremor and is characterized by a rather slow progression with a good prognosis. The PIGD subtype is mainly affected by bradykinetic and rigid motor state and shows a fast progression. Gait difficulties are more often evident in the PIGD patients and predominantly impairing the domains pace, rhythm, variability, asymmetry, and postural control (Galna *et al.*, 2015). It has been argued recently, not to distinguish PIGD as a more severe subtype (Kotagal, 2016), suggesting to implement the PIGD as a marker of disease progression instead of a subcategory.

PD diagnosis is a main prerequisite for an appropriate therapeutic management. There are clinical, pathological, and genetical markers. This diagnosis can be straightforward in patients that show the typical clinical symptom complex and a good response to levodopa therapy. There are also non-motor symptoms however, such as cognitive or behavioral impairments, that commonly occur, particularly in advanced stages of disease progression (Schapira, Chaudhuri and Jenner, 2017). Using standardized clinical criteria, such as the United Kingdom PD brain bank criteria and recently revised Movement Disorders (MDS) Clinical Diagnostic Criteria (Postuma *et al.*, 2015, 2018), can improve the accuracy of the clinical diagnosis (reviewed by Tolosa, Wenning and Poewe, 2006). Error rates in clinicopathological studies on the other hand emphasize the need for additional testing to consolidate differential diagnostic correctness (Rizzo *et al.*, 2016). These tests encompass genetic analysis, levodopa responsiveness test, neurophysiological studies, neuroimaging, and autonomic and olfactory function testing (reviewed by Tolosa, Wenning and Poewe, 2006). Even today, in spite of advances in technical possibilities, the diagnosis continues to be mainly clinical by examining the cardinal symptoms (Tolosa, Wenning and Poewe, 2006; Postuma *et al.*, 2015).

Disease progression is classified by the Hoehn and Yahr scale, which ranges between stage 0 (no clinical signs of the disease) and stage 5 characterizing complete immobility of the patient (Hoehn *et al.*, 1967). Motor symptom severity, disability and impairment is clinically ranked according to the well-established motor section of the Unified Parkinson's Disease Rating Scale (UPDRS III; (Goetz *et al.*, 2008). The progression of PD is not linear but the deterioration is variable, especially in the early years of the disease and in patients with the PIGD subtype (Jankovic and Kapadia, 2001). Other rating scales examine psychiatric manifestations (e.g. depression) and the quality of life (Ebersbach *et al.*, 2006).

1.1.2. Pathogenesis

The pathological hallmark of PD is a region-specific dopaminergic cell loss within the *pars compacta* of the *substantia nigra* (SNc) and the subsequent dopamine depletion of the striatum (reviewed by Humphries, Obeso and Dreyer, 2018). The aforementioned nuclei belong to the basal ganglia (BG) (reviewed by Utter and Basso, 2008; Nelson and Kreitzer, 2014). These are several highly interconnected structures, consisting of the striatum, the external and the internal segment of the *globus pallidus* (GPe and GPi), the subthalamic nucleus (STN) and the compact and the reticular component of the *substantia nigra* (SNc and SNr). Thus, they form a large subcortical network located in the forebrain connecting all cortical areas sequentially with the frontal cortex. They are organized in parallel loops from different domains and are involved in motor and cognitive function. Taking into account this unique construction, the BG are able to coordinate information from various origins and modalities and therefore ensure functions, such as the selection and inhibition of movement (Mink, 1996) or the formation of habit (reviewed by Yin and Knowlton, 2006).

The output nuclei of the BG are the GPi and the SNr. Through the output nuclei, the BG project to the thalamus, the superior colliculus and the pedunculopontine nucleus (PPN). By projecting to the PPN, the BG modulate spinal cord processing, locomotion and postural control (Takakusaki *et al.*, 2003). Cellular degeneration in the area of the PPN could act synergistically with nigrostriatal cell loss, which could also explain the partial resistance to dopaminergic treatment (reviewed by Lewis and Roger A. Barker, 2009; Tubert, Galtieri and Surmeier, 2019).

As initially reported (Alexander, Garrett E., DeLong, Mahlon R., Strick, 1986) and revised later (Redgrave *et al.*, 2010), the cortex sends sensorimotor, cognitive and affective information to subregions of the striatum. They are organized in distinct pathways but also overlap, which results in an integrative function between cognitive, motor, and limbic signals (Mailly *et al.*, 2013; Nelson and Kreitzer, 2014).

The current model of the BG organization consists of three parallel pathways connecting the input and output nuclei of the BG and the SNr. Activity in the direct pathway, arising from inhibitory striatal efferents, results in disinhibition of the

thalamus and facilitates movements. The indirect pathway first passes through the GPe via striatal projections, then to the STN and the GPi/Snr. This pathway suppresses movements by increasing thalamic inhibition. In PD the deprivation of nigrostriatal dopamine increases the indirect pathway activity and perioperative administration of dopamine decreases firing rate of GPi neurons (Levy *et al.*, 2001). The cortex-STN-SNr/GPi-projection is of special interest, since it is known as the “hyperdirect” pathway and is crucial for action cancelling for motor and cognitive programs (Sano *et al.*, 2013). Therefore, it helps to control inhibition of behavior, for example during presence of conflict (Aron, 2006).

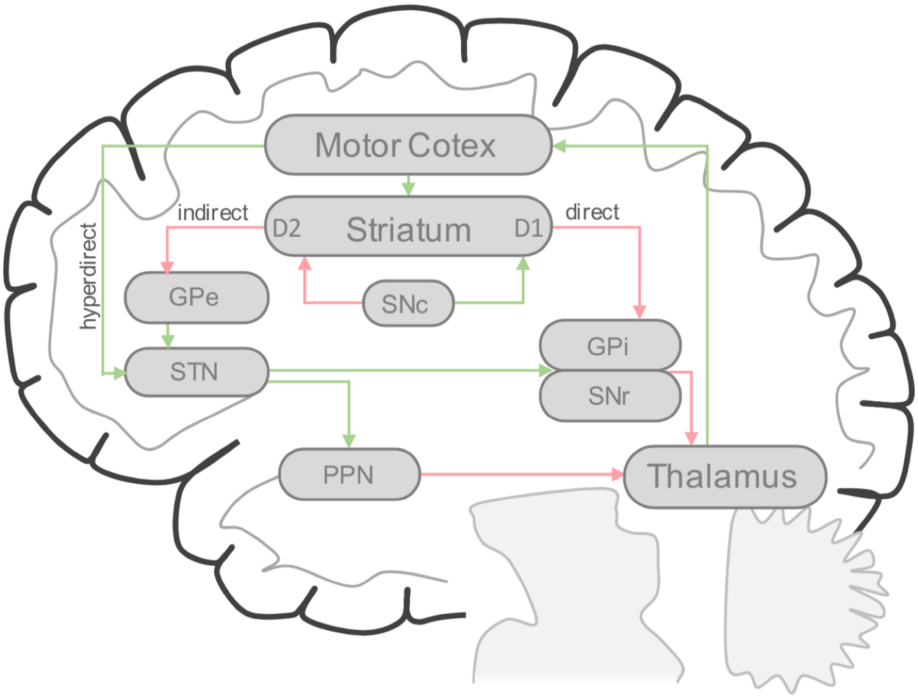

Figure 1: ***Anatomy and functional organization of the basal ganglia (BG).*** The striatum projects via the direct and indirect pathway. The thalamus receives inhibitory input from the SNr and GPi and has excitatory connections to the motor cortex. Due to dopamine depletion there is reduced activity in the direct pathway, which decreases the inhibition of the GPi and SNr. Increased activity of the indirect pathway leads to increased excitatory input to the GPi and SNr. Summed up, there is a stronger inhibition of the thalamus and decreased feedback to the cortex. Adapted and modified from Alexander and Crutcher (1990) and Nambu *et al.* (2000).

Particular attention should be given to the role of the STN. As the sole glutamergic nucleus it is a key node in the control of motor activity. Its stimulation and modulation suppresses symptoms of PD and results in stable improvement of patient's clinical condition (Fasano, Daniele and Albanese, 2012).

The cell loss in PD that disrupts the normal function of the BG is accompanied by the occurrence of intraneuronal inclusions, the Lewy bodies (for a review see Goedert *et al.*, 2013; Kalia and Kalia, 2015). Lewy bodies are abnormally folded, post translationally modified α synuclein proteins that are related to the development of PD. The genetic component in the disease development lies within mutations in the α synuclein encoding gene (SNCA) which can cause accumulation of Lewy bodies in the brain (Polymeropoulos *et al.*, 1997; Konno *et al.*, 2016). Besides, other genetic polymorphisms and mutations have been identified (Farrer, 2006; Hardy *et al.*, 2009; Trinh and Farrer, 2013).

Even though PD is seen as a sporadic disorder, it is assumed to emerge from a multifarious interaction between predisposing genes and environmental impact (Farrer, 2006; Kalia, Kalia and Lang, 2015). Increased risk correlates with exposure to pesticides, consumption of dairy products, history of melanoma and traumatic brain injury. Reduced risk has been related to smoking, caffeine consumption, and physical activity (Ascherio and Schwarzschild, 2016).

1.1.3. Treatment

Parkinson's disease remains incurable, but therapeutic options improve quality of life and movement capacities today. The most common therapeutic means for treating PD are dopamine replacement (Lewitt, 2015) and high frequency deep brain stimulation (DBS) of the STN and the GPi (Fasano, Daniele and Albanese, 2012). In the early stages of the disease, dopamine agonists and levodopa are effective medications. Dopaminergic substitution is thought to decrease pathological *beta* band synchronization and therefore, to improve neuronal communication (Singh, 2018). Pharmacological interventions often become ineffective with disease progression and habituation (for a review see Obeso, Olanow and Nutt, 2000; Salat and Tolosa, 2013). Furthermore, it can induce side effects and fluctuations, so that the patients often suffer from dyskinesia and hyperkinesia (LeWitt, 2008). The high frequency DBS is an effective way of

managing severe symptoms in PD, especially when medication no longer provides sufficient benefits. The STN and GPi are the main targets for relieving the major motor symptoms, whereas the PPN is a newer target for patients with postural instability (Lozano and Lipsman, 2013). To this day, it is not fully understood, how exactly DBS acts on the motor system, why symptoms respond differently to treatments, and why the outcome is often variable (reviewed by Fasano *et al.*, 2015). The optimal treatment for individual patients frequently involves a compromise between the absence of side effects and a suboptimum of benefits (Chen *et al.*, 2006; Benabid *et al.*, 2009). Another interesting emerging approach is adaptive DBS (aDBS), in which stimulation is adjusted to the level of pathological activity (for a review see Beudel and Brown, 2016; Habets *et al.*, 2018). This might be advantageous with regard to efficacy, battery usage, and side effects.

1.1.4. Neuronal control of locomotion in Parkinson's disease

First, it must be stated, that the parkinsonian gait and its underlying pathology is complex and most likely multifactorial. Therefore, there is more than one structure contributing to gait impairments as seen in PD patients.

In order to enable uncomplicated motion sequences in our daily life, a perfectly coordinated system has developed. This facilitates a fast, adaptive and dynamic movement control (Takakusaki, 2013). Locomotion is a manifold process, which requires various interactions, e.g. locomotor rhythm generation, activation, and inhibition of muscles and balance control. But not only descending commands are crucial for smooth movement, there are also afferent feedback mechanisms that allow adjustments to motivational and environmental needs (Nielsen and Sinkjaer, 2002). Through the descending system, the cerebral cortex, the BG, the cerebellum, and the brainstem act on the spinal cord, where the basic locomotion pattern is generated (Takakusaki, 2013). The BG receive input from the cerebral cortex and control volitional, automatic, and emotional processes via projections to the cerebral cortex, the brainstem and the limbic system. Therefore, the supraspinal control is essential for movement initiation, turning and stopping, obstacle avoidance, and adaption of locomotion.

The cerebral cortex is the highest level of locomotor control. The supplementary motor area (SMA) can be found in the dorsomedial frontal cortex, anterior to the leg representation of the primary motor cortex (PMC) and belongs to the supplementary motor complex (SMC). The SMC seems to play a major role in the generation of voluntary movements (reviewed by Nachev, Kennard and Husain, 2008). Patients with PD have an altered SMA activity (for a review see Lefaucheur, 2005). Increased SMA activity and improved motor function after levodopa treatments and SMA stimulation was reported (Hamada *et al.*, 2008). Grey matter atrophy is linked to reduced postural stability and severe gait difficulties (Rosenberg-Katz *et al.*, 2013). Previous studies presented evidence that the primary motor area is involved in movement execution, whereas the SMC and its subregions play a key role in movement preparation.

Miyai *et al*. (2001) reported metabolic responses around medial aspects of the central sulcus during gait. Also the premotor cortex, parietal cortex, basal ganglia and the cerebellum contribute to gait (Fukuyama *et al.*, 1997; Hanakawa, Fukuyama, *et al.*, 1999).

The mesencephalic locomotor region (MLR) is located in the brainstem and an important contributor to locomotion. It is involved in the coordination between anticipatory postural adjustments (APA) and stepping (reviewed by Nutt *et al.,* 2011). Consisting of the cuneiform and subcuneiform nuclei and the PPN, the MLR contributes to descending pathways. They activate central pattern generator (CPG) in the spinal cord and therefore generate locomotor rhythms (Takakusaki *et al.*, 2004). Nevertheless, it is still a matter of debate, which of these nuclei are actually part of the MLR. However, especially the role of cholinergic structures, particularly the PPN, is attracting a lot of attention concerning the control of gait. It has reciprocal connections with different cortical and subcortical structures. It sends descending information to the pontomedullary reticular formation (PMRF) and to the spinal cord. Furthermore, is has connections to the basal ganglia and the thalamus (reviewed by Hamani *et al.*, 2007). Postural instability seems to be associated to cholinergic dysfunctions of the PPN. Alternatively to STN stimulation, the PPN can be used as a DBS target structure, considering its function in postural deficits (Stefani *et al.*, 2007).

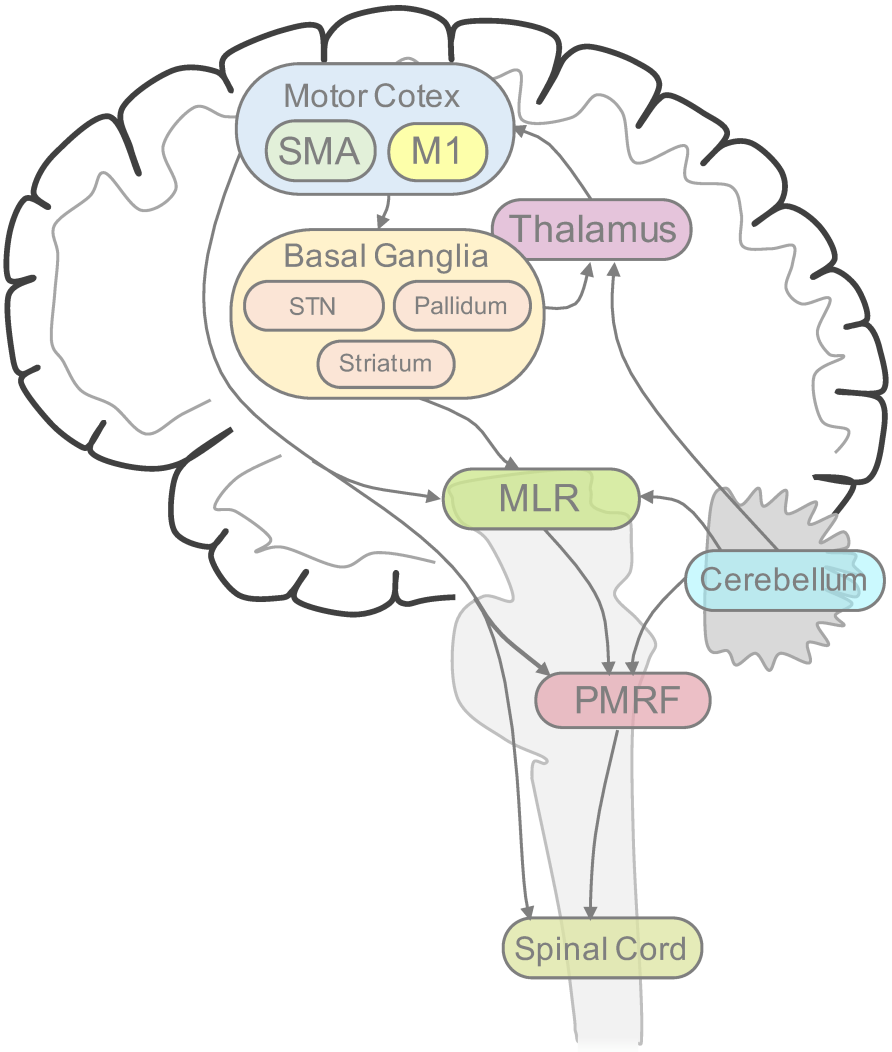

Figure 2: ***The locomotor network.*** A simplified visualization of the hierarchical locomotion concept and the involved brain areas is depicted. Central locomotion impulses originate from the premotor and supplementary motor cortices (SMA). They are transmitted to the spinal cord via the basal ganglia (BG) and modulated by the cerebellum. The mesencephalic locomotor region (MLR) and the pontomedullary reticular formation (PMRF) have integrative functions. Adapted and modified by Nutt, Horak and Bloem (2011).

1.2. Freezing of Gait

FOG is one of the most striking symptoms in advanced PD. Defined as *"brief, episodic absence of forward progression of the feet despite the intention to walk"* (Bloem *et al.*, 2004; Giladi and Nieuwboer, 2008), it is a disabling gait pattern that reduces mobility and compromises the quality of life (reviewed by Nutt *et al.*, 2011). FOG is associated with disease severity and often occurs in advanced stages of PD and other parkinsonian syndromes. FOG is rather heterogeneous and it might not even be a single symptom, but associated with a symptom

complex, consisting of knee trembling in place, shuffling, and complete akinesia (Nutt *et al.*, 2011). On the other hand, the aforementioned could also just reflect different severities of the same symptom.

To sum up, FOG has a huge impact on patient's lives and it is of great importance to uncover the underlying mechanisms to enable an adequate treatment.

1.2.1. Clinical characteristics

FOG occurs primarily while initiating gait, but also during continuous movements and turns in particular. Therefore, it can be addressed as an episodic interference of the locomotor circulatory system. FOG is not only observable in gait (reviewed by Vercruysse *et al.*, 2014), but also affecting upper limb movement, foot tapping, speech, and handwriting (Lewis and Roger A Barker, 2009; Nieuwboer *et al.*, 2009; Nutt *et al.*, 2011). Beside FOG however, other festination manifestations remain uncertain and are still being debated (Vercruysse *et al.*, 2014). The various occurrence of FOG related symptoms led to the conclusion, that the pathology includes dysfunctional mechanisms across neural regions supporting general functions (Nutt *et al.*, 2011). Furthermore, FOG seems to arise despite and independently of the other parkinsonian symptoms, indicating diverging underlying mechanisms. It responds to levodopa therapy which emphasizes the major role of dopamine depletion in the pathogenesis (Fietzek *et al.*, 2013). On the other hand, FOG even occurs in the "ON", medication and rehabilitation can alleviate the festination, but not to the same level as the other parkinsonian symptoms.

There are circumstances that can relieve FOG episodes, e.g. emotion, excitement, auditory cueing, and targets for stepping (Nieuwboer, 2008; Rocha *et al.*, 2014). In general, situations that divert the patients' attention from walking will promote FOG, whereas focusing on stepping will alleviate it (Nutt *et al.*, 2011). Even today, it is unclear how cueing improves gait, but is has been hypothesized that cues compensate the altered BG rhythms and focus the attention on the stepping process (Spaulding *et al.*, 2013). Ginis *et al*, (2018) categorized the roles of cueing as executive (attention focusing), stabilizing (prevention of deterioration), and preparatory (postural control).

1.2.2. Pathophysiology

Multifarious models of the pathophysiology of FOG have been introduced, which are mainly influenced by two important approaches (reviewed by Vercruysse *et al.*, 2014). First of all, FOG does not affect every patient suffering from PD. Therefore, the division into FOG and Non-FOG may help to find neuronal and behavioral markers. Secondly, FOG is associated to severe motor impairments and is affected by diminished cognitive resources. Most hypotheses include different types of pathological synchrony in the aspects of frequency, range and network, triggered by sensory inputs and modulated by cognitive and limbic processes. Since a disruption in many areas of the central nervous system (CNS) could be of importance to the pathogenesis, there are a few hypotheses, which will be outlined hereafter.

Abnormal gait pattern generation

Impaired gait and gait coordination could be the result of an aberrant output from the CPGs located in the spinal cord (Nutt *et al.*, 2011). FOG is associated with problems in the domains step timing (Bhatt, Pieruccini-Faria and Almeida, 2013), bilateral coordination (Plotnik, Giladi and Hausdorff, 2008), stride amplitude (Hausdorff *et al.*, 2003), rhythm and postural control, step scaling and gait symmetry (reviewed by Plotnik, Giladi and Hausdorff, 2012) even between the episodes. Therefore, FOG might occur because of generalized impairment of movement coordination. Plotnik *et al*. (2012) introduced a hypothesis claiming that those allegedly independent gait features have reciprocal connections, which drive the predisposed system into episodes of FOG.

Lack of automaticity of movement

Automaticity is the capacity to execute movements without paying attention to the task. The exercise of dual tasks while walking increases the likelihood of FOG episodes (reviewed by Heremans, Nieuwboer and Vercruysse, 2013). Vandenbossche *et al.* (2013) classify FOG as a de-automatization disorder, in which cognitive failure is insufficiently compensated by other networks. They further stated that cross talk between automatic processes within the BG is responsible for excessive thalamic inhibition and therefore leads to FOG. This theory is supported by studies implementing external cueing as a means to alleviate FOG episodes (Nieuwboer, 2008). FOG could evolve from a disrupted

motor loop of the BG-SMA. Gait imagery studies have been showing hypoactivation of the SMA during gait disturbances (Hanakawa, Katsumi, *et al.*, 1999). Automatic processes, such as walking, therefore become dependent on external stimuli that compensate via the cerebellum-dorsal premotor cortex to maintain the locomotion. Furthermore, increased MLR activity in FOG patients could be of compensatory help to preserve locomotion while the BG are failing.

Abnormal coupling of posture with gait

Freezers have an increased risk of falling (Bloem *et al.*, 2004). This indicates that generating a proper and stable upright posture is impaired. Anticipatory postural adjustments (APAs) are activations of lower limb muscle groups, which are important for maintaining a stable center of mass (Latash *et al.*, 1995). Repetitive APAs occur during Freezing episodes. Jacobs *et al.* (2009) suggest that there is a disruption in BG circuits for preparing motor programs which leads to the disability for coupling regular APAs to stepping movements. Furthermore, Freezers show an impaired postural control, most evident in the backward-forward progression (Heremans, Nieuwboer and Vercruysse, 2013). Posture preparation by the SMA and gait preparation by the motor cortex are coordinated by the PMRF (Schepens, Stapley and Drew, 2008). A breakdown in this coupling of posture and gait could result in FOG episodes.

Frontal executive dysfunction

Executive functions refer to a variety of capabilities, which are located in the frontal lobe of the brain. They act together in functions, e.g. set shifting, working memory and inhibition responses (for a review see Vandenbossche *et al.*, 2013). Those executive functions are damaged in people with PD and FOG (Amboni *et al.*, 2008). They are associated with disruptive processes in the fronto-striatal networks (Lewis *et al.*, 2003; Bartels and Leenders, 2008; Kostić *et al.*, 2012; Tessitore *et al.*, 2012) as decreased connectivity among BG and prefrontal and parietal regions during freezing (Shine *et al.*, 2013). In general, executive dysfunction seems to present an independent determinant factor of FOG (Vercruysse *et al.*, 2012). Since gait depends on attention and executive functions, FOG may be due to an affected cognitive gait control. Therefore, FOG might occur in situations that include obstacle avoidance or turns (Spildooren *et al.*, 2010). Changing an ongoing motor program requires motor, cognitive and

limbic input into the BG circuit. The lack of cognitive control and an inadequate compensation leads to a misbalance and a breakdown of the system.

Neural pathway model

The basal ganglia have an integrative function and allow parallel neural networks to pass and connect their information. This is tightly regulated in the domains of motor, cognitive, and limbic functions. In the parkinsonian dopamine depleted state, the natural balance of that system is lost. The consequence is an excessive inhibition of the thalamus and the PPN. This is associated with disproportionate synchronization within the BG output nuclei, and therefore, with an impairment of ascending and descending pathways resulting in reduction in motor activity and FOG episodes (Lewis and Roger A Barker, 2009).

1.2.3. Treatment

The exact pathophysiology of FOG remains unknown. FOG only shows variable response to levodopa therapy. The treatment is complicated, since it depends on various determinants, such as disease severity, provoking situations, dopamine sensitivity, and comorbidities (for a review see Nonnekes *et al.*, 2015). Levodopa therapy can be both: a curse and a blessing, by partly relieving symptoms (Schaafsma *et al.*, 2003; Ferraye *et al.*, 2008; Fietzek *et al.*, 2013) but sometimes being responsible for worsening it (Espay *et al.*, 2012). Therefore, FOG has recently become an indication for DBS of the STN or the PPN (Stefani *et al.*, 2007; Moreau *et al.*, 2009; Ferraye *et al.*, 2010). Furthermore, electrical spinal cord stimulation has gained some interest for improving gait in PD (Yadav and Nicolelis, 2017; Gilat *et al.*, 2018).

1.2.4. Bicycling in Parkinson's disease patients with FOG

FOG is a devastating symptom in advanced PD, which does not solely occur during gait. Therefore, it is even more interesting to notice that the ability to ride a bicycle is often preserved in patients with severe symptoms of FOG (Snijders, Toni, *et al.*, 2011; Snijders, van Kesteren and Bloem, 2012). This implies that walking and bicycling make use of partly different cerebral structures or pathways including the basal ganglia. To understand this phenomenon, it is crucial to examine specific similarities and differences between bicycling and walking.

According to the concept of the common core (Zehr, 2005), movements such as running, walking, and bicycling share common mechanisms. But even though there are some similarities in pace, muscle groups, and cognitive functions, bicycling and walking differ in sensorimotor input, postural control, and coordination. Walking requires a well-adjusted integration between motor commands and APAs, including bilateral weight shifts (Massion, 2003), which is impaired in patients with FOG (Vandenbossche *et al.*, 2013). Independently from one another, the legs carry out mutual stand and swing phases. Furthermore, bicycling and walking require different dynamic balance controls. PD patients show balance deficits in the backward direction, which is crucial for human upright walking (Carpenter *et al.*, 2004; Horak, Dimitrova and Nutt, 2005). A bicycle has two mechanically attached pedals, which enable the generation of adequate movement amplitudes and simplify coordination between both legs. This might reduce the input on the compromised cortico-thalamo-striatal motor circuit, economizing the limited resources. Storzer *et al*. (2016) found stronger *beta* power suppression in healthy participants during bicycling. They stated that the constant movement might be less sensitive to disruptions. It is very likely that this is an important aspect of the preserved ability to ride a bike. Another explanation focusses on bicycling as a provider of external, tactile, and auditory cues, which are known to be effective in overcoming BG circuitry failure (reviewed by Nieuwboer, 2008). Those cues are thought to activate the motor cortex via alternative pathways and therefore switch automatic motor programs to externally controlled processes (reviewed by Ginis *et al.*, 2018).

This still does not explain why initiating pedaling movements, compared to walking, is possible without problems. A recent study investigated FOG activity while walking with a “walk bicycle”. This device has a low seat without pedals, which requires stepping movements without the need for weight shifts (Stummer *et al.*, 2015). Interestingly, in most patients, FOG was alleviated, whereas in some patients FOG was induced. The authors discussed impaired APA, cueing, and cognitive overload to be competing factors in the opposite results. This highlights the assumption that there are various factors contributing to the occurrence of FOG.

Answering all those questions is of particular importance, since bicycling is a successful therapy in motor impairments (Ridgel, Vitek and Alberts, 2009) and improves cognitive capacity in PD patients (Ridgel *et al.*, 2011; Altmann *et al.*, 2015; Hazamy *et al.*, 2017).

1.3. Neural oscillations

The term “oscillations” describes rhythmic activity patterns, which either occur as a recurrent burst of single cells or synchronous oscillatory activity of larger neuronal groups (reviewed by Gatev, Darbin and Wichmann, 2006). Synchronized oscillatory activity is suggested to play a crucial role in the communication between different brain areas and synchronized firing of neurons is extremely important for information flow in large-scale networks (Schnitzler and Gross, 2005). Neural oscillations can be measured as rhythmic fluctuations at several scales (Buzsáki, Anastassiou and Koch, 2012), e.g. with electroencephalography (EEG) measurements or local field potentials (LFP) recordings (for a review see Jackson and Bolger, 2014). While EEG and LFP are different techniques, they are both thought to record similar neural oscillatory activity. Oscillations are characterized by defined frequencies (Pfurtscheller and Lopes da Silva, 1999) and today it is well known that oscillatory activity is pathologically altered in different neurological disorders (Herrmann and Demiralp, 2005; Gatev, Darbin and Wichmann, 2006). Regarding Parkinson’s disease (PD), there is major interest in the oscillations occurring in the *beta* band (Brown, 2006).

1.3.1. Measurement of neural oscillations

The current thesis focusses on the measurement of neural oscillation using EEG. EEG is a highly established non-invasive method that allows to record electrical potentials directly from the scalp (for a review see Henry, 2006; Jackson and Bolger, 2014). The surface electrodes are used for monitoring switches in electric potentials over time. Therefore, it records rhythmic electrical signals and enables the measurement of cerebral activity during movement exertion in the upright position (reviewed by Mehta and Parasuraman, 2013). Recording signals during movement, such as walking, is limited by movement artifacts (Islam, Rastegarnia and Yang, 2016). Recording LFPs is another and invasive technical possibility of

analyzing brain activity (Engel *et al.*, 2005; Buzsáki, Anastassiou and Koch, 2012). Electrodes are implanted therapeutically in the treatment of neurological diseases. Using those electrodes allows to record from deep brain structures, such as the BG.

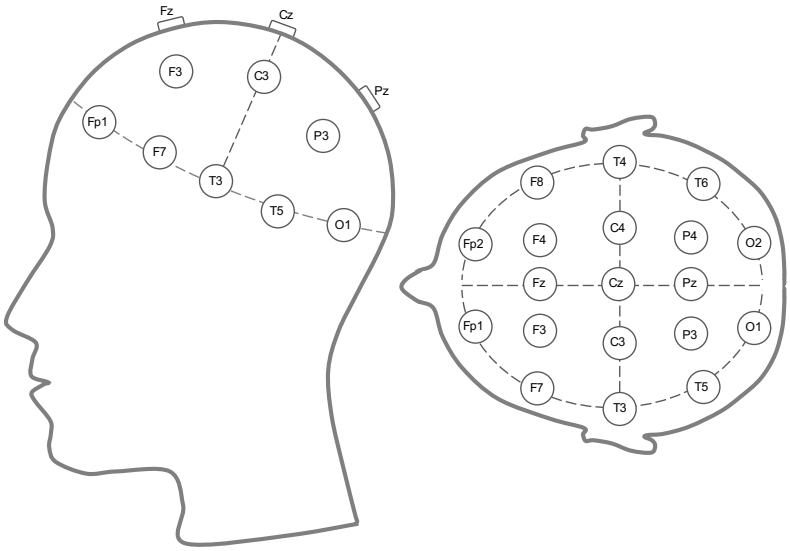

Figure 3: ***Schematic illustration of electroencephalogram (EEG).*** EEG is a well-established technique to measure neural oscillations**.** The electrical brain activity can be recorded with an 18-electrode cap according to the international 10 - 20 system (Jasper, 1958).

1.3.2. Analysis of neural oscillations

The electrophysiological signal recorded during the measurement can be decomposed and transformed by using the Fourier transformation, presenting phase and amplitude values as a function of frequency (Cohen, 2014). Analyzing those parameters provides important information about brain network connectivity.

There are five clinically and scientifically well-established frequency bands: *delta* (< 4 Hz), *theta* (4 - 7 Hz), *alpha* (8 - 12 Hz), the abovementioned *beta* frequency (13 - 30 Hz), and *gamma* (> 30 Hz). Slow frequency oscillations might be a representation of large-scale neuronal network communication whereas high frequency oscillation could reflect more local neuronal populations (Canolty and Knight, 2010).

1.3.3. Modulation of *beta* oscillations during movement

Beta oscillations in EEG and LFP recordings are mostly detected over the central "Rolandic" areas, the sensorimotor cortex. They are predominantly noticeable during preparation and performance of voluntary movement but also during motor imagery tasks or movement observation. *Beta* oscillations synchronize and cover large networks and therefore connect cortical and subcortical areas (for a review see Kilavik *et al.*, 2013). Central *beta* rhythms tend to desynchronize prior and during voluntary movements. It is reported for various body parts, such as isolated foot (Pfurtscheller *et al.*, 1997), finger (Stancák and Pfurtscheller, 1996), and shoulder movements (Stančák *et al.*, 2000), and lasts for the whole period of movement. It decreases during motor preparation and imagery (Pfurtscheller and Neuper, 1997; Müller-Putz *et al.*, 2007), treadmill walking (Severens *et al.*, 2012), and robot aided walking (Wagner *et al.*, 2012). It increases when movement is no longer performed (Neuper and Pfurtscheller, 1996; Müller-Putz *et al.*, 2007) or when contraction or posture becomes stable. Elevated *beta* oscillations at rest or after movement are seen as the representation of an idling state of the motor cortex (Pfurtscheller, Stancák and Neuper, 1996). Engel and Fries (2010) propose that *beta* oscillations in general play a major role for the maintenance of the actual motor state.

1.3.4. Neural oscillations in Parkinson's disease

In animal models of PD an irregular discharge of neurons in the STN, the GPe, and the GPi was reported (reviewed by Hammond, Bergman and Brown, 2007). This breakdown of the physiological separated firing rate of individual neurons leads to neuronal synchrony that can be recorded in the BG and cortex (Wichmann, 2019). In the dopamine depleted parkinsonian state this is observable in elevated *beta* band (13 - 35 Hz) synchronization in the BG. As mentioned before, exaggerated *beta* band activity is linked to slowed movements and therefore, associated with bradykinesia. Interestingly, the *gamma* band amplitude is abnormally coupled to the *beta* activity and is also linked to bradykinesia (Wichmann, 2019). Even stimulation at *beta* frequencies applied on the cortex and STN electrodes results in slower movements and worsens parkinsonian symptoms (Fogelson *et al.*, 2005; Chen *et al.*, 2007). Cortical *beta* oscillations are most likely the driver of increased *beta* band activity in the BG

(Lalo *et al.*, 2008; Litvak *et al.*, 2011; Sharott *et al.*, 2018). This driving mainly affects the upper *beta* band whereas the lower *beta* band in the STN is most exaggerated and best suppressed by stimulation and levodopa treatment (reviewed by Oswal, Brown, and Litvak, 2013).

Previous EEG studies found high *beta* band oscillatory activity in frontal electrodes related to FOG (Scholten, Govindan, *et al.*, 2016). Shine *et al*. (2014) introduced increased *theta* frequency bands during FOG as a conflict associated signal. They even observed increased oscillatory activity in the *beta* band in parietal regions during transition from walking to freezing episodes and interpreted their results as miscommunication between frontal areas and the motor cortex. Storzer *et al.* (2017) reported *beta* synchronization around 18 Hz in the STN in known Freezers even in the absence of FOG, indicating a certain predisposition for FOG episodes.

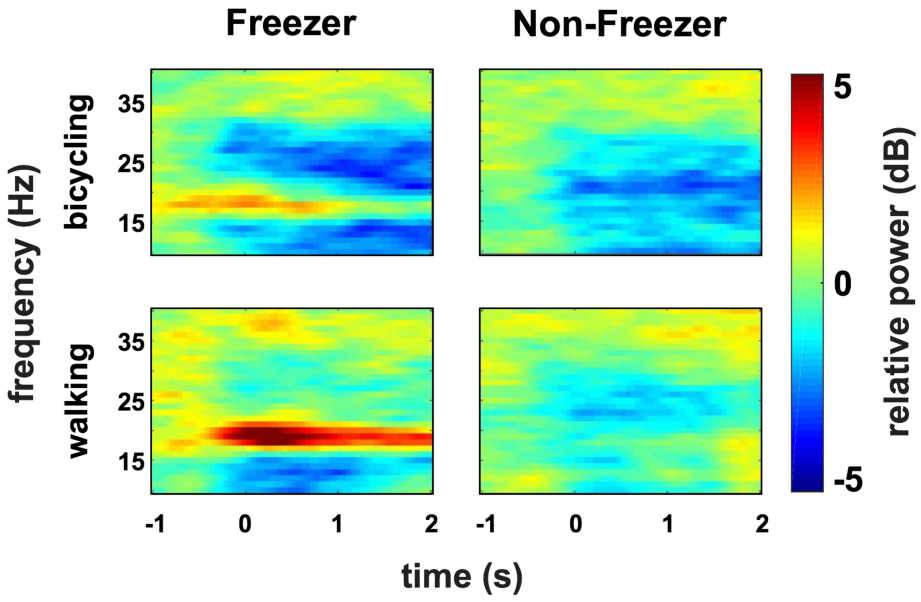

Figure 4: Beta power modulation during movement initiation in Freezers and Non Freezers. The grand average plot is showing changes of *beta* band activity during the initiation of walking and bicycling in the STN. Recordings were done the day after implantation of electrodes for deep brain stimulation (DBS). Power decreases just prior to the movement (t =0) and remains suppressed for the entire movement cycle. Bicycling is associated with stronger *beta* power suppression than walking. Furthermore, there is a Freezing specific 18 Hz signal during walking and bicycling. Adapted from Storzer *et al.*, (2017).

2. Aims

The aim of the present study was to examine movement associated cortical oscillatory activity in PD patients with and without FOG.

Specifically, the goal was to understand why bicycling and walking, two rather similar forms of movement, are impaired to different extents in patients suffering from PD with and without FOG. Recently, Storzer *et al.* (2017) reported a freezing specific 18 Hz oscillatory signal in LFP recordings from the STN. This was the first time, a narrow band oscillatory signal was demonstrated in direct relationship to FOG. Consequently, that raised the question of the signal's origin. Hence, it is of great importance to localize the source of pathological synchronization and to examine, if this narrow band oscillation can only be seen in the STN or if it can also be observed in the motor cortex. Getting to the bottom of this question would deliver deep insights into the connection between the motor cortex and the BG. Furthermore, it would contribute to the understanding of FOG and thus, potentially support the development of new therapeutic approaches.

3. Publication

LETTERS: NEW OBSERVATIONS

Freezing of Gait Does Not Modulate Beta Oscillations in Mesial Cortical Motor Areas

Many patients with Parkinson's disease (PD) and freezing of gait (FOG) are still able to ride a bicycle easily.[1] Recently, Storzer and colleagues[2] described an increase of oscillatory activity ~18 Hz in local field potential (LFP) recordings from the subthalamic nucleus characteristic for patients with FOG. Here, we examined movement-associated cortical oscillatory activity in freezers and nonfreezers during bicycling, walking, and turning using mobile electroencephalography.

We studied 20 PD patients with FOG (freezers), 13 PD patients without FOG (nonfreezers), and 16 age-matched healthy controls. Each measurement started with a rest measurement, that is, sitting or standing followed by sequences of movement (bicycling or walking) to investigate movement initiation. After each walking sequence, participants performed 180° turns. Cortical beta activity (13-35 Hz) was compared between the 3 groups. Power changes were expressed relative to baseline, and analyses were focused on the Cz electrode. To specifically investigate FOG-related differences, turns with and without freezing were compared in freezers. To provide evidence for negative findings, we computed the Bayes factor for selected comparisons.[3] By convention, a Bayes factor <0.33 is considered substantial evidence in support of the null hypothesis[4] (see Supplementary Material for methodological details).

The analysis of gait parameters revealed impairments of walking in freezers (see Supplementary Table 1). However, a linear mixed model revealed no effect of group, χ^2 (2) = 0.81, P = .67; that is, freezers did not show altered cortical beta power. The Bayes factor for the main effect of group was 0.22, providing evidence for equal beta power across groups. When comparing cortical beta power in freezing and nonfreezing turns, the Bayes factor was 0.32, providing evidence for equal power in both conditions. No narrowband oscillation at ~18 Hz was observed in any group or condition, but broad-band suppression of power in the beta band was evident during all types of movements for all groups (Fig. 1A). We detected a main effect of movement type on beta power, χ^2 (2) = 22.34, P < .001. Post-hoc pairwise testing showed a stronger beta power suppression in bicycling than in walking (t-ratio = −3.55, P = .002) and turning (t-ratio = −4.76, P < .001), but no difference between walking and turning (t-ratio = −1.23, P = .44; Fig 1B).

With these findings, we replicated that bicycling and walking are associated with suppression of cortical oscillatory activity in the beta band, which is stronger in bicycling compared to walking.[5] Our analyses revealed no differences in oscillatory activity in the beta band between groups, not even in the presence of freezing. As we could not detect a cortical equivalent of the characteristic, subthalamic ~18 Hz signal reported previously, our findings indicate a subordinate role of the cortical motor areas in the generation of FOG. These results instead may suggest a wholly subcortical generation of the reported ~18 Hz signal.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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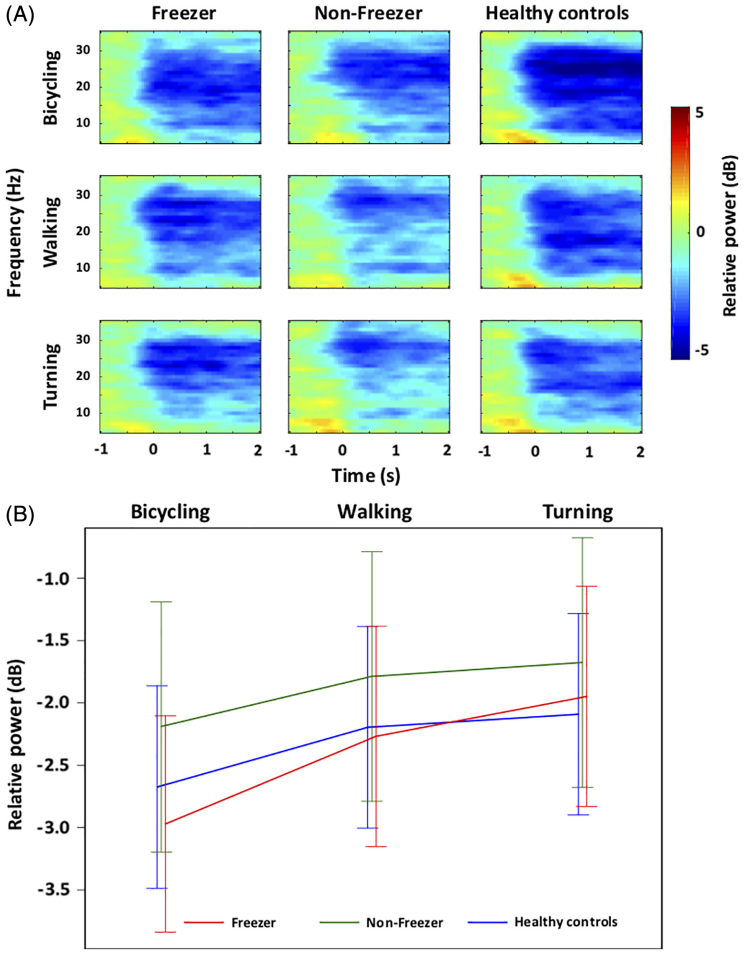

FIG. 1. (A) Group average time frequency representations of power changes relative to baseline (dB; color-coded) in freezers, nonfreezers, and healthy controls, time-locked to movement initiation (t = 0). (B) Representation of power differences (dB) relative to baseline during movement initiation in freezers, nonfreezers, and healthy controls. [Color figure can be viewed at wileyonlinelibrary.com]

4. Methods

4.1. Participants

20 PD patients with FOG (65.53 ± 7.27 years) participated in this study, 13 PD patients without FOG (61.67 ± 8.14 years), and 16 age-matched healthy controls (63.29 ± 7.24 years). One patient terminated the measurement after 2 minutes of continuous movement due to fatigue. Data of one patient had to be excluded due to severe movement artifacts in the EEG data. Exclusion criteria were dementia, depression, and acute comorbidity affecting the gait. Patients were tested OFF medication (washout period > 12 h) and OFF DBS (> 30 min). Motor state and history of FOG was assessed with Part III of Unified Parkinson's Disease Rating Scale (UPDRS, Goetz *et al.*, 2008) and the Freezing of Gait Questionnaire (FOG-Q, (Giladi *et al.*, 2000). First, Freezing was defined with the Timed Up and Go Task (TUG, Richardson, 1991) and secondly, referring to Snijders *et al*. (2012), by four rapid full turns. Cognitive state was assessed using the Mattis Dementia Rating Scale (MDRS) and the Frontal Assessment Battery (FAB). The study was approved by the local ethics committee (study number: 4294) of the Medical Faculty of the Heinrich Heine University Düsseldorf and was performed in accordance with the Declaration of Helsinki (World Medical Association, 2013). All participants gave their prior written informed consent.

Patient	Sex/ Age	Disease duration (years)	subtype	UPDRS III OFF scores	DBS duration (months)	Levodopa equivalent dose (mg/day)
FOG_1	W55	24	Hypokinetic-rigid	41	108	440
FOG_2	M70	17	Hypokinetic-rigid	60	76	830
FOG_3	W71	17	Tremor-dominant	67	160	560
FOG_4	M67	14	Hypokinetic rigid	43	25	1430
FOG_5	M72	7	Equivalent	60	4	690
FOG_6	M74	22	Hypokinetic-rigid	42	15	660
FOG_7	M56	15	Hypokinetic-rigid	49	14	1660
FOG_8	M62	9	Equivalent	42	5	520
FOG_9	M53	15	Hypokinetic-rigid	26	36	1060
FOG_10	M64	25	Hypokinetic-rigid	53	4	1000
FOG_11	M72	18	Equivalent	61	90	680
FOG_12	W63	27	Tremor-dominant	51	57	430
FOG_13	W74	14	Hypokinetic-rigid	39	31	n.a.
FOG_14	M58	8	Equivalent	58	4	680
FOG_15	W63	9	Hypokinetic-rigid	60	4	580
FOG_16	M75	8	Tremor-dominant	65	84	300
FOG_17	M67	8	Hypokinetic-rigid	39	12	1680
FOG_18	M56	25	Hypokinetic-rigid	43	78	480
FOG_19	W68	18	Hypokinetic-rigid	30	42	1520
FOG_20	W72	17	Tremor-dominant	44	72	220
N-FOG_1	M58	14	Equivalent	49	35	1410
N-FOG_2	M73	9	Hypokinetic-rigid	25	3	940
N-FOG_3	M58	18	Hypokinetic-rigid	36	36	1310
N-FOG_4	M64	12	Tremor-dominant	52	79	80
N-FOG_5	M63	10	Hypokinetic-rigid	41	25	1110
N-FOG_6	M76	6	Tremor-dominant	34	4	480
N-FOG_7	M60	15	Hypokinetic-rigid	39	43	1360
N-FOG_8	M48	10	Hypokinetic-rigid	51	25	460
N-FOG_9	M68	12	Equivalent	42	4	480
N-FOG_10	M63	6	Equivalent	49	3	860
N-FOG_11	M56	11	Tremor-dominant	46	50	350
N-FOG_12	M52	4	Equivalent	31	22	330
N-FOG_13	M64	6	Hypokinetic-rigid	34	4	300

Table 1: ***Demographic and clinical characteristics of Freezers and Non-Freezers.***
FOG = Freezer, N-FOG = Non- Freezer, UPDRS = Unified Parkinson's Disease Rating Scale, DBS = Deep brain stimulation.

4.2. Experimental design and procedure

Participants either started with bicycling or walking. The succession of conditions was pseudorandomized and counterbalanced through the subjects. Every condition began with a two-minute baseline rest period, i.e., sitting or standing. To study movement initiation and termination, participants completed an alternating sequence of 10 s of movement, i.e., bicycling and walking, and 10 s of rest. For a detailed description see Storzer *et al*. (2016, 2017). In case of walking, participants had to perform an 180° turn that was cued by an acoustic signal 10 s after movement termination and followed by an additional rest period of 10 s. The sequence was repeated for 30 times. The measurement was completed after two minutes of continuous movement.

Bicycling took place on a stationary bicycle. Walking was performed on a 4-m-long gait analysis plate (Zebris FDM 2 in combination with Noraxon MyoPressure MR3.8, USA) enabling the analysis of spatiotemporal gait parameters. Continuous walking was performed in a 50 m long hallway.

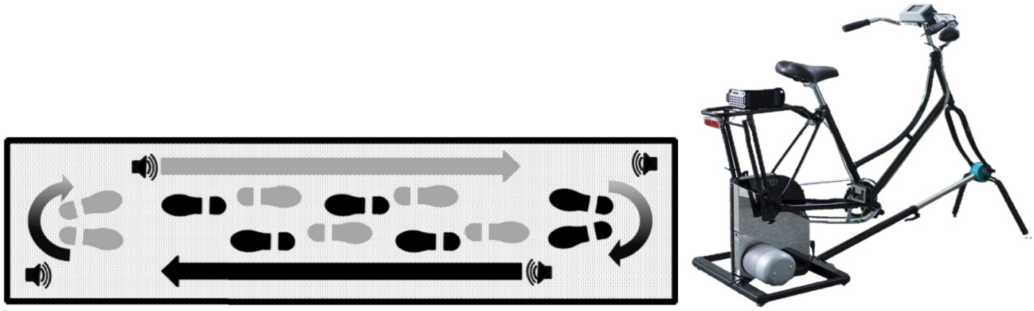

Figure 5: ***Experimental Setup.*** Depicted is a schematic illustration of the paradigm which was introduced by Storzer *et al.* (2016, 2017). Patients started with 2 minutes baseline period, either while sitting on the bike or standing. This was followed alternating by 10 seconds of movement, either pedaling or walking on a special gait analysis plate, again followed by 10 seconds of rest. In the walking condition the participants had to fulfil a turn in between. In total, 30 acoustically cued initiation, termination, and turning movement were captured with an EEG. The bicycle condition took place on a simulator consisting of a Dutch-style bicycle on an ergometer (see Gratkowski *et al.*, (2017) for details).

Participants were asked to bicycle and walk at their own convenient cadence and uniform across conditions. Cadence of both conditions was exploited as revolutions per minute (rpm) and strides per minute (spm). First, turns among the groups were compared to investigate cortical differences followed by the analysis of turns with and without freezing episodes in the group of patients with FOG.

Two independent raters evaluated the turns of the patients in three categories (1 = freezing, 2 = non-freezing, 3 = uncertain).

4.3. Data acquisition and preprocessing

As in Storzer *et al.* (2016, 2017) data were recorded with a sampling rate of 2048 Hz with a transportable EEG amplifier (Porti amplifier, TMSi, Enschede, Netherlands) and the open software packages OpenBCI and Svarog (Durka *et al.*, 2012). The amplifier was attached to a waist belt. EEG was measured with an 18-electrode cap (TMSi, Enschede, Netherlands) in accordance with the international 10 - 20 system (Jasper, 1958). A water-based ground electrode integrated in a wristband was used and EEG signals were referenced against an average reference. Furthermore, electromyographic (EMG) data of three leg muscles (*tibialis anterior*, *biceps femoris* and *rectus femoris*) were collected by bipolar surface EMG electrodes placed 2 cm apart on the muscles. Movement artifacts were reduced by using shielded cables for EEG and EMG. Bilateral goniometers were used to track the knee angle. Data were analyzed with the Matlab-based FieldTrip toolbox (Oostenveld *et al.*, 2011) using Matlab R2015b (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 eliminate power line noise. Data were visually examined to identify movement artifacts. Time periods including artifacts were discarded. Data were decomposed by means of independent component analysis (ICA). Components displaying the spatial or temporal signs of eye blinks were excluded and the remaining components projected back to the scalp channels. Reference-free EEG data were obtained using the Hjorth transform as a spatial filter (Hjorth, 2018).

4.4. Initiation and termination of movement

Power spectra were calculated for the baseline rest condition, i.e., sitting and standing. Data were separated into 1 s fragments with an overlap of 50 %. The fast Fourier transform (FFT) was calculated for every segment by means of a single Hanning taper and spectra averaged over segments. Movement initiation, termination, and turning were studied by calculating time-frequency decomposition with a sliding Hanning window of 1 s duration and a step size of

0.005 s. Power alterations were expressed as power change in decibel (dB) relative to the baseline rest condition. To determine movement initiation and termination the goniometer signal was used as described in Storzer *et al*. (2016). Afterwards, the accuracy of the selected initiations was verified visually and adapted, if necessary (0.4 % of initiations and 2 % of terminations).

5. Statistics

Analyses were focused on the Cz electrode because of the prevalence of oscillatory activity being localized to pre- and postcentral gyri, premotor cortices, and SMA (Wieser *et al.*, 2010a; Gwin *et al.*, 2011; Wagner *et al.*, 2012; Jain *et al.*, 2013). Power changes during movement relative to the baseline rest period were analyzed in the *beta* band (13 - 35 Hz). Baseline was defined from -2 to -1.2 s before initiation (Heinrichs-Graham *et al.*, 2014). In line with Storzer *et al.* (2016, 2017), relative *beta* power changes locked to movement initiation and turning were averaged in the time window from -0.5 s to 1 s. Power was equally averaged in the time window from 0.5 s to 2 s around movement termination.

Evaluating freezing episodes during turns the interrater reliability was assessed using Cohen`s kappa (κ)(Cohen, 1960; Landis and Koch, 1977). Differences in baseline-corrected power, baseline log power, and cadence were analyzed by fitting linear mixed – effects models using the package lm4e 1.1 – 1.3 (Bates *et al.*, 2015) for R version 3.4.0. Thus, data from all participants could be included as linear mixed – effects model compensating for missing data.

In each model, the fixed effect structure was defined as the 2-level factor movement type (*bicycle, walking*) and the 3-level factor group (*freezer, non-freezer, healthy control*). Factors were sum coded and all interactions were included in the model. Comparing *beta* power changes between turns with and without freezing in the group of freezing patients, random intercepts and random slopes for patients were included.

Factors were sum coded and we identified the normality of residuals by visual inspection. The Wald Chi square test, integrated in the ANOVA function of the car package 2.1 – 4 (Fox and Weisberg, 2011) was assessed to obtain *p*-values.

Interactions were examined with post-hoc test using the R package lsmeans 2.36-3 (Lenth, 2016). Finally, Turkey correction was applied for multiple testing.

All other variables were tested with IBM SPSS statistics, version 24 (IBM Deutschland GmbH, Ehningen, Germany). The Kolmgorov-Smirnov test was applied to check for normality of data distribution. Two–sided paired samples t-tests were utilized in case of normally distributed data. Otherwise, the non-parametric Wilcoxon signed-rank (Mann Whitney test) test was used. For all tests, the significance level was set to 0.05. To correct for multiple comparison, the adaptive Bonferroni correction (Holm, 1979) was used.

6. Results

6.1. Behavioral data

Groups showed differences in behavioral patterns. Using Cohen's kappa (κ) for evaluating turns an interrater reliability of 0.86 was achieved. Cadence was significantly affected by movement (β = -3.20, p < 0.001) reflecting a higher cadence in bicycling than in walking. There were significant interactions in the bicycling condition reflecting that patients with FOG bicycle with lower cadence than healthy controls (β = -5.15, p < 0.01). Furthermore, an interaction in the walking condition was found revealing that patients with FOG were walking with higher cadence than patients without FOG (β = -5.64, p < 0.01).

Parameter	FOG	Non-FOG	Healthy Controls	p-value
TUG (s)	30.28 ± 26.20	14.75 ± 3.91	10.71 ± 1.48	< 0.001
TURN (s)	15.92 ± 18.53	4.10 ± 1.13	2.58 ± 0.79	< 0.001
Step length (cm)	70.24 ± 36.09	112.00 ± 20.50	127.15 ± 11.85	< 0.050
Pace (km/h)	1.99 ± 1.11	3.18 ± 0.61	3.89 ± 0.37	< 0.001

Table 2: ***Behavioral data, including Timed Up and Go task (TUG), full turns (TURN), step length, and pace of all groups.*** Freezers showed impairments in all conditions, needed longer to fulfill the gait course, and walked slower with smaller steps. FOG= Freezer, Non- FOG = Non- Freezer.

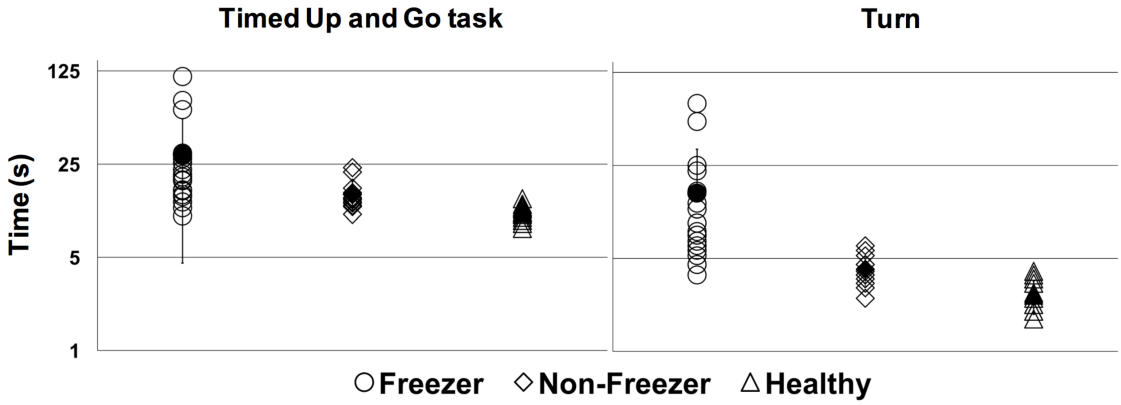

Figure 6: ***Behavioral parameters during gait.*** Walking task (left) and 360° turns around body axis (right). PD patients with FOG needed more time to complete the task reflecting impaired motion sequences (TUG: χ^2 = 24.395, p < 0.001; turn: χ^2 = 30.201, p < 0.001).

6.2. *Beta* power changes locked to movement initiation

Relative power changes locked to movement initiation were apparent in the *beta* band both for bicycling and walking for all groups. The mixed model revealed a significant effect of movement type (β = -0.37, p < 0.001) reflecting a stronger *beta* power suppression in bicycling than in walking but no difference between walking and turning (β = 0.11, p > 0.05). There was neither a difference between Freezers and Non-Freezers (β = -0.11, p > 0.05) nor between Non-Freezers and healthy controls (β = 0.29, p > 0.05). Furthermore, there were no differences in cortical activity between turns with FOG and turns without FOG (β = 0.66, p > 0.05).

6.3. *Beta* power changes locked to movement termination

Time frequency representations showed a *beta* power increase relative to the baseline rest condition (*beta* rebound) for bicycling and walking in all groups. There was no difference neither between movement types (β = 0.02, p > 0.05) nor between groups (*Freezers* vs. *Non- Freezer* (β = 0.12, p > 0.05), *Non–Freezer* vs. *healthy controls* (β = 0.08, p > 0.05)).

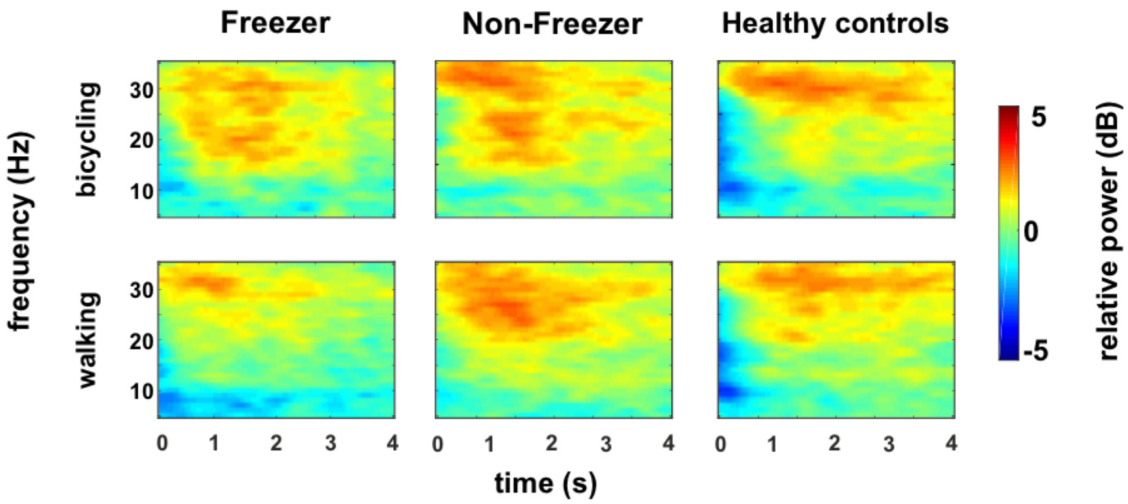

Figure 7: ***Time frequency representation of movement termination in Freezers, Non-Freezers, and healthy controls.*** Grand average time-frequency plots showing movement termination (t = 0). As reported in Arens et al. (2018), there was no difference in *Beta* power related to movement initiation. Furthermore, there was no difference in *Beta* power related to movement termination (unpublished data).

6.4. Baseline *Beta* power

As power changes relative to the baseline rest condition, i.e., sitting and standing, were compared, it was also tested for baseline differences in general. Baselines were found to be different between sitting and standing (β = 0.47, p < 0.001) reflecting less *beta* baseline power during upright posture.

7. Discussion

This thesis concentrated on the different cortical oscillatory activity observable in PD patients with and without *Freezing of gait* during bicycling and walking. Therefore, two main questions were investigated. First, is there a difference in the activity of the motor cortex during freezing episodes, as it was reported for the STN previously? Secondly, this work wanted to reveal the mechanisms, why Freezing affects bicycling less than walking, even though the two movements are similar. In line with earlier works, a stronger *beta* power suppression was found during bicycling than during walking. But most interestingly, there were no differences in the activity of the motor cortex during Freezing episodes, which seems to be counterintuitive in the clear presence of Freezing related gait difficulties. Hereafter, some possible explanatory approaches will be discussed.

7.1. Baseline differences

The “awake resting state” is a commonly used experimental condition, which is typically accepted to mark baseline brain activity. As such, it defines deviations from the baseline as activation or deactivation (Gusnard and Raichle, 2001). The body position is meaningful for various cognitive processes and can change the sensory threshold. Therefore, orthostatic variation alter both motor function of lower and upper extremity (Cuisinier, Olivier and Nougier, 2007), and cognitive functions, such as speech (Stone *et al.*, 2007) and anxiety (Lipnicki and Byrne, 2008). Usually, actions like sitting and standing in upright position are taken for granted. The elementary processes are autonomic and controlled without great attentional demand. Interestingly, earlier studies have shown that the abovementioned activities indeed often need attentional or cognitive control (reviewed by Woollacott and Shumway-Cook, 2002). In this study, while comparing *beta* power between sitting and standing, a baseline difference was realized that was not seen in the preceding studies. Here, standing was associated with lower *beta* power compared to sitting. Lower *beta* power is usually associated with an active state of the sensorimotor cortex and enhanced cortical excitability (Neuper and Pfurtscheller, 2001). Standing may be regarded as a simple behavior, but the preservation of postural balance with an unsupported trunk is attentional demanding and involves the processing of

various sensory signals (Nashner, 1976; Woollacott and Shumway-Cook, 2002). This might result in a more active cortical motor state in standing than sitting. Furthermore, there are postural responses continuously occurring during motionless stance. They are associated with slow negative shifts (N1) in EEG amplitudes (Varghese *et al.*, 2015) and evoke from proprioceptive and cutaneous efferents from the lower extremities (Dietz, Quintern and Berger, 1985). This physiological negativity seems to originate in the SMA and shows the cortical involvement during quiet, undisturbed stance (Maki and McIlroy, 2007; Marlin *et al.*, 2014). It has to be noted, that a lot of the studies examining postural stability work with imperative stimuli, warning cues and external perturbations, which were not applied during our baseline measurement. Therefore, comparisons have to be made with caution.

Furthermore, increased arousal while standing in an upright posture could be due to hemodynamic reactions and higher catecholamine levels. During standing the venous pressure is reduced, resulting in a higher heart rate. So far, there have only been studies comparing heart rate and the *beta* band activity from moving from supine position to an upright sitting posture (Chang *et al.*, 2011), but not between quiet sitting and quiet standing.

Baseline activity is important, because it raises the question of an absolute *beta* power threshold. Heinrichs-Graham *et al*. (2016) proposed a model, claiming that the PMC has an individual *beta* power threshold that must be undercut to enable movement. In the context of our results, it raises the question, if walking initiation solely requires less *beta* power suppression because of an already lower level of baseline *beta* power. Here, relative *beta* power was examined instead of absolute *beta* power to have comparable results with the preceding studies of our group and did not address this specific question.

7.2. Stronger *beta* suppression in bicycling

The importance of different oscillatory activity in the *beta* band during movements, such as bicycling and walking, was shown before. In line with our own work and previous studies (Bulea *et al.*, 2014; Storzer *et al.*, 2016), we replicated that bicycling and walking are associated with a *beta* power decrease over motor cortex and SMA locked to movement initiation. Since decreased *beta*

power seems to be somehow related to the elevated cortical excitability (Seeber *et al*., 2014), the stronger *beta* power suppression during bicycling has an important role for the functional difference of the types of movement. It is very likely, that this is one of the main features of the pathophysiological mechanisms that explain why the ability to ride a bike is still preserved in patients with FOG. The stronger *beta* power suppression was now observed regardless of the population and the point of recordings, i.e. young and older healthy participants, Freezers and Non-Freezers, cortex or BG. Therefore, bicycling induces a prevalent reduction of *beta* power in the entire motor network.

A main feature could be the more continuous movement of bicycling that goes along with a regular motor output and with an uninterrupted feedback to both feet. This is reflected by the stronger *beta* power suppression. Indeed, during continuous movement *beta* activity remains suppressed (Erbil and Ungan, 2007; Gwin and Ferris, 2012), while it rebounds during isometric motion (Gwin and Ferris, 2012). In comparison to walking, bicycling requires simple limb movements only. This characteristic reduces the influence on the motor system. On the other hand, a stronger desynchronization can be an indicator for task complexity with a greater need for processing information (Pfurtscheller and Lopes da Silva, 1999). Furthermore, previous studies of our group reported that walking was associated with a stronger phase-dependent power modulation than bicycling in young healthy participants (Storzer *et al.*, 2016) indicating a reduced need of cortical control of ongoing movements. The authors even reported a stronger *alpha* power suppression during walking, which is linked to attention demanding processes, and underlines the high impact on the motor system.

7.3. No Freezing specific cortical differences

FOG occurs most frequently when patients begin to walk, pass narrow passages, fulfill turns, or approach a destination (Giladi *et al.*, 1992). Environmental, emotional, and cognitive influences have further remarkable effects on FOG (Nutt *et al.*, 2011). It combines motor assignments with cognitive and emotional tasks and also requires motor preparation and execution (Takakusaki, Tomita and Yano, 2008). Therefore, our paradigm was perfectly suitable to examine FOG episodes. Interestingly, neither at the initiation nor at the termination of movement

we could observe any differences in cortical oscillatory *beta* activity between groups. This was unexpected in the presence of clear behavioral differences in gait parameters. Freezers show abnormal spatiotemporal gait pattern even in the absence of FOG. This includes greater gait variability (Hausdorff *et al.*, 2003), smaller steps at higher cadence (Nutt *et al.*, 2011), accelerated muscle activations (Nieuwboer *et al.*, 2004), impaired bilateral coordination (Plotnik, Giladi and Hausdorff, 2008), and compromised postural adjustments prior to gait initiation (Jacobs *et al.*, 2009).

The cortex has a major role in various gait related functions. For example, the control of the lower limbs is driven by the precentral gyrus, coordinated tasks are regulated by the premotor area and the SMA. Motor planning takes place in the dorsolateral prefrontal cortex and integrative tasks are processed in the pre-SMA (reviewed by Lewis and Shine, 2016). There is some evidence that connects cortical areas with the pathogenesis of FOG. Scholten *et al.* (2016) found synchronization from 13 - 30 Hz over the prefrontal cortex related to upper limb freezing. But patients were tested in the stimulation “ON” state and correlation of upper limb freezing and FOG is a matter of debate anyways (Barbe *et al.*, 2014). Interestingly, Tinkhauser *et al*. (2019) reported electrophysiological differences in *beta* band activity between upper and lower limb movements. Thus, results cannot be easily translated. Recently, Günther *et al.* (2019) did not find significant changes during FOG episodes, irrespective of the frequency band. Other studies have reported prefrontal abnormal *theta* oscillations during different gait task (Shine *et al.*, 2014; Handojoseno *et al.*, 2015). On the other hand Fabre *et al.* (1998) found a normal frontal perfusion in PD patients with FOG using single photon emission tomography (PET) indicating that Freezing is not related to severe frontal lobe dysfunction. Furthermore, Maidan *et al.* (2019) found FOG not to be associated with impairments in the ventral attention network, but in the dorsal attention network.

As mentioned above, patients in the present study exhibited alterations in pace, cadence, and step length, which is assumed to play a crucial role in the generation of FOG episodes (Plotnik, Giladi and Hausdorff, 2012). Reduction in step length stems from a malfunction between SMA and the BG (Iansek, Huxham and McGinley, 2006; Chee *et al.*, 2009). The so called sequence effect leads to

a progressive step length reduction culminating in FOG episodes (Chee *et al.*, 2009). Especially an underactivation of the SMA is reported to be associated with FOG (Hanakawa, Katsumi, *et al.*, 1999; Snijders, Leunissen, *et al.*, 2011). As no cortical differences during start-hesitations were found, the analysis was expanded and focused on turns among groups. But even though turning is the strongest trigger for FOG episodes, FOG was not observable at every turn the patients completed. As PD in general, FOG is often asymmetrical, compromising one foot or being evoked by turning into one direction. In the following the focus lay on the group of Freezers only, comparing turns with and without clear signs of FOG. But even in the unquestionable presence of FOG, there was no difference in *beta* band activity in the motor cortex. Even though main effects of the SMA would be seen more in frontal electrodes, activity of the Cz electrode would also reflect activity of the SMA (Lang *et al.*, 1991). Therefore, freezing specific effects would have been expected, if FOG was a direct result from frequency specific malfunction of the SMA or the PMC. Furthermore, there are only few cases reported, in which patients with isolated SMA lesion developed FOG symptoms (Hashimoto, 2006).

7.4. Lack of motor drive or disruption of normal motor output?

Even today, it is not clear, if FOG occurs as a lack of motor drive or as a blockage against a normal motor output. PD is associated with exaggerated synchronized *beta* band activity in the STN (Brown, 2006; Hammond, Bergman and Brown, 2007; Jenkinson and Brown, 2011; Singh *et al.*, 2013), which is linked to bradykinesia (Fogelson *et al.*, 2005; Pogosyan *et al.*, 2009). Following Storzer and colleagues (2017) on the 18 Hz signal from LFP recordings in the STN, raises the question: What is its functional role and why is this activity not seen it in the motor cortex? Answering those questions could shed light into the darkness and contribute to find diagnostic and therapeutic approaches.

There are two possible ideas about the origin of the pathological signal: First, it could originate from the motor cortex. The motor cortex of course plays a key role in the generation of locomotion. The STN receives various cortical and subcortical information (Temel *et al.*, 2005). The integrated information is being

sent to the SMA, primary motor, and ventral premotor cortex by passing the ventrolateral thalamic nuclei (Hoover and Strick, 1993). There is strong cortico-subthalamic coherence between mesial areas of the motor cortex and the STN being strongest between the SMA and the STN. It is of special relevance, that the STN shows neuronal synchronization in the cortical *beta* rhythms (Sharott *et al.*, 2018). Of course, it is possible that a narrow oscillatory band originates in the motor cortex and is passed to the BG where it can be recorded as LFP. On the other hand dopamine depletion could change the control of the BG over thalamo-cortical loop causing oscillations that are transmitted to the BG via the cortex (Pavlides, Hogan and Bogacz, 2015). Furthermore, the lack of dopamine can trigger an imbalance between the hyperdirect and direct pathway in favor of the hyperdirect pathway, also resulting in oscillations (Leblois *et al.*, 2006). But since no cortical difference in the clear presence of major FOG episodes could be found, it is rather unlikely, that it is an oscillation with origin in the motor cortex.

Previous work centered around two main models describing the origin of subcortical oscillatory activity. One idea includes models for the striatal origins of *beta* oscillations in LFP recordings due to dopamine depletion and increased cholinergic drive (McCarthy *et al.*, 2011). Damodaran *et al.*, (2015) assume that a misbalance of D1 and D2 projecting neurons accompanied by increased inhibitory interneuron activity leads to an increasing prevalence of interneuron *beta* bursts. Instead of a misbalance, the dopamine depletion could also induce synchronized pauses, which allows the projection neurons to fire at *beta* frequencies (Corbit *et al.*, 2016).

Evidence is suggesting that cortical oscillations < 30 Hz drive the basal ganglia and higher frequency oscillations from the STN drive the cortex (Williams *et al.*, 2002; Fogelson *et al.*, 2006).

The most popular hypothesis addresses the STN as the potential origin of aberrant *beta* oscillations (Li *et al.*, 2016). Alternatively, the oscillation could be a result from STN and GPe interaction (Holgado, Terry and Bogacz, 2010) and negative feedback loops (for a review see Humphries, Obeso and Dreyer, 2018). Holt and Netoff (2014) also found coupling between GPe and STN to contribute to pathological synchronization. In their model, pathological *beta* oscillations were only seen in the presence of normal cortical input (no pathological

synchronization, when removing cortical input), which implies the need for internal and external drive to generate the aberrant signal.

The STN specific *beta* band oscillation seems to represent an integrative malfunctioning in the basal ganglia. Among the different pathways, the motor circuit is segregated from other circuits, i.e. the prefrontal, limbic and oculomotor pathway. Nevertheless, on the level of the basal ganglia the different pathways are open for interconnections (Joel and Weiner, 1994). Taken into account FOG being especially vulnerable for emotional, visual, and environmental influences, it seems much likely, that the main problem lies within the basal ganglia. A freezing specific 18 Hz oscillation from the STN underlines the hypothesis of the "noisy signal" (Marsden and Obeso, 1994; Brown and Eusebio, 2008), indicating that the disease causes a specific basal ganglia pattern that disrupts local and distinct functions. Furthermore, the removal of BG output (by inducing lesions) has resulted in reduced instead of worsened parkinsonian symptoms (reviewed by Wichmann, 2019). This suggests, that the BG activity does not only disrupt information processing, but actively inhibits the information pathway that emerge from the BG.

Storzer *et al*. (2017) suggested that the pathological increase in *beta* power might mirror a certain predisposition to freeze. Therefore, certain additional tasks trigger freezing episodes by increasing the motor, cognitive, or limbic load on the already stressed system.

7.5. Why is bicycling less affected than walking in Parkinson's disease?

Storzer *et al*. (2018) suggested that the ability to ride a bike is unaffected because of the lower computational demand on motor networks.

Riding a bicycle is not only easier for PD patients but furthermore, it improves PD motor symptoms (Ridgel *et al.*, 2015). To enable an ongoing motor process, the motor cortex relies on somatosensory input from the periphery. This includes efferents from joint receptors, muscle spindles and cutaneous reflexes. Some studies have proven that the proprioceptive system is impaired in patients suffering from PD (for a review see Conte *et al.*, 2013), which results in a lack of

peripheral afferent input and a disturbed motor output. Therefore, there are stronger afferents projecting to the cortex.

Regarding the idea of Snijders *et al*. (2011, 2012) and Storzer *et al.* (2017) bicycling seems to reduce the computational load on the striato-thalamo-cortical loop. This reduced impact could result in less disturbance on the cortical – BG circuits, which therefore decreases the pathological synchronization. Furthermore, bicycling seems to improve cognitive functions in patients with PD in a dual task study (Altmann *et al.*, 2015). The authors explain this by an increased arousal during the exercise, leading to increased catecholamine and dopamine levels. Walking, as a more complex motor task, shows less benefit from the catecholamine triggered arousal and is more vulnerable for dual task disturbances.

Snijders *et al.* (2011) proposed that the effects of a rapidly changing visual scene during bicycling could have an impact on the pathogenesis. This would not explain, however, why freezers riding on a stationary bicycle without changing visual inputs also reveal preserved bicycling skills.

Another interesting idea includes evolutionary aspects. Walking is an evolutionary strengthened way of locomotion, whereas bicycling is a movement skill developed during childhood. Freely chosen stride frequency during walking is way more economical compared to bicycling (Sardroodian *et al.*, 2015). Even though walking and bicycling feature comparable movement patterns, it was hypothesized, that walking results from evolutionary consolidated interaction of the musculoskeletal and neural system. Bicycling, as a during childhood acquired skill, is generated by neural centers initially consolidated for locomotion. Lacquaniti *et al.*, (2013) stated, that there are different CPG layers developing from childhood and Sardroodian *et al.*, (2015) concluded, that pedaling might be generated in one of those added CPG layers. Taking into consideration the lack of automaticity in PD, this can explain why walking, as an automatic motor program, is more disturbed in FOG than the during childhood acquired bicycling.

8. Limitations

In this work, it was tried to match PD patients for disease severity and levodopa equivalent dose (Tomlinson *et al.*, 2010) since FOG in PD is linked to those factors (Giladi *et al.*, 2001; Macht *et al.*, 2007). But even though there were only small discrepancies regarding to disease severity, Freezers had longer disease duration and were affected more severely. Group size was chosen similar to earlier works (Scholten, Govindan, *et al.*, 2016; Scholten, Klotz, *et al.*, 2016) reducing the chance of missing differences due to small group sizes.

There are studies indicating that brain activity may be related to exercise intensity (Bailey *et al.*, 2008). In the present study, cadence differed among groups. Opinions about the effect of cadence on the cortical activation are inconsistent (Stancák and Pfurtscheller, 1995, 1996; Pastötter, Berchtold and Bäuml, 2012), but it might have had an effect on cortical activity (Brümmer *et al.*, 2011).

The use of EEG has a great temporal resolution and is applicable for mobile measurements. Progress in the hardware systems enables free movement in space. But measurements during exercising remain challenging because of artifact contamination that affects the integrity of the neuronal electro- cortical activity. Those can stem e.g. from stepping or electrode movement. Healthy participants show more body movement and less rigidity than PD patients, whereas patients suffer from increased neck tone (Franzén *et al.*, 2009), which also affects the EEG signal. Due to those artifacts, e.g. in temporal and occipital areas at lower frequencies, it is possible that frontal activity in this frequency range or activity in other frequency bands was partly covered up.

The study at hand concentrated on *beta* band activity recorded at the Cz electrode because of its location over the leg area of the motor cortex and its importance in motor execution and human gait (Miyai *et al.*, 2001; Raethjen *et al.*, 2008; Wieser *et al.*, 2010b; Do *et al.*, 2011). As a consequence, freezing associated cortical activity in other cortical areas could be missed. Furthermore, in the human motor cortex, both lower extremities are mapped close to the midline (Jasper and Penfield, 1949). Because of this topographical location and the poor spatial resolution of EEG recordings, it cannot be differentiated between

activity of both feet. Since PD is a strongly lateralized disease, it would have been helpful to discuss cortical activity linked to individual foot movement.

Another aspect is, that patients were asked to bicycle and walk at a cadence of 40 rpm and 40 spm. This might differ from the self-preferred cadence, so that any influence of this during the movements cannot be ruled out. Sometimes, participants were asked to slow down or speed up. The cortex and the STN enable and inhibit behavior via different oscillatory frequency bands (Cavanagh and Frank, 2013). Modulation of cortical activity because of those commands could have influenced the measurement (Zhang *et al.*, 2008). However, not to control the cadence would have resulted in a clear discrepancy regarding the motor output between the two conditions.

Finally, physiological activity, such as heart rate and blood pressure, which is accompanied by *beta* activity during EEG recordings (Cole, 2017) was not measured. Therefore, the possibility cannot be ruled out that different levels of fitness and therefore cardiovascular factors influenced the measurements. However, major effects are not expected here.

9. Conclusion

This study compared cortical brain activity of PD patients with and without FOG during active bicycling and walking. Even though Freezers were clearly discernable due to their striking differences and impairments in various gait parameters, no cortical differences in the *beta* power activity of the motor cortex between Freezing and Non-Freezing PD patients could be found. Furthermore, there was no equivalent for the 18 Hz noisy signal found in the STN by Storzer and colleagues. These results indicate a subordinate role of the PMC in the generation of FOG.

Furthermore, the generation of movement in PD patients with FOG seems to be unimpaired. It is more likely that FOG occurs because of disturbed coupling of cognitive and integrative functions at the level of the BG. This might be important for future treatment strategies, for example optimizing of stimulation adjustments or the use of transcranial stimulation in order to relieve freezing symptoms.

Lastly, all the work of the past years has shown that FOG is a multifarious symptom. FOG affects various brain areas and impairs multiple brain functions. Today, it can be concluded, that FOG is a paroxysmal phenomenon that is unlikely originating from of a focused, structural impairment. It seems to occur due to dysfunctions within a highly interconnected neural system that usually adjusts to dynamic and rapid changes in the daily environment. With this work one additional small piece to the puzzle was provided, that one day hopefully leads to the decoding of the enigma of FOG.

10. Outlook

This thesis and the underlying studies help in the understanding of the role of the motor cortex in the generation of the severe symptom of FOG.

Locomotion depends on a perfectly adjusted interplay between different cortical and subcortical regions. As mentioned before, it seems most likely, that there are various pathological processes contributing to the symptom. These are located at different levels of the motor networks, for example PMC, SMA, STN, and PPN. This elucidates the great importance of simultaneous recordings from separate brain regions to disclose motor network activity and connections associated with FOG. It is crucial to understand the information processing and transmission, during normal gait, during the transition between gait and freezing and finally, during ongoing freezing episodes.

Therefore, it would be interesting, to have the same paradigm used in our study tested with the concurrent recording of LFP and EEG (Gratkowski *et al.*, 2017). This would show the direct comparison between cortical and subcortical activity and would once and for all eliminate the possibility of the 18 Hz signal to be seen in the motor cortex. Another attempt could be simultaneous LFP and intracranial EEG (iEEG). Even though iEEG only reflects a very restricted sample of the brain structures, it is immune to artifact contamination (reviewed by Jerbi *et al.*, 2009) and provides precise data of neuronal activity (Buzsáki, Anastassiou and Koch, 2012). Using this, further insight can be provided into cortical phase amplitude coupling (De Hemptinne *et al.*, 2015; Kondylis *et al.*, 2016). Interestingly, using iEEG as well, Crowell *et al.* (2012) found no significant increase in *beta* band activity in the brain of patients with PD. This finding confirms that exaggerated *beta* activity, usually observable in the STN, is not represented at cortical levels. Since this is in line with the results presented in this thesis, further investigations would be interesting.

Another idea would be the simultaneous recording of MEG with LFP (Hirschmann *et al.*, 2011, 2013; Oswal *et al.*, 2016) or EEG. MEG is characterized by a good spatial resolution compared to EEG but was long time limited by the dependence of a restrictive scanner. Combined EEG and MEG reduces the chances of missing brain activity due to differences in sensitivity (reviewed by Ahlfors and

Mody, 2019). Due to recent advances in portable MEG techniques there is now the possibility to record real time MEG (Boto *et al.*, 2018) and to combine this in hybrid MEG/EEG devices (Boto *et al.*, 2019). That allows new experimental designs and could be a potential approach for mapping brain activity during motor tasks.

Another commonly used technique is functional magnetic resonance imaging (fMRI), which allows human brain imaging based on different blood-oxygen levels during locomotor tasks. Using fMRI is an established method for investigating brain activity and metabolism associated with FOG (Shine *et al.*, 2013). It is an indirect measurement and since it relies on metabolic processes, it comprises a certain time delay. Furthermore, due to machine conditions it cannot measure multi-joint lower limb movement, e.g. bicycling and walking, as the head is fixed and severe movement degrades the quality of the data (Wylie *et al.*, 2014). There are, however, techniques to combine fMRI and bicycling with special devices (Mehta *et al.*, 2009), but it has to be taken into consideration that real bicycling in an upright position and with free head movements, differs from bicycling in a supine position. Nevertheless, those are interesting methodologies for further investigations of movement related brain activity. FMRI combined with virtual reality paradigms (VR) also shows promising results and insights into neural correlates underlying FOG (Peterson *et al.*, 2014; Gilat *et al.*, 2015). VR in general offers some auspicious approaches for rehabilitation by improving impaired gait features and alleviating FOG (Janeh *et al.*, 2019). An interesting compromise between EEG and fMRI is the near infrared spectroscopy, which now enables brain imaging in freely moving subjects (Piper *et al.*, 2014; Herold *et al.*, 2017).

In future studies, it would be valuable to investigate the impact of real environmental motor cortex behavior. This enables to record brain activity influenced by the need for balance control and adjustments to rapidly changing environments. Even though our bicycle was not completely fixed and therefore allowed some subsequent balance adjustments, outside pedaling requires more complex body functions. The bicycle simulator in the study can already be used to play videos while bicycling. This could be particularly interesting for EEG and

LFP recordings during bicycling while presenting videos of different environments, obstacles, and so on.

In this thesis, the focus lies on FOG with diverse provoking factors. Therefore, it might be relevant to divide FOG patients into different subgroups based on their triggering events: start, turn, narrow spaces, upon reaching destinations, and open runway (Schaafsma *et al.*, 2003). Including them into research will help to disentangle the potentially different underlying causes.

All together, these projects will deliver deeper insights into the understanding of FOG. This is of great importance because gait impairments still have an enormous impact on mobility. Therefore, developing new therapeutic strategies will support many patients in living an unimpaired life.

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