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Preoperative Stratification of Gait Outcome from Subthalamic Nucleus Stimulation

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Dekan:	Professor Dr. B. Pichler

1.	Berichterstatter:	Professor Dr. med. Daniel Weiß
2.	Berichterstatter:	Privatdozent Dr. B. Bender

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List of abbreviations

PD	Parkinson’s disease
STN	Subthalamic nucleus
SNr	Substantia nigra pars reticulata
GPi	Globus pallidus internus
GPe	Globus pallidus externus
Vim	Nucleus ventrointermedius internus
PPN	Pedunculopontine nucleus
SNc	Substantia nigra pars compacta
DBS	Deep Brain Stimulation
FOG	Freezing of gait
FOG-AC	Freezing of Gait Assessment Course
UPDRS	Unified Parkinson’s Disease Rating Scale
PIGD	Postural instability and gait disability
LEDD	Levodopa-equivalent daily dose
PDQ-39	Parkinson’s Disease Questionnaire
CAPSIT-PD	Seven meters timed walking test from Core Assessment Program for Surgical Interventional Therapies in Parkinson’s Disease
ROM	Range of motion

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1. Introduction

"… the patient can no longer exercise himself by walking in his usual manner, but is thrown on the toes and forepart of the feet; being, at the same time, irresistibly impelled to take much quicker and shorter steps, and thereby to adopt unwillingly a running pace. In some cases, it is found necessary entirely to substitute running for walking; since otherwise the patient, on proceeding only a very few paces, would inevitably fall."

An Essay on the Shaking Palsy. James Parkinson. 1817

Improvement of general gait parameters after deep brain stimulation of the subthalamic nucleus (STN-DBS) in Parkinson's Disease (PD) is a reported outcome in several studies. However, the specific effect of STN-DBS on Freezing of Gait (FOG), which is among the core disabling symptoms of PD that deteriorates quality of life of PD patients (Moore et al., 2008), remains controversial and the extent of improvement is somewhat unpredictable (Fleury et al., 2016). In this study we focused on finding precursors, i.e. clinical and kinematic variables, which are indicators of a favorable FOG outcome.

1.1. Definition, etiology and clinic of Parkinson's disease

James Parkinson described PD for the first time in 1817 as "shaking palsy". Afterwards it was further investigated by Jean-Martin Charcot and renamed by him as the Parkinson's disease (Goetz, 2011).

It is a common slow progressive neurodegenerative disorder. The prevalence is 41/100,000 between ages 40 to 49 and increases gradually with aging to 1903/100,000 at subjects older than age 80. Moreover, a higher prevalence of PD (twice as common) is shown in men than in woman (Van Den Eeden et al., 2003, Baldereschi et al., 2000).

Approximately at 10-15% of the cases PD is known to be inherited, however majority of the cases are sporadic. Through gene mutations, some important

pathways such as alpha-synuclein proteostasis, mitochondrial function, oxidative stress, calcium homeostasis and axonal transport could be disturbed. In addition, neuroinflammation is assumed to contribute to a disturbance of the pathways (Poewe et al., 2017). The most important genes are *SNCA*, *LRRK2*, *GBA*, *PARKIN* and *PINK1*. *SNCA* gene encodes alpha-synuclein. Point mutations or multiplications of this gene cause heritable autosomal dominant PD. Mutations in *LRRK2* gene cause impairment in lysosomal autophagy and increased aggregation of alpha-synuclein. *LRRK2* mutations are associated with autosomal dominant PD with incomplete penetrance. *GBA* gene encodes glucocerebrosidase and its mutations cause an impairment in lysosomal autophagy. Patients with these mutations have approximately a 4-fold increased risk for developing PD. Patients with severe GBA mutations have an earlier age of onset, a rapid disease progression and increased risk for developing dementia. Mutations in *PARKIN* and *PINK1* genes are causes of early onset autosomal recessive PD through impaired mitophagy and result in accumulation of dysfunctional mitochondria (Simon et al., 2020).

Probably the disease is caused by a complicated and not yet understood interaction of the environment and genetic factors (Kalia and Lang, 2015). For example, the incidence is greater in people exposed to pesticides and in people who have suffered a traumatic brain injury and it is lower in cases of smokers and caffeine consumers (Ascherio and Schwarzschild, 2016, Poewe et al., 2017). Furthermore, calcium channel blockers (Gudala et al., 2015) and statins (Bai et al., 2016) are assumed to lower the risk of PD in a few studies. Due to contradictory findings in different studies, these substances should be further investigated to confirm these results.

Diagnosis of PD is based on the clinical features after UK Parkinson's Disease Society Brain Bank criteria (Hughes et al., 1992). The disease shows both motor symptoms and non-motor symptoms. Among motor symptoms, bradykinesia is a mandatory sign for PD diagnosis. This could be accompanied by rigidity and rest tremor with a frequency of 4-6 Hz. In advanced stages, axial symptoms appear additionally, such as speech problems, dysphagia, postural instability and gait disorders including FOG (Kalia and Lang, 2015, Gibb and Lees, 1988). Motor

features in PD are heterogeneous. Patients mostly have one of the symptoms predominantly; either tremor, which is called tremor-dominant subtype or bradykinesia, which is called akinetic-rigid subtype. There is also a group with mixed motor symptoms, namely equivalent subtype (Jankovic et al., 1990). Non-motor symptoms are manifold. Among these are depression, autonomic dysfunction, sleep disruption and cognitive symptoms including mild cognitive impairment, executive dysfunction and dementia (Seppi et al., 2011, Schapira et al., 2017).

1.2. Pathophysiology of Parkinson's Disease

PD affects nerve cells mainly in the basal ganglia and is caused by the absence of dopamine due to the loss of dopamine-producing cells in the basal ganglia, more specifically in the ventrolateral substantia nigra pars compacta (SNc). In early stages, the loss of dopaminergic neurons is limited to ventrolateral substantia nigra and becomes more widespread during further stages. Neuronal loss can be seen in many other brain regions; such as hypothalamus, locus coeruleus, nucleus basalis of Meynert and amygdala (Dickson, 2012). It is suggested and supported by pathological research that the loss of dopaminergic cells starts long before the onset of motor symptoms. This explains the distinct loss of dopaminergic neurons even in early stages of the disease (Dijkstra et al., 2014, Iacono et al., 2015). Beside these features, imaging studies as well as post-mortem examinations also showed a cholinergic denervation in basal forebrain, even in early PD with a worsening through appearance of dementia. Subcortical cholinergic degeneration seems to be related to dopamine non-responsive gait and balance impairments (Bohnen and Albin, 2011). Falls and FOG are found to be associated with degeneration of cholinergic terminals. Thalamus has a key role on the appearance of falls and caudate nucleus on the appearance of FOG respectively (Bohnen et al., 2019). Another important feature is the intracellular accumulation of alpha-synuclein protein. The inclusion of misfolded parts of alpha-synuclein proteins in cell bodies or processes of neurons, which are called Lewy bodies or Lewy neurites (Wakabayashi et al., 2013, Spillantini et al., 1997).

Recent studies showed that some species of alpha-synuclein oligomers are toxic. However, the mechanism inducing cell death remains hitherto unclear. The Lewy pathology starts in cholinergic and monoaminergic brainstem neurons and olfactory system (Balestrino and Schapira, 2020). Limbic system and neocortex are also affected with disease progression. Braak staging is a classification of the degree of alpha-synuclein pathology in Parkinson's disease. In this model it is claimed that the disease may originate from the enteric nervous system and Lewy pathology spread from the gut up through the vagal nerve to the brain. In stage I the lower brain stem and the olfactory nerve are affected. In stage II the pathology is observed in raphe nuclei and the medulla oblongata. In stage I and II the subjects are asymptomatic. In stage III Lewy bodies are seen in substantia nigra and basal nucleus of Meynert. In stage IV Lewy pathology spreads further mesocortex and allocortex. In stage V and VI alpha-synuclein inclusions are found in limbic and neocortical brain. Alpha-synuclein is assumed to spread through neurons in a prion-like pattern (Brundin et al., 2016). These features are not specific to PD individually, but they are specific for a definitive diagnosis of PD when they occur simultaneously (Poewe et al., 2017).

The lack of dopamine results in increased GABAergic inhibition of thalamocortical projections and causes an imbalance within the basal ganglia circuits. This includes two different pathways which are described as the direct and indirect pathways. These two have opposite effects on target structures. Excitation of the direct pathway excites thalamic neurons, which also has an excitatory effect on cortical neurons. Excitation of the indirect pathway has an inhibiting effect on motor cortex via inhibition of the thalamic neurons. There is a balance between the activity of these two pathways in healthy subjects, which enables voluntary movements to be performed smoothly. With the loss of dopaminergic neurons in PD, there is an increased amount of activity coming out of the indirect pathway. This is clinically responsible for cardinal symptoms of PD. Due to lack of dopamine, striatal neurons containing D2 receptors could not be inhibited as in the normal case, which causes an increased inhibition of Globus pallidus externus (GPe) and then disinhibition of Subthalamic nucleus (STN). As a result, Globus pallidus internus (GPi) and Substantia nigra pars reticulata (SNr) receives

increased excitatory outputs from STN. On the other hand, striatal neurons containing D1 receptors cannot be excited due to dopamine deficiency and cannot inhibit GPi and SNr.

In summary, reduced striatal dopamine leads to increased inhibitory output from the Gpi and SNr through direct as well as indirect pathways (Lanciego et al., 2012). These changes keep the thalamus in an overly inhibited state. This increased inhibition of the thalamocortical pathway suppresses movements. Basal ganglia motor loop showing indirect and direct pathways is depicted in Figure 1.

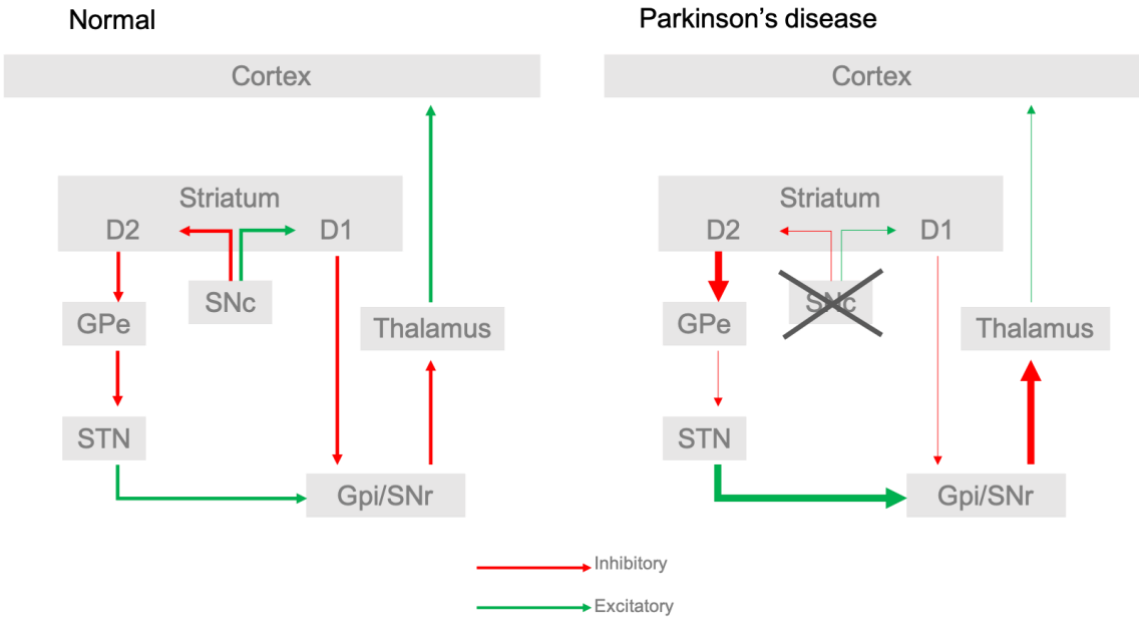

Figure 1: Basal ganglia motor loop
D1: Dopamine receptor D1 subtyp; D2, Dopamine receptor D2 subtyp; SNc, Substantia nigra pars compacta; STN, Nucleus subthalamicus; SNr, Substantia nigra pars reticulata. Adapted from (Lanciego et al., 2012).

1.3. Medical treatment of Parkinson's Disease

With respect to neurodegeneration, a causal therapy of PD does not exist yet. Disease-modifying treatments such as monoamine oxidase (MAO) inhibitors, substances reducing oxidative stress or reducing microglial activation failed to provide evidence (Balestrino and Schapira, 2020). Trials testing immunotherapy targeting the spread of alpha-synuclein showed positive results from phase I

studies. Drugs targeting *GBA* pathway showed promising results in preclinical studies (Balestrino and Schapira, 2018).

Effective symptomatic treatment of PD with drugs or DBS has developed far. An initial medical treatment with dopamine replacement therapy, in particular with levodopa and dopamine agonists, shows significant improvement of symptoms of PD and the quality of life. Levodopa can cross the blood-brain barrier, but the dopamine cannot. Once levodopa crosses the blood-brain barrier and enters the central nervous system by DOPA decarboxylase, it is converted into dopamine and stimulates the dopamine receptors directly.

Dopamine agonists activate dopamine receptors and mimic the effect of dopamine. Due to their interaction with other receptors and their side effects compared to other therapies ergoline derived agonists, such as bromocriptine, cabergoline and pergolide, are not introduced as first choice anymore (Rizek et al., 2016). Non-ergoline agonists such as pramipexole, ropinirole, rotigotine, piribedil and apomorphine are used mostly in younger patients to reduce the risk of early motor fluctuations, despite potential side effects (Connolly and Lang, 2014). Serious side effects of dopamine agonists include hallucinations, psychosis, sleep attacks, and peripheral edema (Borovac, 2016). Impulse control disorders such as gambling, hypersexuality, compulsive shopping, hobbyism and binge eating are also serious adverse effects of dopamine agonists (Moore et al., 2014). These adverse effects also depend on the cumulative levodopa equivalent dosage, where higher cumulative dosage raises susceptibility to neuropsychiatric adverse effects in particular (Weintraub and Mamikonyan, 2019).

As the disease progresses, the effect of the medications may become unstable throughout the daily profile, such that motor fluctuations including involuntary hyperkinetic movement or uncontrolled off-periods occur few hours after medication intake (wearing-off). After 15 years of treatment, up to 95% of the patients experience motor fluctuations and up to 50% of the patients experience neuropsychiatric complications including hallucinations (Hely et al., 2005). Drugs to stabilize levodopa concentration exist and these are administered with levodopa. The combination of levodopa with catechol-O-methyl transferase

inhibitors and MAO-B inhibitors are effective on motor fluctuations as well as continuous device-aided therapies. The occurrence of choreic dyskinesias is closely related to the levodopa levels in plasma (Fabbrini et al., 2007). Wearing offs are caused by drops in dopamine levels in plasma. Probably this will be compensated in early PD, because the cells in SNc are probably still able to produce and store enough dopamine. As PD advances, the nerve cells break down progressively and they are not able to compensate the dopamine levels anymore. Another reason causing motor fluctuations might be the slowness of the digestive system, which prevents levodopa from being absorbed properly. Gastric emptying in PD is slow and irregular. Due to slow gastric emptying plasma concentration of levodopa lowers and due to irregular gastric emptying the absorption of levodopa is also irregular which may result in motor fluctuations (Djaldetti et al., 1996, Bestetti et al., 2017).

1.4. Deep brain stimulation

The physiological mechanism underlying DBS therapy is still not entirely understood. However, several lines of experimental evidence help to understand some of the mechanisms involved. Animal models of PD as well as decades of pathophysiological and clinical research also shed light on the mechanism of DBS therapy. It was shown that the neuronal activity in the STN and GPi is increased in PD (Wichmann et al., 1994) due to enhanced inhibition coming from the striatum as a result of dopamine deficiency. This causes inhibition of the thalamus and decreased excitation of the cortex. Decreased excitation of the cortex relates to the motor symptoms of PD. Lesions of these structures generate significant improvement in motor functions (Bergman et al., 1990). High-frequency electrical stimulation through surgically implanted electrodes showed similar effects compared to a lesion on the motor symptoms of PD, but without a non-reversible brain damage (Poewe et al., 2017) and it allows a fine titration and adaptations during disease progression (Weiss et al., 2013). Early studies suggested that high frequency stimulation of STN and GPi suppresses the neural activity in the surrounding area of the stimulating electrode and decreases the output of

stimulated nucleus (Agnesi et al., 2013, Welter et al., 2004). A study on parkinsonian rodents aiming to optically deconstruct neural circuitry found that direct stimulation of afferent axons projecting to the STN region had beneficial effects on motor symptoms (Gradinaru et al., 2009). A review article summarizing the main hypotheses on how the stimulation works on single neuron level presented four main points: i) inactivation of voltage dependent ion-channels resulting in a depolarization blocking, ii) target neurons driven to a high-frequency state by activating the neuronal membrane, iii) activation of the inhibitory afferents to STN causing a synaptic inhibition, iv) neurotransmitter depletion resulting in synaptic failure (Breit et al., 2004).

Another important aspect, which may help us understand the PD pathology as well as how DBS on PD symptoms works, is the altered local field potentials, particularly through pathological increase in the power of beta-frequency (13-35 Hz) in STN. This power is not constantly elevated, but it fluctuates and the intermittent elevated power intervals are called “beta bursts”. The short beta bursts are physiological and the longer beta bursts are assumed to be related to motor symptoms of PD (Brown et al., 2001, Kuhn et al., 2004, Tinkhauser et al., 2018). Levodopa administration as well as activation of DBS decrease the power of this activity and improve the motor symptoms of PD (Kuhn et al., 2008). The causal relationship between beta-bursts and PD symptoms remain unclear. Nevertheless, beta-burst is increasingly used as a marker for an adaptive stimulation to increase its efficacy (Little et al., 2013).

Different targets of DBS with respect to localization of the electrodes for PD are investigated through the years (Krack et al., 2019). Vim-DBS was only effective on tremor and not effective on other motor symptoms (Benabid et al., 1996). Therefore, Vim-DBS, in particular electrodes with close proximity to dentato-rubro-thalamic tract, will be only considered in patients with tremor dominant PD without any other motor symptoms (bradykinesia and rigidity). Patients with predominant tremor benefit also from stimulation of zona incerta (Krack et al., 2019). STN-DBS and GPi-DBS is the state of the art therapy for patients with debilitating motor fluctuations under best medical treatment (Deep-Brain Stimulation for Parkinson's Disease Study et al., 2001). STN-DBS improves

motor symptoms, alleviates motor fluctuations up to twelve years at patients with advanced stages of PD (Lau et al., 2019, Limousin and Foltynie, 2019, Krack et al., 2019). Tremor and rigidity have the best response among the symptoms (Rizzone et al., 2014). High-frequency electrical stimulation of the GPi reduced dyskinesias in particular, whereas the effect on akinesia is less pronounced and is variable across studies (Volkmann et al., 1998, Deep-Brain Stimulation for Parkinson's Disease Study et al., 2001, Odekerken et al., 2013, Odekerken et al., 2016, Follett et al., 2010). For both targets, STN and GPi, there are long term studies (longer for STN compared to GPi), however just a few studies exist comparing both targets (Deuschl et al., 2013a, Odekerken et al., 2013, Odekerken et al., 2016, Follett et al., 2010). STN-DBS is shown to be superior at reducing the medication after surgery (Xu et al., 2016). GPi-DBS is assumed to prevent the deterioration of postural instability and gait disability better than STN-DBS (St George et al., 2010). However, it remains uncertain if this directly relates to the effect of stimulation or the reduction of levodopa doses after STN-DBS in opposite to GPi-DBS. Both targets show a similar effect on drug resistant rest tremor (Landi et al., 2003, Wong et al., 2018).

1.5. Axial motor symptoms

Axial motor symptoms include “midline symptoms” such as gait disturbance including FOG or postural instability and postural changes such as camptocormia, but also dysphagia and speech problems. In idiopathic PD, these symptoms may become dominant after 10-15 years in advanced phases and respond less well to possible treatments (Hely et al., 2005), whereas in atypical PD this may occur much earlier possibly even at the beginning of the disease (Ebersbach et al., 2013). Moreover, axial disability during disease progression is associated with an increased risk of death (Lau et al., 2019).

In this study, we will mainly focus on and discuss kinematic gait measures and FOG. FOG causes reduced mobility and falls. As a result, patients lose their independence and nursing home placements come into the picture (Weiss et al., 2019). In general, FOG reduces the quality of life greatly (Moore et al., 2007).

1.5.1. Parkinsonian Gait

Parkinsonian gait is characterized by abnormal slowness, small and shuffling steps, reduced arm swing and stooped posture. It is linked to the difficulties in changing directions and modulating velocity (Albani et al., 2014). Three-dimensional kinematic analysis has been widely used in the past years to describe the pathological features of gait in an objective way. Previous studies showed that PD patients have reduced gait velocity, stride and step length; unchanged or compensatory increased cadence compared to age matched healthy controls (Morris et al., 1994, Allert et al., 2001, Knutsson, 1972, Stern et al., 1983, Ebersbach et al., 2013). The duration of double-limb support phase of stance is also increased (Plotnik et al., 2011, Albani et al., 2014). Range of motion (ROM) at hip, knee and ankle level are reduced (Collomb-Clerc and Welter, 2015), which are described as the degree of the joint movement during the gait cycle and calculated as the difference between the maximum and minimum angle of the joint.

1.5.2. Freezing of Gait

As briefly mentioned in the preceding section, FOG leads to falls and therefore to serious injuries and immobility (Giladi and Nieuwboer, 2008, Latt et al., 2009). Additionally, it results in reduced quality of life and increases the risk of the need for accommodation in a nursing home (Weiss et al., 2019). FOG is a special episodic phenomenon of inhibition of stepping forward, which occurs suddenly and lasts for a couple of seconds. During these episodes the patients are unable to move forward and they feel as if their feet are fixed on the ground (Snijders et al., 2008). Episodes last mostly only a few seconds, may however persist over 30 seconds (Schaafsma et al., 2003). It is defined as "*brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk*" (Nutt et al., 2011, Cebi et al., 2020). About 35% of PD patients experience FOG (Perez-Lloret et al., 2014). FOG is mostly referred to within advanced PD, but rarely it is also observed in early stages of PD (Giladi et al., 1992). In early stages of PD about 7.1% of patients suffer from FOG (Giladi et al., 2001) and up to 80% of patients experience FOG in advanced stages of PD (Nieuwboer and Giladi,

2013). Especially patients without levodopa therapy are prone to from FOG. FOG may also be seen in other neurological diseases like vascular parkinsonism, ischemic stroke (Fasano et al., 2017), normal pressure hydrocephalus (Giladi et al., 1997), neuroinflammatory disease (Fietzek et al., 2018), progressive supranuclear palsy and multiple system atrophy (Xie et al., 2015, Weiss et al., 2019).

Risk factors for developing FOG in PD are investigated in the last years and found to be related to left-sided disease onset, early lower limb or gait symptoms (Ou et al., 2018), predominant axial symptoms, higher daily dose of levodopa, akinetic-rigid subtype, lower education (Zhang et al., 2016), more cognitive and sleep disturbances (Banks et al., 2019), balance disorders, early falls, hallucinations (Ou et al., 2018), depression (Herman et al., 2019) and anxiety (Weiss et al., 2019, Ehgoetz Martens et al., 2018).

FOG is difficult to study because it is mostly unpredictable and appears in complex situations. This makes its detection in gait laboratories challenging. Most of the studies about FOG rely on subjective patient reporting, but not all the patients are able to provide an objective estimation. Therefore, provoking tests for clinic and laboratory settings are developed and validated. To differentiate freezers from non-freezers Snijders and colleagues proposed an algorithm. The patients, who report having the feeling their feet being glued on the floor; which could not be verified by the examiner during provoking tests etc. are classified as “probable freezers”. The patients with freezing seen by the examiner are classified as “definite freezers” independent from what they report about having freezing. The patients without reporting freezing and also no freezing seen by examiner are classified as “non-freezers” (Snijders et al., 2012).

Three different characteristics of FOG are described as “akinetic presentation”, “trembling in place”, and “shuffling steps” (Schaafsma et al., 2003). Freezing episodes can be classified by their onset such as gait initiation, walking, passing through narrow spaces or turning. Another stratification builds subgroups by three different triggers: motor, cognitive and limbic (Ehgoetz Martens et al., 2018,

Weiss et al., 2019). Patients can overcome FOG with focused attention and external stimuli (cues) (Giladi and Nieuwboer, 2008).

Several kinematic abnormalities are observed during FOG episodes, such as difficulties of toe or foot in leaving the ground, trembling in place with a frequency of 3-8 Hz, increase in cadence accompanied by decrease in step length, asymmetry of the foot (means one foot affected more than the other) (Nutt et al., 2011). Often before FOG occurs, an involuntary acceleration of the gait with accompanying sequential decrease in stride length is observed. Reported precursors for FOG and falls are reduced step length, decreased velocity, increased cadence, stride-to-stride variability (Hausdorff et al., 1998) and lower limb asymmetry (Plotnik et al., 2005, Ricciardi et al., 2015, Cebi et al., 2020). Also, gait asymmetry is found to be associated with the FOG occurrence (Fasano et al., 2011, Plotnik et al., 2008).

The pathophysiology of FOG is assumed to differ from appendicular parkinsonian symptoms, like bradykinesia and rigor. FOG begins to occur mostly in medication off condition and it may be responsive to dopaminergic medication. With the disease progression it may become levodopa resistant. Rarely, also levodopa induced FOG is observed (Espay et al., 2012). These patients do not experience FOG in medication off condition, but they exhibit FOG after levodopa exposition. In the following parts we will report and discuss about non-levodopa induced freezing of gait.

The underlying pathophysiology of this mysterious phenomenon could not be understood so far. It is assumed to be the consequence of dysfunctional processes at the cortical and subcortical level. Presumably pedunculopontine nucleus (PPN) plays an important role in the development of FOG, due its role in the initiation and maintenance of locomotion (Skinner et al., 1990).

Several models are hypothesized to explain the development and occurrence of FOG (Nieuwboer and Giladi, 2013).

First of these models, the “threshold model”, belongs to Plotnik and colleagues, who suggested that FOG gets triggered by accumulation multiple motor deficits such as reduction of step length, deterioration in gait rhythmicity as well as in

bilateral step coordination and increase in asymmetry. If these accumulating motor deficits reach a critical threshold, FOG would be induced (Plotnik et al., 2012). This hypothesis received experimental support, since reduced step length followed by a reduced step to step amplitude would cause FOG (Chee et al., 2009). Increased FOG episodes during turning, which requires asymmetrical step sizes and bilateral coordination, could also be explained by this hypothesis (Spildooren et al., 2010).

The "interference model", belonging to Lewis and Baker, suggests a breakdown in processing during contemporaneous limbic load during motor tasks. It is assumed to lead to an interference between different loops within the basal ganglia, which leads to an inhibition of PPN (Lewis and Barker, 2009). This model explains the occurrence of FOG during a dual task.

In the "cognitive model" Vandenbossche and colleagues point to a probable conflict-resolution deficit (Vandenbossche et al., 2012). They suggest deficits in automaticity and executive functioning lead to FOG. This model is supported by the observation, that freezers demonstrate severe executive dysfunctions compared to non-freezers (Heremans et al., 2013). For example, PD patients with FOG have lower scores in frontal tests such as frontal assessment battery (FAB), verbal fluency and ten-point clock test (TPCT) than patients without FOG (Amboni et al., 2008). It is also shown that gait is not an automatic function and requires attention, even in young and healthy subjects. A complementary study detected a delayed motor switching at step initiation in PD patients with FOG, but without impaired cognitive switching (Smulders et al., 2015).

The "decoupling model" was proposed by Jabos and colleagues. They observed prolonged anticipatory postural adjustments (APAs) in PD patients, which can be described as the displacement of the center of mass of the body by activating the trunk and leg muscles prior to step initiation. These observations suggest a decoupling in APAs associated to FOG (Jacobs et al., 2009, Nieuwboer and Giladi, 2013).

1.6. Effect of STN-DBS on axial symptoms, gait and FOG

Effect of STN-DBS on axial symptoms

Although the beneficial effect of DBS on appendicular motor symptoms (limb tremor, rigidity and bradykinesia) is well established, the axial motor symptoms do not respond to DBS to the same extent (St George et al., 2010).

The analyses of the axial motor items from Unified Parkinson's Disease Rating Scale (UPDRS) III motor scores (gait, postural stability and speech) showed a favorable short-term effect (6-12 months) of STN-DBS on these items through different studies (Fasano et al., 2015). However, longer term follow-ups up to eleven years show mostly a deterioration of the improvement in the following years. For example, a 76% improvement of postural stability at one year deteriorates to 17% at 5-years follow-up and gait deteriorates from 71% to 37% within this period (Gervais-Bernard et al., 2009). These findings were concordant with other publications (Moro et al., 2010, Fasano et al., 2010, Rizzone et al., 2014, Schupbach et al., 2005, Rodriguez-Oroz et al., 2005). One of the published longest follow-ups (eleven years) showed also the loss of the effect of STN-DBS on axial symptoms. Postural stability and speech had the worst response. Gait improvement remained significant at the latest assessment, however with a progressive loss of efficacy over the time (Rizzone et al., 2014). Another recent study observed the same fact and their prediction model suggested that dopaminergic medication and STN-DBS become ineffective on axial symptoms approximately twelve years after STN-DBS (Lau et al., 2019).

The worsening over the years is probably related to degeneration of cerebral non-dopaminergic lesions i.e. pathways during disease progression such as cholinergic, serotonergic and noradrenergic pathways (Weiss et al., 2019), which explains the poor response of the symptoms to medication and DBS (Fasano et al., 2010, van Nuenen et al., 2008, Lang and Obeso, 2004).

Effect of STN-DBS on gait

As mentioned above, the existing studies mostly analyze the gait outcome by a single gait item 29 from UPDRS motor part (part III), which is not sufficiently sensitive to quantify FOG. To this end, specific FOG evaluation parkours have

been suggested (Ziegler et al., 2010). An additional measure to evaluate different gait components is to use kinematic assessments of gait parameters (Mancini et al., 2011). The studies concentrating on gait and particularly on the response of kinematic gait parameters to DBS showed that STN-DBS improves spatial parameters such as step length, gait velocity but not temporal parameters (Faist et al., 2001, Ferrarin et al., 2005). Additionally, gait variability and gait asymmetry (Johnsen et al., 2009) as well as ROM of hip, knee and shank improved by STN-DBS (Ferrarin et al., 2005). The effect of STN-DBS on gait parameters was similar to the effect of levodopa. However, combination of both levodopa and STN-DBS induced a greater improvement on kinematic gait parameters compared to STN-DBS or levodopa alone, therefore it is assumed that both therapies have a synergistic effect on gait (Ferrarin et al., 2005, Collomb-Clerc and Welter, 2015, Faist et al., 2001, Lubik et al., 2006).

STN-DBS as well as GPi-DBS improves, besides kinematic gait parameters, the quiet standing postural control; however, worsens dynamic postural control (especially STN-DBS). Stimulation of SNr and PPN in contrast have no effect on kinematic gait parameters. Yet, it is reported to improve APAs and gait postural control (Collomb-Clerc and Welter, 2015). However, contradictory to these findings, one study was able to show that the stimulation of SNr improved swing time asymmetry, which is one of the temporal gait parameters (Scholten et al., 2017).

Effect of STN-DBS on freezing of gait

There are only a few studies focusing on FOG as the outcome measure. These studies mostly analyze only FOG item (item 14) of UPDRS part II. Most of these studies were able show an initial improvement of FOG after STN-DBS with a worsening in the following years.

A recent paper focusing retrospectively on item 14 analyzed 331 PD patients, 265 of which with preoperative FOG. 166 patients showed FOG only in medication off condition, 99 showed persisting FOG in medication on condition. One year after STN-DBS, 56 patients had FOG only in medication off condition, 125 had a therapy resistant FOG and six had FOG only in medication on

condition. In summary, 1/3 of patients had an improvement of FOG one year after STN-DBS (Karachi et al., 2019).

Secondary analysis of EARLYSTIM-trial showed a decrease in number of freezers from 52% to 34% at 24 months after STN-DBS (Barbe et al., 2019).

An important prospective controlled study focused on FOG at six and twelve months using a self-reported FOG scale “the New Freezing of Gait Questionnaire” (NFOGQ) as the primary outcome. They enrolled 24 patients in the STN-DBS group (20 of 24 patients with FOG) and 17 patients in the best medical treatment (BMT) arm (15 of 17 patients with FOG). Eight of the 20 freezers from STN group became non-freezers at six months, two of four non-freezers became freezers. On the other hand, 15 baseline freezers from BMT group stayed as freezers and one of two baseline non-freezers become freezers at six months follow-up. In summary, STN-DBS increased the possibility to become a non-freezer at six months. Accordingly, a reduction in severity of FOG was observed. However, 45% of patients still experienced FOG after the operation, but with a reduced severity (Vercruysse et al., 2014).

Another study involving 28 freezers out of 123 PD patients that utilized Stand Walk Sit Test to distinguish the freezers showed that stimulation was less effective than levodopa to alleviate gait problems including FOG. 10% of patients show no improvement of FOG one year after surgery. Because most of the patients suffered from levodopa sensitive FOG and improved mostly after STN-DBS, the authors conclude that STN-DBS alleviates the levodopa sensitive FOG. Nonetheless, in some cases STN-DBS may not alleviate FOG as a monotherapy (Ferraye et al., 2008).

A study analyzing a longer time period in a smaller cohort of 20 patients showed a stable improvement of “off-period FOG” over five years after STN-DBS (Romito et al., 2009). Another study reported an improvement of about 57% at one year follow-up, which was unchanged at five years and then worsened at eleven years follow-up (Rizzone et al., 2014).

Despite studies showing an improvement of FOG, some publications suggest that FOG and postural instability may worsen or even be induced after DBS (Follett

et al., 2010). Especially if the electrodes are misplaced in medial, anterior and cranial region; FOG would worsen or be induced through the activation of pallado-thalamic fibers (Fleury et al., 2016). For example, hypokinetic gait and FOG as a side effect of GPi-DBS is a known phenomenon (Wolf et al., 2016). The stimulation of the lateral part of STN correlates with better clinical improvement, lower stimulation parameters and postoperative reduction of dopaminergic medication (Wodarg et al., 2012).

As seen above, FOG tends to improve after STN-DBS. However, investigated on single patient level, axial symptoms as well as FOG is shown to improve in some cases, stay unchanged and even aggravate in other cases following DBS (Fasano et al., 2015), hence the effect remains controversial (Fleury et al., 2016, van Nuenen et al., 2008).

Approach to patients with axial symptoms

Because axial symptoms including FOG do not always respond to DBS, it is recommended that the decision to operate patients with poor levodopa responsive gait and postural disorders should be considered carefully (Welter et al., 2002). Even some clinics consider the presence of axial motor symptoms as a general contraindication for surgery (Fasano et al., 2015). Most studies showed that the levodopa responsive symptoms also respond well to STN-DBS. However, as mentioned above, STN-DBS may lose the effect on axial symptoms over time. Therefore, in advanced PD patients with predominantly axial symptoms, various approaches such as combined STN and SNr stimulation (Weiss et al., 2013, Valldeoriola et al., 2019) and low frequency stimulation (Khoo et al., 2014) were developed to improve axial symptoms, but still with a limited effect. Another approach is the “better side reduction”, which means reduction of stimulation amplitude for the side with longer step length. This provides an improvement of gait asymmetry and is found to be related to improvement in frequency and duration of freezing (Fasano et al., 2011).

1.7. Preoperative stratification of patients with FOG for STN-DBS

When response of the specific symptoms varies, it becomes important to stratify patients and to try to identify indicators of favorable therapeutic outcomes. These could make the decision for STN-DBS easier and make it possible to consult the patients.

Predictive factors for general motor outcome

General motor outcome after STN-DBS can be predicted from the preoperative levodopa response of PD (Deuschl and Agid, 2013, Charles et al., 2002, Follett et al., 2010). Furthermore, younger age (Charles et al., 2002, Russmann et al., 2004) and shorter disease duration is assumed to be related to a better outcome (Welter et al., 2002). Although the concept of predictability of motor outcome by preoperative levodopa response is valid for short-term observations, it probably does not predict medium-term improvement (Piboolnurak et al., 2007, Fasano et al., 2010). Furthermore, long-term motor outcome can be predicted by certain baseline motor features such as UPDRS gait and postural stability scores as well as preoperative levodopa-equivalent daily dose (LEDD) (Fasano et al., 2010). Localization of electrodes is another predictive factor for the outcome (Wodarg et al., 2012). Functional sweet spots and connectivity between stimulation site and other brain regions predict clinical motor outcome (Horn et al., 2017, Dembek et al., 2019). Moreover, genetic factors are also critical for motor outcome after STN-DBS (Artusi et al., 2019).

Prediction of axial symptoms

Previous studies report an improvement of gait and balance after STN-DBS if the symptoms are preoperatively levodopa responsive (Fasano et al., 2015, Vercruysse et al., 2014, Potter-Nerger and Volkmann, 2013). FOG is probably similar and does not respond to STN-DBS, if it continues to exist under optimal dopaminergic condition (Stolze et al., 2001, Davis et al., 2006).

A recent meta-analysis showed, through a regression model, that preoperative levodopa response of UPDRS III score and severity of gait disorder in medication off condition predicts the short and long-term effect of STN-DBS on gait. They also showed that FOG outcome could be predicted with preoperative levodopa

response of the MDS-UPDRS III total score. Disease duration and levodopa equivalent daily dose, age at surgery or disease duration did not correlated to a better outcome (Schlenstedt et al., 2017).

In a large group of patients, Karachi and colleagues showed that 1/3 of patients had an improvement of FOG after STN-DBS as mentioned above. They found a correlation between preoperative FOG severity in medication off and postoperative severity of FOG in both medication off and on condition. In other words, preoperative FOG severity in medication off condition predicts residual postoperative FOG (Karachi et al., 2019).

The secondary analysis of the EARLYSTIM-trial focusing on FOG was able to demonstrate that the patients with longer disease duration have residual freezing more often compared to those who had a shorter disease duration (Barbe et al., 2019).

1.8. Hypothesis

The limitation in most of the studies about FOG was that they used UPDRS III item 29 to determine gait and UPDRS II item 14 to determine FOG. Merely a handful of studies focused on FOG-Questionnaire or the N-FOG-Questionnaire, which rely on subjective patients reporting and are mostly not able distinguish between “probable” and “definite” freezers. More specific features of gait that are related to FOG, such as stride length, velocity or asymmetry, cannot be determined by UPDRS or FOG-Questionnaires (Schlenstedt et al., 2017). In addition, most studies were retrospective in nature.

To the best our knowledge, there are no prospective studies that focused on quantitative clinical FOG outcomes and their relation to kinematic gait parameters.

In this work, we characterized idiopathic PD patients preoperatively with respect to their gait function including FOG severity and gait kinematics. We observed their clinical outcome postoperatively with the aim to identify preoperative clinical

and kinematic features that correlate to a favorable FOG outcome. Among clinical parameters we concentrated on preoperative levodopa response of motor UPDRS III, which has been reported as a predictive factor in a recent meta-analysis (Schlenstedt et al., 2017). As a second clinical parameter we decided on preoperative levodopa response of FOG, because there are many evidences for a better outcome if the symptoms are preoperatively levodopa responsive (Charles et al., 2002). Furthermore, we investigate the relation of the preoperative severity of FOG in medication off condition with the outcome (Karachi et al., 2019) and the preoperative levodopa response of postural instability and gait disability (PIGD) subscore from UPDRS III.

Among kinematic parameters we concentrated on stride length and stride velocity, because it has shown that STN-DBS modulates these kinematic features (Potter-Nerger and Volkmann, 2013, Collomb-Clerc and Welter, 2015), which are also related to FOG (Mitchell et al., 2019). Additionally, we have searched for further kinematic features correlating to a better FOG outcome and decided for ROM at knee and shank level, referring to the literature showing that these features would improve with STN-DBS (Collomb-Clerc and Welter, 2015).

Main Hypotheses:

I. Preoperative levodopa response of motor UPDRS III score indicates a better outcome of FOG after STN-DBS
II. Preoperative levodopa response of FOG-AC indicates a better outcome of FOG after STN-DBS
III. Preoperative levodopa response of postural instability and gait disability (PIGD) subscore indicates a better outcome of FOG after STN-DBS
IV. Preoperative levodopa response of stride velocity indicates a better outcome of FOG after STN-DBS
V. Preoperative levodopa response of stride length indicates a better outcome of FOG after STN-DBS

Additional exploratory descriptive analyses:

VI. Preoperative severity of FOG-AC indicates a worse outcome of FOG after STN-DBS

VII. Preoperative levodopa response of ROM at knee level indicates a better outcome of FOG after STN-DBS

VIII. Preoperative levodopa response of ROM at shank indicates a better outcome of FOG after STN-DBS

IX. Preoperative levodopa response of swing time asymmetry indicates a better outcome of FOG after STN-DBS

X. Prediction analysis

2. Materials and methods

2.1. Patients

All experiments were conducted with written informed consent and the approval of the ethical committee of the University of Tubingen (355/2015BO1).

Patients were in our inpatient clinic as STN-DBS candidates for a regular screening-visit for STN-DBS, because they either suffered from medication-resistant tremor or motor fluctuations under best medical treatment. 24 PD patients were recruited among consecutive candidates for STN-DBS therapy. Inclusion criteria to participate in our gait observation study were disease duration longer than five years as well as age over 18 and under 80. The presence of FOG was not an inclusion criterion. Cognitive impairment (Mini Mental State Examination Score < 25), participation in other trials and chronic pathological conditions were defined as exclusion criteria (Cebi et al., 2020).

After screening, 18 of 24 patients had an OP indication, i.e. we confirmed their motor fluctuations or therapy resistant tremor and there were no contraindications. These patients underwent bilateral STN-DBS. The remaining six patients (ID1, 7, 8, 10, 13, 24) remained under best oral medical treatment (BMT) and were not referred to DBS owing to the lack of objective therapy resistant tremor, absence of objective dopaminergic fluctuations or favorable control of motor fluctuations after oral therapy adjustment according to existing standards (Deuschl et al., 2013b, Schuepbach et al., 2013).

2.2. Study design

The study design is given as Figure 2 and the study protocol including the performed tests and scales is given in Table 1.

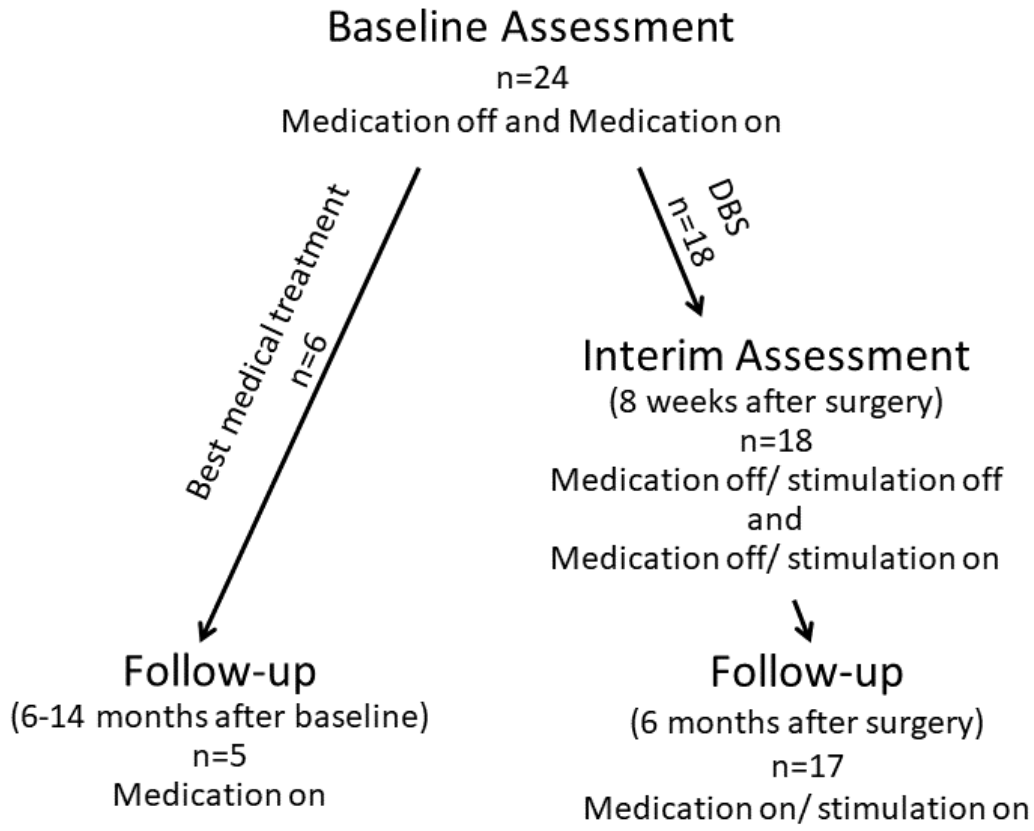

Figure 2: Study design
24 patients were enrolled. Six patients continued on best medical treatment, 18 patients underwent bilateral STN-DBS. One patient from best medical treatment group and one patient from STN-DBS group dropped out of the study and no follow-up assessment was done.

Table 1: Study protocol

	Baseline assessment		Interim assessment		Follow-up
	Medication off	Medication on	Medication off/ stimulation off	Medication off/ stimulation on	Medication on/ stimulation on
CAPSIT-PD timed walking test*	X	X	X	X	X
Freezing of Gait Assessment Course*	X	X	X	X	X
Push and Release Test*	X	X	X	X	X
MDS-UPDRS I	X				X
MDS-UPDRS II	X				X
MDS-UPDRS III	X	X	X	X	X
MDS-UPDRS IV	X				X
Berg Balance Scale	X	X			X
PDQ-39	X				X

***** Opal® wearable inertial sensors (APDM Inc., Portland, OR, USA) were used on three body regions (lower extremities and lumbar) for a detailed gait and balance analysis.

We conducted a “baseline assessment” for single included patient (*n*=24) during screening-visit. As mentioned above 18 of 24 patients received afterwards bilateral STN-DBS and six patients remained under BMT. 18 patients with STN-DBS underwent an “interim assessment” eight weeks after surgery. “Follow-up” assessments were performed on 22 patients (five patients with best medical treatment and 17 patients with STN-DBS) 6-14 months after baseline assessment for BMT group and six months after surgery for STN-DBS group. Two patients, one from BMT group (ID24), one from STN-DBS group (ID2) dropped out of the study on their own request.

Because the number of patients remained under BMT was very small, it would not have been meaningful to analyze these patients as a control group. Therefore, we only analyzed the data from STN-DBS group. The data of BMT group was not further analyzed.

2.2.1. Baseline Assessment

All patients with written informed consent underwent the “baseline” assessment in two conditions:

i) Clinical off condition (medication off): after overnight withdrawal of all dopaminergic medication and
ii) Clinical on condition (medication on): 30 minutes to one hour after taking 1.5 times of the morning levodopa equivalent dosage as Madopar LT®.

The following tests and assessments were conducted under both conditions:

i) CAPSIT-PD (seven meters timed walking test from Core Assessment Program for Surgical Interventional Therapies in Parkinson’s Disease),
ii) Freezing of Gait Assessment Course (FOG-AC) (Ziegler et al., 2010) and
iii) Push and Release Test (Jacobs et al., 2006) with Opal® wearable inertial sensors (APDM Inc., Portland, OR, USA) at three body regions (lower extremities and lumbar) for a detailed gait and balance analysis.

ID23 was not able to complete CAPSIT-PD in medication off condition, so we are not able to report this data. Kinematic data quality of ID16 was not adequate for analysis. As such, corresponding data could not be reported.

Furthermore MDS-UPDRS part III was performed under both conditions to ensure the efficacy of dopaminergic medication on PD symptoms and Berg Balance Scale to detect the change in balance.

Additionally, MDS-UPDRS part I, II and IV and Parkinson’s disease Questionnaire (PDQ-39) were assessed.

After DBS screening, 18 patients had undergone surgery for bilateral STN-DBS. Medtronic quadripolar deep brain stimulation lead model 3389 was implanted in 17 patients and model 3387 in one patient (ID 4). All 18 patients received Activa PC Neurostimulator as impulse generator.

There were no complications during surgeries. Three patients experienced falls within the first eight weeks from surgery without any damage to the DBS system

(ID 9, 12, 20), two of whom were treated at the outpatient clinic. One of them experienced a severe fall and underwent surgery due to a radius fracture. Another patient showed mild symptoms of a psychosis (ID 15) ten weeks after surgery, which was reversible after reducing stimulation voltage and administrating clozapine 25 mg/day (Cebi et al., 2020).

2.2.2. Interim Assessment

An “interim assessment” was performed on DBS patients eight weeks after surgery to evaluate the efficacy of DBS. Patients were brought in to the inpatient clinic for a regular programming session and underwent assessment under two conditions after overnight withdrawal of all dopaminergic medication:

i) Medication off/stimulation off condition,
ii) Medication off/stimulation on condition.

The stimulation arrest prior to medication off/stimulation off assessment was minimum 30 minutes.

Similar to “Baseline Assessment”, the following tests were conducted under both conditions:

i) CAPSIT-PD,
ii) FOG-AC and
iii) Push and Release Test again with Opal® wearable inertial sensors.

Furthermore MDS-UPDRS part III was performed under two conditions to detect the efficacy of stimulation.

No data is missing from this assessment.

2.2.3. Follow-up

A follow-up was conducted six months after surgery in best medical condition, which is medication on/stimulation on condition. We decided to perform the follow-up assessment six months after the operation to ensure that the postoperative stun effect would have fully disappeared. Moreover, we chose to assess the gait and FOG outcome in the treatment state close to the regular daily life condition. Therefore, we decided for the medication on/stimulation on

condition. An additional assessment in medication off condition with the reinsertion of levodopa afterwards would not have reflected the true daily life conditions of the patient. Another reason for our decision not to perform a levodopa challenge was that we already assessed the pure stimulation effect at the eight weeks interim assessment.

Same tasks and tests as baseline assessment were conducted.

Kinematic data quality of ID 3 from follow-up assessment was not adequate for analysis.

2.3. Experiment materials

2.3.1. Gait kinematics

Gait analysis was performed to identify abnormalities in patient's gait cycles as well as to observe changes between different conditions. Three wearable inertial Opal® sensors (APDM Inc., Portland, OR, USA) were used to assess a detailed gait analysis. These sensors were attached to both ankles and lumbar. They compromised tri-axial accelerometer, gyroscope, and magnetometer.

"The Instrumented Long Walk (lWALK)" plugin of Mobility Lab® software (APDM Inc., Portland, OR, USA) was used to automatically compute kinematic gait measures during the CAPSIT-PD timed walking test.

Gait parameters (Table 2) are categorized as spatial (distance related) and temporal (time related) parameters. A third category is angular displacement, which contains ROM.

Table 2: Common gait parameters and their definitions

Temporal Gait Measures	
Cadence	Stepping rate (steps/minute)
Gait Cycle Time	Duration of a gait cycle (seconds)
Double Support	% of a gait cycle where both feet are on the ground (%)
Swing	Average % of a gait cycle where either foot is off the ground (%)
Stance	Average % of a gait cycle where either foot is on the ground (%)
Spatial Gait Measures	
Stride length	Distance between two successive points of foot floor contact of the same foot (% of Subject's height)
Stride velocity	Walking speed (% of Subject's height/ seconds)
Angular Displacement	
Joint Range of Motion	The difference between initial and final angular positions of the joints (Degrees)

Adapted from Mobility Lab user's guide (APDM, 2013)

PD patients show abnormalities in stride velocity, stride and step length (Knutsson, 1972), duration of double-limb support phase of stance, ROM at hip, knee and ankle level (Collomb-Clerc and Welter, 2015). STN-DBS improves the spatial parameters such as step length, gait velocity (Faist et al., 2001, Ferrarin et al., 2005), gait variability, gait asymmetry (Johnsen et al., 2009) as well as ROM of hip, knee and shank (Ferrarin et al., 2005). Based on this reasoning, we focused on the above-mentioned parameters in our study.

Mobility Lab® software does not compute asymmetry automatically, which is an important gait feature highly related to FOG. We calculated swing time asymmetry (STA) using the following formula:

$$\text{Swing time asymmetry} = 100\% \times \frac{|\text{SWTleft} - \text{SWTright}|}{\max([\text{SWTleft}, \text{SWTright}])}$$

As reported above, kinematic data quality on two patients was not adequate for analysis (ID16 in baseline medication off condition and ID3 in follow-up). As such, data could not be reported.

2.3.2. Tests

2.3.2.1. CAPSIT-PD timed walking test

This timed walking test is part of the Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT-PD) Committee for motor evaluation (Defer et al., 1999). The patients are required to walk seven meters back and forth as fast as possible including turning. The number of steps, time and freezing episodes are recorded.

2.3.2.2. Freezing of Gait Assessment Course (FOG-AC)

This specific test detects severity of freezing. The patients are required to complete following steps in this specific order:

1. Sit for 30 seconds,
2. Stand up and walk one meter to a square floor mark (40 x 40 cm),
3. Turn 360° clockwise and counter-clockwise on this floor mark,
4. Walk two meters to a door, open and walk through it,
5. Turn around and come back to the chair.

The tasks walking to the floor mark, turning clockwise, turning counter-clockwise and walking through the door should be rated separately.

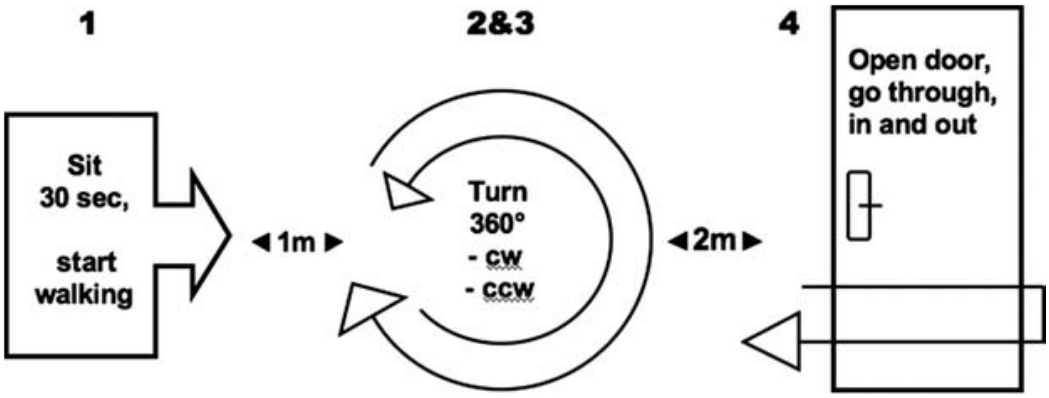

Figure 3: Pictogram of the Freezing of Gait Assessment Couse (Ziegler et al., 2010)

Patients need to repeat the parkour three times:

i) As a single task,

ii) As a dual task where the patient is required to carry a tray with a plastic cup full of water and

iii) As a triple task with “carrying” as well as counting out loud backwards from 100 subtracting seven each time.

Severity of freezing is scored as follows:

0 = No festination and no FOG

1 = Festination or any hasting steps

2 = FOG, which the patient is able to overcome himself

3 = Abortion of task or need for interference by examiner to overcome FOG.

If the patient is not able to perform the task, he/she is assigned the highest point 36 (Ziegler et al., 2010).

2.3.2.3. Push and Release Test

Push and Release Test is used to determine postural stability. Patient stands comfortable with eyes open. Examiner places his or her hands on patient’s scapulae and instructs patient to push back and then releases the supporting hands from the patient’s scapulae. The patients are instructed to regain balance, if necessary, by taking a step (Jacobs et al., 2006).

Test is scored as follows:

0 = Recovers independently with one step of normal length and width

1 = Two or three small steps backward, but recovers independently

2 = Four or more steps backward, but recovers independently

3 = Steps but needs to be assisted to prevent a fall

4 = Falls without attempting a step or unable to stand without assistance

2.3.2.4. Berg Balance Scale

In this test, patients are required to complete 14 different tasks to prove balance abilities. Patients receive points between zero and four for each task depending on how safely they perform the task. Four points is for a good and independent performance. Zero points are assigned if the patient is not able to perform the task. Sum of these points is the patient's final score, a maximum score of 56 points represents the best and minimum zero represents the worst outcome (Berg et al., 1992).

2.3.2.5. MDS-UPDRS

This test is a revised version of the UPDRS, which was published in 2007 by the Movement Disorder Society (MDS) (Goetz et al., 2008). Compared to old version in the new version FOG items were refined, in the new version there is also a FOG item in the motor examination part.

It detects the severity of four different aspects in PD in four parts:

I. Non-motor experiences of daily living (13 items),
II. Motor experiences of daily living (13 items),
III. Motor examination (18 items),
IV. Motor complications (six items).

Each item can be rated between zero and four points. Higher points represent a higher level of disability.

The use the MDS-UPDRS for the study has been approved by Movement Disorders Society.

Additionally, we calculated the postural instability and gait disability (PIGD) subscore to detect the severity of postural instability and gait as sum of items 3.10-3.12 from MDS-UPDRS part III. We decided not use the MDS-UPDRS II items 2.12 and 2.13, that depend on patient reporting and probably were not sensitive enough to the clinical transitions that occurred within up to 30 minutes between conditions during baseline and interim assessments.

2.3.2.6. PDQ 39

The PDQ-39 is a self-reporting questionnaire with 39 items to score the quality of life covering eight different dimensions (mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily discomfort). Lower scores reflect a better quality of life (Jenkinson et al., 1997).

2.4. Classification of freezer and non-freezer

The algorithm from Snijders et al. has been used to differentiate freezers from non-freezers, which we reported in the introduction section in detail. We only defined the patients as “confirmed freezers”, if the FOG was observed by the examiner, for example during CAPSIT-PD timed walking test or FOG-AC (Snijders et al., 2012).

2.5. Statistics

We performed statistical analyses with IBM SPSS statistics version 25.0 (IBM Deutschland GmbH, Ehningen, Germany). The descriptive statistics were reported as mean ± SD for parametric data and median [min-max] for non-parametric data depending on distribution. We used the Kolmogorov–Smirnov test (p<0.05) to test for normal distribution and paired sampled t-test for parametric data and Wilcoxon signed-rank test or sign test for non-parametric data to compare the preoperative and postoperative parameters. First, we conducted the analysis for the entire group. Afterwards we re-analyzed the data for patients with FOG as a subanalysis. To define the parameters associated with

favorable freezing of gait outcome after STN-DBS we used the Spearman correlation. We corrected the results for multiple testing using the false discovery rate (Benjamini and Hochberg, 1995).

We did not design this study primarily as a predictive one. The reason for that was the limited sample size. However, after analyzing the data, as mentioned above, we decided to perform a further prediction analysis with an exploratory intent. Here, we evaluated whether valid predictions of the freezing of gait outcome could be made from the preoperative measures. For this purpose, we used a stepwise multiple regression model. Dependent variable was the FOG outcome and this was calculated as improvement of FOG-AC from baseline medication off condition to six months follow-up. The variables showing a significant correlation with the FOG outcome at six months were used as independent variables. These findings should not be acknowledged as confirmatory. Our aim was to generate hypothesis for further studies.

3. Results

3.1. Baseline

24 consecutive PD patients (17 male) were recruited among DBS candidates during an inpatient screening visit. The mean age of the patients was 66.0±6.9 years, median disease duration was 12.6±5.5 years. The Mini-Mental State Examination (MMSE) median score was 30 [26-30] (median [min-max]) points. The baseline LEDD was 1219±600 mg/d. A detailed overview on patient's characteristics is given in Table 3.

Table 3: Patient characteristics at baseline assessment

ID	Disease duration (years)	Age (years)	Gender	LEDD (mg/d)	MMSE Score	Freezing of Gait	DBS-Indication
1	12	65	m	341	29	0	0
2	7	59	m	813	30	0	2
3	17	70	f	821	28	1	1
4	5	74	f	0*	26	0	2
5	10	73	m	2281	30	1	1
6	15	78	m	1830	30	1	1
7	13	61	m	1331	29	1	0
8	12	60	m	1098	29	1	0
9	9	60	m	1198	30	1	1
10	5	66	m	525	29	0	0
11	12	71	m	1460	30	1	1
12	10	59	m	2069	29	1	1
13	12	75	m	998	30	1	0
14	24	62	m	2081	29	1	1
15	8	65	f	1633	28	1	1
16	20	61	f	833	30	1	1
17	11	69	m	800	30	0	2
18	13	66	m	1158	30	0	1
19	5	75	m	1198	30	1	1
20	13	62	f	1221	30	1	1
21	27	73	m	2438	30	0	1
22	13	73	f	981	30	1	1
23	11	54	f	1200	29	1	1
24	18	54	m	949	29	1	0

m=male, f=female; LEDD= Levodopa equivalent daily dosage; MMSE: Mini-Mental State Examination; Freezing of gait: 0=non-freezer, 1= definite freezer; DBS-Indication: 0= no indication, 1=motor fluctuations, 2=therapy resistant tremor; *Patient had therapy resistant tremor

From these 24 patients screened, 18 (eleven males, seven females) underwent STN-DBS. Six patients (ID1, 7, 8, 10, 13, 24) had no severe motor fluctuations or therapy resistant tremor and continued best medical treatment. In detail, ID1 and ID13 had no more disabling tremor and ID7, 8, 10 and 24 had no severe motor fluctuations after modification of their medication plan.

As we further analyze only the data from 18 patients, who received STN-DBS afterwards, we would like to report about the characteristics of these patients separately. Their mean age was 66.9±6.9, their mean disease duration was 12.8±6.0 years and their median MMSE score was 30 [min 26-max 30]. The LEDD at baseline was 1334±147 mg/d.

As we have reported in the methods section, the patients underwent the "baseline" assessment in two conditions:

i) Clinical off condition (medication off): after overnight withdrawal of all dopaminergic medication,
ii) Clinical on condition (medication on): 30 minutes to one hour after taking 1,5 time of the morning levodopa equivalent dosage as immediate release levodopa preparation (Madopar LT®).

Entire group: There was a significant improvement in MDS-UPDRS III (p<0.001) and PIGD subscore, a sum of items 10-12 from MDS-UPDRS III, (p<0.001) between medication off and medication on condition. Berg Balance Scale (p<0.001) improved significantly. CAPSIT-PD showed improvements in time (p<0.001) and the number of steps (p<0.001). A significant improvement of joint ROM at shank (p<0.001), at knee level (p=0.003), improvement of stride length (p<0.001) and velocity (p=0.003) were observed from kinematic gait parameters (Cebi et al., 2020).

Freezing patients: MDS-UPDRS III (p<0.001), PIGD subscore (p<0.001) and Berg Balance Scale (p=0.003) improved between medication off and medication on condition. CAPSIT-PD showed improvements in time (p=0.002) and the number of steps (p=0.002). Freezing patients showed an improvement in the same gait parameters as entire group in joint ROM at shank (p=0.002), at knee level (p=0.002), stride length (p=0.002) and velocity (p=0.008). Gait cycle time

and swing time asymmetry did not differ between the conditions (Cebi et al., 2020).

A detailed overview is given in Table 4.

Table 4: Results based on clinical scores from baseline assessment
A: results of entire group

	Baseline		*T*-value/ *Z*-value	*p*-value	*n*
	Medication off	**Medication on**			
MDS-UPDRS III [c]	47.78±14.35	26.39±10.71	11.02	**<0.001***	18
PIGD subscore [c]	5.44±2.92	2.39±2.09	5.08	**<0.001***	18
Push and Release Test [a]	1 [0-4]	1 [0-4]		0.070	18
Berg Balance [b]	43 [9-56]	55 [10-56]	-3.19	**0.001***	18
CAPSIT-PD time [b]	28 [11-533]	16 [9-42]	-3.44	**0.001***	17
CAPSIT-PD steps [b]	54 [18-500]	26 [18-65]	-3.46	**0.001***	17
ROM shank [b]	37.63 [10.10-74.12]	66.99 [26.69-81.71]	-3.62	**<0.001***	17
ROM knee [b]	38.05 [16.30-53.44]	49.20 [26.76-56.13]	-3.01	**0.003***	17
Mean stride length [b]	42.38 [11.22-80.43]	73.30 [25.92-85.22]	-3.29	**0.001***	17
Mean stride velocity [b]	41.20 [7.17-84.65]	62.27 [23.31-89.80]	-3.01	**0.003***	17
Mean gait cycle time [b]	1.09 [0.64-1.65]	1.12 [0.94-1.35]	-0.40	0.687	17
Swing time asymmetry [b]	3.80 [0.23-40.57]	7.23 [0.30-34.82]	-0.40	0.687	17

(mean ± SD) / (Median [min-max])
Two-sided p-values are provided. [a] sign test, [b] Wilcoxon signed-rank test, [c] paired sample t-test
*significant after FDR correction
ID23 was not able to complete CAPSIT-PD in medication off condition
Kinematic data quality of ID16 at medication off condition was not adequate for analysis

B: results of freezing patients

	Baseline		*T*-value/ *Z*-value	*p*-value	*n*
	Medication off	**Medication on**			
MDS-UPDRS III [c]	49.92±16.24	26.85±12.30	10.422	**<0.001***	13
PIGD subscore [c]	6.77±2.05	2.62±1.98	7.360	**<0.001***	13
Push and Release Test [a]	2 [0-4]	1 [0-4]		0.125	13
Berg Balance [b]	42 [9-56]	53 [10-56]	-2.937	**0.003***	13
CAPSIT-PD time [b]	38.5 [12-533]	16 [9-42]	-3.061	**0.002***	12
CAPSIT-PD steps [b]	62.5 [25-500]	27 [21-65]	-3.061	**0.002***	12
CAPSIT-PD freezing [b]	0 [0-32]	0 [0-0]	-1.342	0.180	12
ROM shank [b]	36.63 [10-10 74.12]	66.06 [26.68-78.95]	-3.059	**0.002***	12
ROM knee [b]	34.19 [16.30-51.25]	49.05 [26.76-54.04]	-3.059	**0.002***	12
Mean stride length [b]	39.78 [11.22-80.43]	69.96 [25.92-84.66]	-3.059	**0.002***	12
Mean stride velocity [b]	34.58 [7.17-84.65]	61.10 [23.31-89.80]	-2.667	**0.008***	12
Mean gait cycle time [b]	1.05 [0.64-1.65]	1.15 [0.94-1.35]	-0.078	0.937	12
Swing time asymmetry [b]	4.42 [0.23-40.57]	6.68 [0.30-34.82]	-0.628	0.530	12

(mean ± SD) / (Median [min-max])
Two-sided p-values are provided. [a] sign test, [b] Wilcoxon signed-rank test, [c] paired sample t-test
*significant after FDR correction
ID23 was not able to complete CAPSIT-PD in medication off condition
Kinematic data quality of ID16 at medication off condition was not adequate for analysis

Results of performed anamnestic scales at baseline are given in Table 5: MDS-UPDRS part I for nonmotor experiences of daily living, MDS-UPDRS part II for motor experiences of daily living, MDS-UPDRS part IV for motor complications and PDQ 39 for quality of life.

Table 5: Results based on anamnestic scores from baseline assessment

	Baseline (*n*=18)
MDS-UPDRS I	10.28±4.09
MDS-UPDRS II	17.33±8.09
MDS-UPDRS IV	6.67±4.17
PDQ39 Mobility	49.58±25.15
PDQ39 Activities of daily living	43.29±20.47
PDQ39 Emotional well-being	27.08±18.92
PDQ39 Stigma	26.04±20.82
PDQ39 Social support	20.37±18.13
PDQ39 Cognition	24.31±17.40
PDQ39 Communication	12.96±12.53
PDQ39 Bodily discomfort	27.32±20.37

(mean ± SD)

3.2. Interim assessment

18 patients with STN-DBS received an interim assessment to detect the efficacy of DBS eight weeks after surgery. The assessment was conducted in two conditions after overnight withdrawal of all dopaminergic medication:

i) Medication off/stimulation off
ii) Medication off/stimulation on

Entire group: Total MDS-UPDRS III score as well as PIGD subscore showed a significant improvement at interim assessment medication off/stimulation on compared to medication off/stimulation off (p=0.000, p=0.006). Push and Release Test results remained unchanged. CAPSIT-PD showed also a significant difference between two conditions in time (p=0.002) and the number of steps (p=0.004). Among spatiotemporal and kinematic gait parameters, a significant improvement of joint ROM at shank (p=0.006) and at knee level (p<0.001), as well as an improvement of stride length (p=0.028) were observed. Stride velocity, gait cycle time and swing time asymmetry did not change between the conditions (Cebi et al., 2020).

Freezing patients: Similar to entire group, total MDS-UPDRS III score (p<0.001), PIGD subscore (p=0.019), CAPSIT-PD in time (p=0.006) and number of steps (p=0.017) showed a significant improvement. From spatiotemporal and kinematic gait parameters a significant improvement of joint ROM at shank (p=0.000) and at knee level (p=0.002) were observed. Stride length, stride velocity, gait cycle time and swing time asymmetry did not differ between the conditions (Cebi et al., 2020).

The results from interim assessment are provided in Table 6.

Table 6: Results from interim assessment
A: results of entire group

	Interim Assessment		*T*-value/ *Z*-value	*p*-value	*n*
	Medication off/ stimulation off	**Medication off/ stimulation on**			
MDS-UPDRS III [c]	50.39±16.43	33.33±11.11	6.386	**<0.001***	18
PIGD subscore [c]	4.61±2.89	3.22±2.58	3.129	**0.006***	18
Push and Release Test [a]	1 [0-4]	1 [0-4]		1.000	18
CAPSIT-PD time [b]	23.5 [12-360]	15 [9-93]	-3.068	**0.002***	18
CAPSIT-PD steps [b]	42.5 [21-500]	29.5 [20-175]	-2.868	**0.004***	18
CAPSIT-PD freezing [b]	0 [0-9]	0 [0-8]	-2.000	0.046	18
ROM shank [b]	48.22 [11.10 -79.21]	62.11 [20.08-78.48]	-2.722	**0.006***	18
ROM knee [b]	42.01 [20.31-52.68]	47.38 [28.71-55.49]	-3.593	**<0.001***	18
Mean stride length [b]	47.21 [12.36-84.63]	61.06 [21.22-80.82]	-2.199	**0.028***	18
Mean stride velocity [b]	47.44 [9.97-81.28]	59.67 [21.83-84.97]	-1.938	0.053	18
Mean gait cycle time [b]	1.14 [0.59-1.45]	1.05 [0.88-1.36]	-0.675	0.500	18
Swing time asymmetry [b]	7.15 [0.24-47.37]	7.17 [0.92-50.31]	-0.414	0.679	18

(mean ± SD) / (Median [min-max])
Two-sided p-values are provided. [a] sign test, [b] Wilcoxon signed-rank test, [c] paired sample t-test
*significant after FDR correction

B: results of freezing patients

	Interim Assessment		*T*-value/ *Z*-value	*p*-value	*n*
	Medication off/ stimulation off	**Medication off/ stimulation on**			
MDS-UPDRS III [c]	51.08±17.14	34.15±12.11	4.874	**<0.001***	13
PIGD subscore [c]	5.31±2.72	3.69±2.59	2.719	**0.019***	13
Push and Release Test [a]	1 [0-3]	1 [0-3]		1.000	13
CAPSIT-PD time [b]	29 [13-360]	16 [9-93]	-2.746	**0.006***	13
CAPSIT-PD steps [b]	54 [26-500]	36 [24-175]	-2.378	**0.017***	13
CAPSIT-PD freezing [b]	0 [0-9]	0 [0-8]	-2.00	0.046	13
ROM shank [b]	40.61 [11.10-71.86]	53.77 [20.08-74.32]	-2.621	**0.009***	13
ROM knee [b]	39.48 [20.31-49.05]	44.82 [26.71-52.81]	-3.110	**0.002***	13
Mean stride length [b]	43.37 [12.36-77.10]	57.78 [21.22-77.64]	-2.201	0.028	13
Mean stride velocity [b]	47.82 [9.97-81.28]	57.47 [23.50-79.67]	-1.642	0.101	13
Mean gait cycle time [b]	1.07 [0.59-1.45]	1.01 [0.88-1.36]	-0.664	0.507	13
Swing time asymmetry [b]	6.99 [0.31-47.37]	10.11 [0.92-50.31]	-1.153	0.249	13

(mean ± SD) / (Median [min-max])
Two-sided p-values are provided. [a] sign test, [b] Wilcoxon signed-rank test, [c] paired sample t-test
*significant after FDR correction

3.3. Outcome

17 patients with STN-DBS received a postoperative characterization six months after surgery. One patient was not available for follow-up due to voluntary drop out (ID2).

A significant reduction in the LEDD was observed from baseline to follow-up (LEDD at baseline 1365±630 mg/d, at follow-up 864±488; t=3.600, p=0.002) (Cebi et al., 2020).

Detailed information on the stimulation parameters is provided in Table 7.

Table 7: Stimulation parameters at follow-up

ID	Contacts	Amplitude (V)	Pulse width (µs)	Frequency (Hz)	Contacts	Amplitude (V)	Pulse width (µs)	Frequency (Hz)
3*	2- C+	3.5	60	130	10- C+	3.2	60	130
4	2- C+	3.1	60	130	10- 11+	4.2	60	130
5*	2- C+	3.3	60	130	10- C+	3.7	60	130
6*	2- C+	1.7	60	130	10- C+	1.5	60	130
9*	3- C+	2.0	90	130	11- C+	2.1	90	130
11*	2- 3+	3.2	60	130	10- 11+	3.5	60	130
12*	2- 3+	4.0	60	130	11- 10+	3.0	60	130
14*	3- C+ 2- 1+	3.1 1.8	60 60	125 125	10-11- 9+	2.9	60	125
15*	3- C+	2.0	60	130	10- C+	1.6	60	130
16*	2- C+	1.8	60	130	10- C+	2.0	60	130
17	3- C+	2.5	60	130	10- C+	2.2	60	130
18	2- C+	2.7	60	130	10- C+	3.2	60	130
19*	2- C+	3.4	60	125	10- C+	2.9	60	125
20*	2- 3+	2.9	60	130	10- C+	1.6	60	130
21	2- C+	1.5	60	130	10- C+	1.3	60	130
22*	2- C+	3.7	60	130	10- C+	3.2	60	130
23*	2- C+	2.3	60	130	11- 9+	6.0	60	130

C: Generator case. Electrode contact numbers 0-1-2-3 are left sided, contact numbers 8-9-10-11 right sided.
*freezers.
ID14 had an interleaving stimulation on left sided electrode.

Entire group: There was a significant improvement in MDS-UPDRS III (p<0.001), PIGD subscore (p=0.002) and Push and Release Test (p=0.013) between baseline medication off and follow-up medication on/stimulation on. Berg Balance

Scale (p=0.013) and CAPSIT-PD improved also a significant difference between two conditions in time (p=0.017) and the number of steps (p=0.009). Based on spatiotemporal and kinematic gait parameters a significant improvement of joint ROM at shank (p=0.008), and at knee level (p=0.005), as well as an improvement in stride length (p=0.012) were observed. Stride velocity, gait cycle time and swing time asymmetry did not change (Cebi et al., 2020).

Freezing patients: There was a significant improvement in MDS-UPDRS III (p<0.001), PIGD subscore (p<0.001) and Push and Release Test (p=0.012) between baseline medication off and follow-up medication on/stimulation on. Berg Balance Scale (p=0.019) and CAPSIT-PD showed also a significant difference in time (p=0.041) and the number of steps (p=0.028); number of freezing episodes remained unchanged. Based on spatiotemporal and kinematic gait parameters a significant improvement of joint ROM at shank (p=0.010), at knee level (p=0.010), of stride length (p=0.013) and stride velocity (p=0.013) were observed. Gait cycle time and swing time asymmetry did not change (Cebi et al., 2020).

Based on other performed anamnestic scales, in entire group as well as in freezing subgroup, MDS-UPDRS IV for motor complications was significantly improved from baseline to follow-up. MDS-UPDRS I, MDS-UPDRS II and PDQ 39 did not show a statistically significant improvement in entire group. In PDQ 39 there was a significant worsening in communication and bodily discomfort. In the freezer subgroup PDQ 39 showed an improvement in activities of daily living subscore (p=0.011) (Cebi et al., 2020).

The results from the follow-up are given in Table 8.

Table 8: Results from follow-up and comparison to baseline assessment
A: results of entire group

	Baseline **Medication off**	**Follow-up** **Medication on/ stimulation on**	***T*-value/ *Z*-value**	***p*-value**	***n***
MDS-UPDRS III [c]	47.59±14.77	28.88±11.94	6.065	**<0.001***	17
PIGD subscore [c]	5.71±2.78	2.82±2.74	3.738	**0.002***	17
Push and Release Test [a]	1 [0-4]	0 [0-4]		**0.013***	17
Berg Balance Scale [b]	43 [9-56]	56 [11-56]	-2.482	**0.013***	17
CAPSIT-PD time [b]	32 [11-533]	15 [11-257]	-2.386	**0.017***	16
CAPSIT-PD steps [b]	55 [21-500]	25.5 [18-330]	-2.612	**0.009***	16
CAPSIT-PD freezing [b]	0 [0-32]	0 [0-43]	-0.365	0.715	16
ROM shank [b]	37.63 [10.10-74.12]	67.37 [14.56-80.42]	-2.669	**0.008***	15
ROM knee [b]	38.05 [16.30-52.05]	49.96 [23.55-59.25]	-2.783	**0.005***	15
Mean stride length [b]	42.38 [11.22-80.43]	69.59 [13.59-88.03]	-2.499	**0.012***	15
Mean stride velocity [b]	41.20 [7.17-84.65]	64.77 [18.76-79.62]	-2.761	0.078	15
Mean gait cycle time [b]	1.09 [0.64-1.65]	1.09 [0.85-1.35]	-0.557	0.955	15
Swing time asymmetry [b]	3.45 [0.23-12.29]	7.88 [1.09-41.49]	-2.045	0.041	15

(mean ± SD) / (Median [min-max])
Two-sided p-values are given. [a] sign test, [b] Wilcoxon signed-rank test, [c] paired sample t-test
*significant after FDR correction
ID2 lost to follow-up
ID23 was not able to complete CAPSIT-PD in medication off condition
Kinematic data quality of ID16 at baseline medication off and of ID3 in follow-up condition was not adequate for analysis

B: results of freezing patients

	Baseline **Medication off**	**Follow-up** **Medication on/ stimulation on**	***T*-value/ *Z*-value**	***p*-value**	***n***
MDS-UPDRS III [c]	49.92±16.24	31.08±11.54	5.125	**<0.001***	13
PIGD subscore [c]	6.77±2.05	2.85±2.73	5.447	**<0.001***	13
Push and Release Test [a]	2 [0-4]	0 [0-3]		**0.012***	13
Berg Balance Scale [b]	42 [9-56]	55 [11-56]	-2.355	**0.019***	13
CAPSIT-PD time [b]	38.5 [12-533]	15 [11-257]	-2.045	**0.041***	12
CAPSIT-PD steps [b]	62.5 [25-500]	27 [22-330]	-2.197	**0.028***	12
CAPSIT-PD freezing [b]	0 [0-31]	0 [0-43]	-0.365	0.715	12
ROM shank [b]	36.63 [10.10-74.12]	67.42 [14.56-79.69]	-2.578	**0.010***	11
ROM knee [b]	34.19 [16.30-51.25]	49.12 [23.55-59.25]	-2.578	**0.010***	11
Mean stride length [b]	39.78 [11.22-80.43]	69.69 [13.60-88.04]	-2.490	**0.013***	11
Mean stride velocity [b]	34.58 [7.17-84.65]	64.93 [18.76-79.62]	-2.134	**0.033***	11
Mean gait cycle time [b]	1.05 [0.64-1.65]	1.08 [0.85-1.26]	-0.533	0.594	11
Swing time asymmetry [b]	4.42 [0.23-40.57]	8.03 [1.09-41.49]	-1.245	0.213	11

(mean ± SD) / (Median [min-max])
Two-sided p-values are given. [a] sign test, [b] Wilcoxon signed-rank test, [c] paired sample t-test
*significant after FDR correction
ID2 lost to follow-up
ID23 was not able to complete CAPSIT-PD in medication off condition
Kinematic data quality of ID16 at baseline medication off and of ID3 in follow-up condition was not adequate for analysis

C: anamnestic scores of entire group

	Baseline	Follow-up	*T*-value	*p*-value	*n*
MDS-UPDRS I [c]	10.41±4.18	11.06±5.63	-0.555	0.587	17
MDS-UPDRS II [c]	17.76±8.13	17.47±9.86	0.172	0.866	17
MDS-UPDRS IV [c]	7.06±3.94	3.82±3.86	4.974	**<0.001***	17
PDQ39 Mobility [c]	51.91±23.84	52.94±29.95	-0.192	0.850	17
PDQ39 Activities of daily living [c]	43.38±21.10	34.31±21.22	1.896	0.076	17
PDQ39 Emotional well-being [c]	27.70±19.32	34.07±16.15	-1.621	0.125	17
PDQ39 Stigma [c]	27.21±20.84	28.31±22.86	-0.259	0.799	17
PDQ39 Social support [c]	20.10±18.65	20.59±17.95	-0.120	0.906	17
PDQ39 Cognition [c]	24.27±17.94	21.32±15.99	0.783	0.445	17
PDQ39 Communication [c]	12.75±12.88	25.98±20.39	-3.628	**0.002[n]**	17
PDQ39 Bodily discomfort [c]	28.43±20.43	39.71±28.34	-2.708	**0.016[n]**	17

[c] paired sample t-test
*significant after FDR correction
[n] significant negative correlation, means a significant worsening

D: anamnestic scores of freezing patients

	Baseline	Follow-up	*T*-value	*p*-value	*n*
MDS-UPDRS I [c]	10.54±4.22	11.15±5.52	-0.447	0.663	13
MDS-UPDRS II [c]	18.92±8.07	19.15±9.12	-0.114	0.911	13
MDS-UPDRS IV [c]	7.38±3.12	4.46±3.87	4.275	**0.001***	13
PDQ39 Mobility [c]	53.27±21.47	55.00±27.46	-0.263	0.797	13
PDQ39 Activities of daily living [c]	47.44±20.66	35.26±21.63	3.012	**0.011***	13
PDQ39 Emotional well-being [c]	29.81±19.46	35.58±15.74	-1.322	0.211	13
PDQ39 Stigma [c]	32.21±19.57	28.37±21.14	0.983	0.345	13
PDQ39 Social support [c]	23.08±19.59	24.36±18.78	-0.249	0.808	13
PDQ39 Cognition [c]	24.52±17.95	21.16±16.45	0.712	0.490	13
PDQ39 Communication [c]	13.46±14,25	26.92±22.09	-3.074	**0.010** [n]	13
PDQ39 Bodily discomfort [c]	28.21±21.12	35.90±26.44	-1.683	0.118	13

[c] paired sample t-test
*significant after FDR correction
[n] significant negative correlation, means a significant worsening

3.4. Improvement of freezing of gait

A subgroup analysis was performed focusing on FOG in patients with definite FOG (*n*=13) to investigate FOG outcome after STN-DBS. For this purpose, FOG-AC scores between different conditions were compared. At baseline assessment a significant improvement of FOG-AC from medication off to medication on condition (*p*=0.002) was observed. In baseline medication off condition five patients (ID3, ID5, ID6, ID22, ID23) were not able to perform the FOG-AC, therefore they were assigned the highest value from this test (36 points).

Also, a significant improvement was shown at interim assessment from medication off/stimulation off to medication off/stimulation on condition (*p*=0.003) (Cebi et al., 2020).

Our primary outcome was the improvement of FOG-AC in follow-up compared to baseline medication off condition, which was significantly better at follow-up (*p*=0.003). The results are demonstrated in Table 9 (Cebi et al., 2020).

FOG-AC scores for individual patients are given in Table 10 and FOG-AC scores at each assessment and condition are given in Figure 4 as box plots (Cebi et al., 2020).

Table 9: Freezing of gait outcome

	Baseline Medication off	**Baseline Medication on**	***Z*-value**	***p*-value**	***n***
FOG-AC [b]	24 [11-36]	1 [0-36]	-3.061	**0.002***	13

	Interim Medication off/ stimulation off	**Interim Medication off/ stimulation on**	***Z*-value**	***p*-value**	***n***
FOG-AC [b]	17 [3-36]	5 [0-36]	-2.937	**0.003***	13

	Baseline Medication off	**Follow-up Medication on/ stimulation on**	***Z*-value**	***p*-value**	***n***
FOG-AC [b]	24 [11-36]	0 [0-36]	-2.986	**0.003***	13

(Median [min-max])
Two-sided p-values are given. [b] Wilcoxon signed-rank test
*significant after FDR correction

Table 10: FOG-AC scores of each patient (Cebi et al., 2020)

ID	Baseline Medication off	Baseline Medication on	Interim Assessment Medication off/ stimulation off	Interim Assessment Medication off/ stimulation on	Follow-up Medication on/ stimulation on
3	36	36	36	36	36
5	36	2	7	1	0
6	36	1	22	5	0
9	16	0	22	22	4
11	36	0	36	4	2
12	11	0	4	0	0
14	24	0	7	5	0
15	22	0	17	0	0
16	21	2	14	3	1
19	22	20	32	31	30
20	17	3	3	0	0
22	36	7	36	22	5
23	36	0	14	11	0

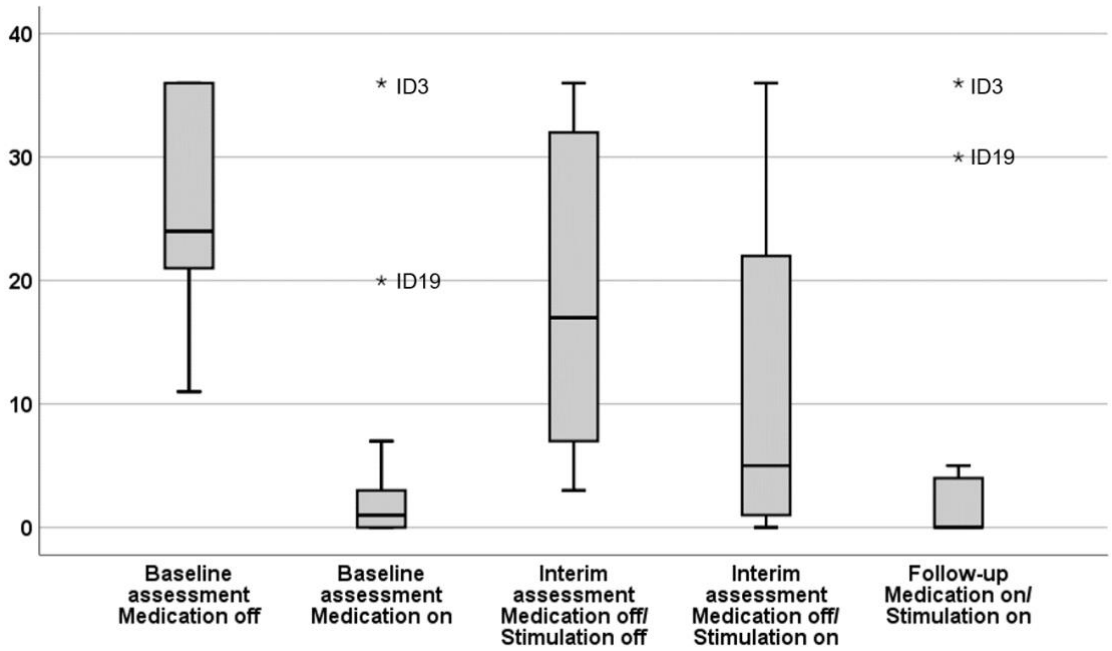

Figure 4: Severity of freezing of gait in different conditions (Cebi et al., 2020)
Results are given as box plots. x-axis: therapeutic condition; y-axis: score of the Freezing of Gait Assessment Course.

3.5. Correlations: Surrogates linked to a better freezing of gait outcome

The difference between FOG-AC scores at baseline medication off condition and at follow-up medication on/stimulation on condition were built and labelled as the FOG outcome. Correlations were then formed to identify clinical and kinematic features linked to a favorable FOG outcome after STN-DBS.

From clinical features, we found a significant correlation between preoperative levodopa response of FOG-AC and FOG outcome (p<0.001). Moreover, preoperative levodopa response of PIGD subscore (p=0.004) and severity of FOG-AC in preoperative medication off condition (p=0.016) correlated to a better postoperative FOG outcome. Preoperative LEDD, age, disease duration, preoperative severity of MDS-UPDRS III in medication off and preoperative levodopa response of MDS-UPDRS III score did not correlate to a better outcome (Cebi et al., 2020).

Correlations between FOG outcome and gait parameters were also analyzed. We found significant correlations between FOG outcome and preoperative levodopa response of ROM at shank (p=0.005), at knee level (p=0.001) and stride length (p=0.004). Preoperative levodopa response of stride velocity, gait cycle time and swing time asymmetry were not related to a better outcome. Details of correlations are depicted in Table 11 and Figures 5-10 (Cebi et al., 2020).

Table 11: Clinical and kinematic variables correlating to a better FOG outcome (Cebi et al., 2020)

	Correlation Coefficient	***p*-value**	***n***
Preoperative LEDD	0.459	0.115	13
Age	0.177	0.562	13
Disease duration	0.202	0.508	13
Preoperative levodopa response of FOG-AC	0.957	**<0.001***	13
Preoperative severity of FOG-AC in medication off condition	0.649	**0.016***	13
Preoperative levodopa response of PIGD subscore	0.743	**0.004***	13
Preoperative severity of MDS-UPDRS III in medication off condition	-0.028	0.929	13
Preoperative levodopa response of MDS-UPDRS III	0.425	0.147	13
Preoperative levodopa response of ROM shank	0.746	**0.005***	12
Preoperative levodopa response of ROM knee	0.817	**0.001***	12
Preoperative levodopa response of stride length	0.761	**0.004***	12
Preoperative levodopa response of stride velocity	0.394	0.205	12
Preoperative levodopa response of gait cycle time	-0.113	0.727	12
Preoperative levodopa response of swing time asymmetry	0.458	0.135	12

Two-sided p-values are given.
*significant after FDR correction

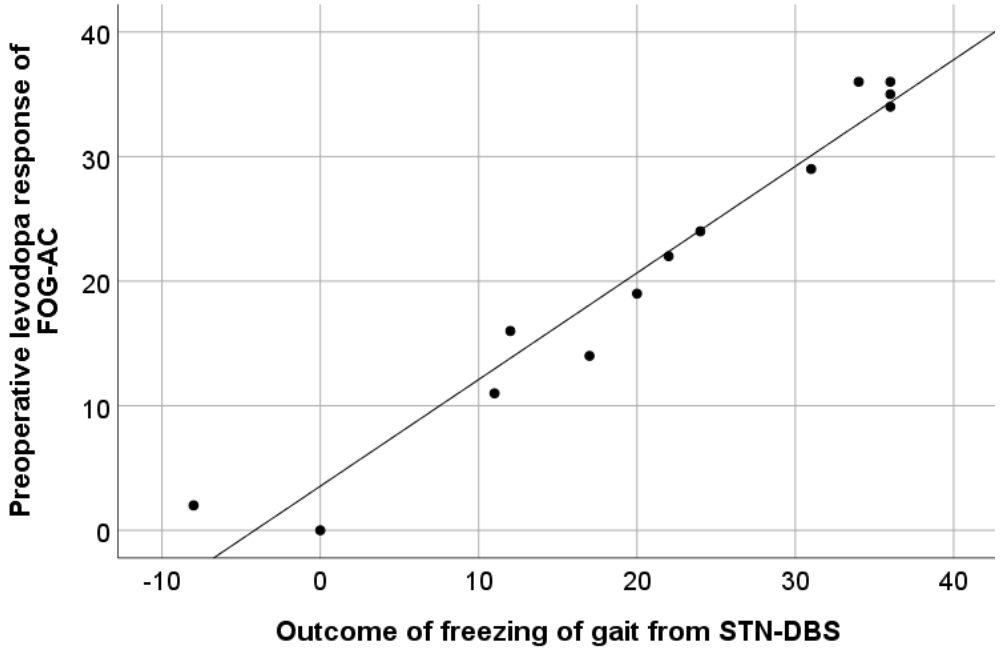

Figure 5: Correlation between FOG outcome and preoperative levodopa response of FOG-AC (Cebi et al., 2020)

Preoperative levodopa response of FOG-AC calculated as improvement of FOG-AC from baseline medication off to baseline medication on condition. Postoperative FOG outcome, calculated as improvement of FOG-AC from baseline medication off to follow-up medication on/stimulation on condition (r=0.957; p<0.001).

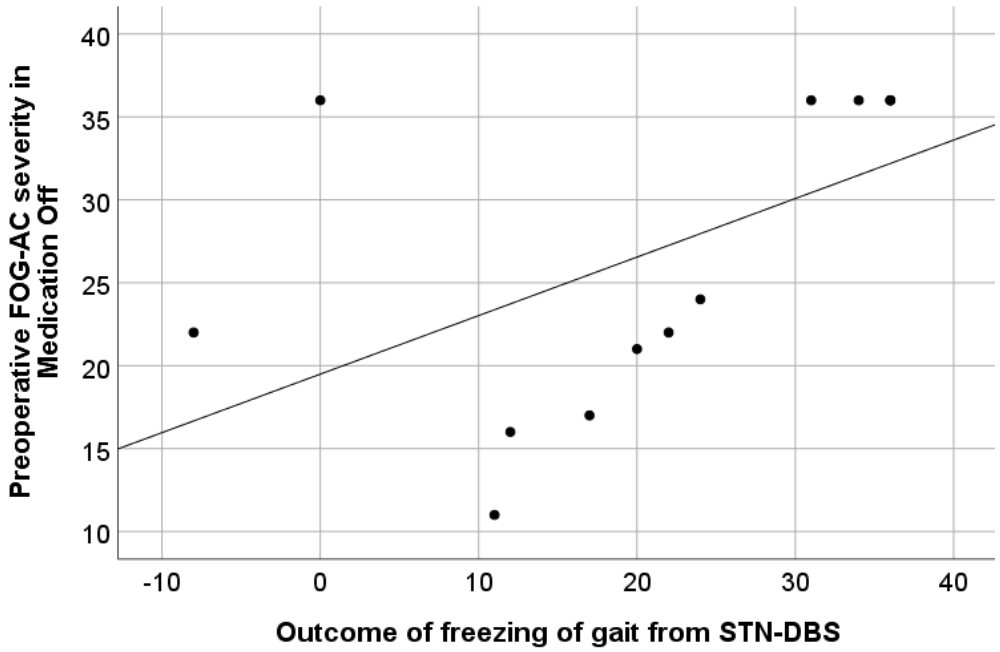

Figure 6: Correlation between FOG outcome and preoperative FOG-AC severity in medication off condition (Cebi et al., 2020)

FOG outcome calculated as improvement of FOG-AC from baseline medication off to follow-up medication on/stimulation on condition (r=0.649; p=0.016).

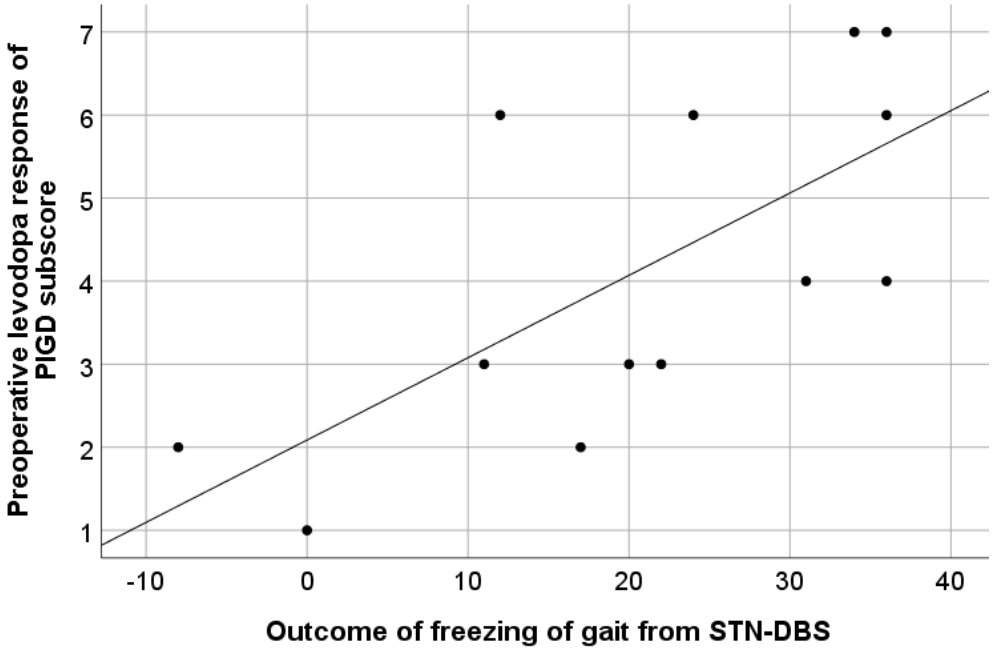

Figure 7: Correlation between FOG outcome and preoperative levodopa response of PIGD subscore (Cebi et al., 2020)

Preoperative levodopa response of PIGD subscore calculated as improvement of PIGD subscore from baseline medication off to baseline medication on condition. Postoperative FOG outcome calculated as improvement of FOG-AC from baseline medication off to follow-up medication on/stimulation on condition (r=0.743; p=0.004).

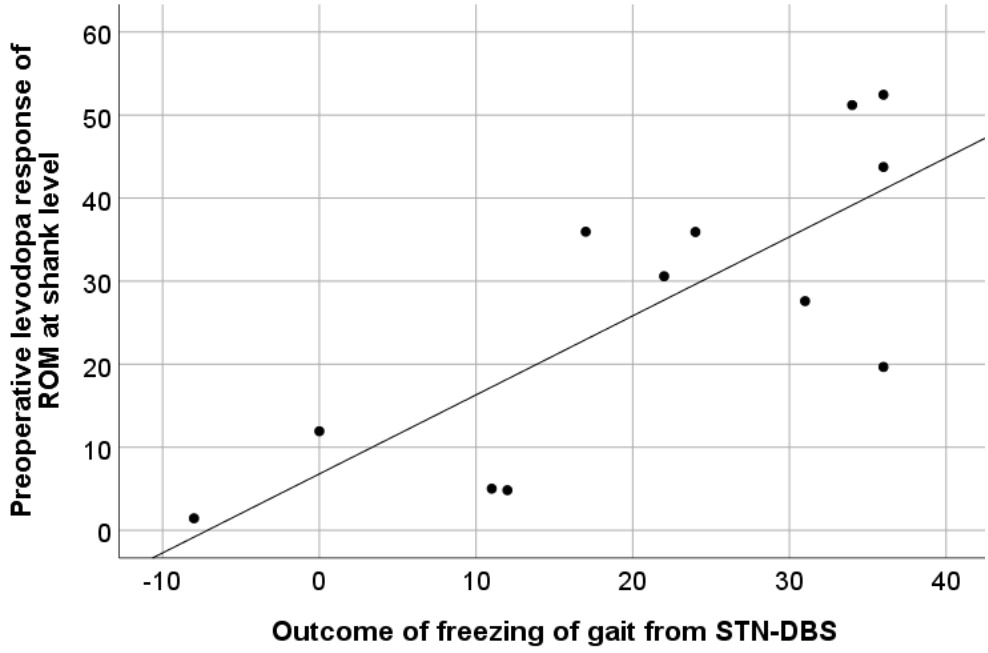

Figure 8: Correlation between FOG outcome and preoperative levodopa response of ROM at shank level (Cebi et al., 2020)

Preoperative levodopa response of ROM at shank level, calculated as improvement of ROM at shank level from baseline medication off to baseline medication on condition. Postoperative FOG outcome calculated as improvement of FOG-AC from baseline medication off to follow-up medication on/stimulation on condition (r=0.746; p=0.005).

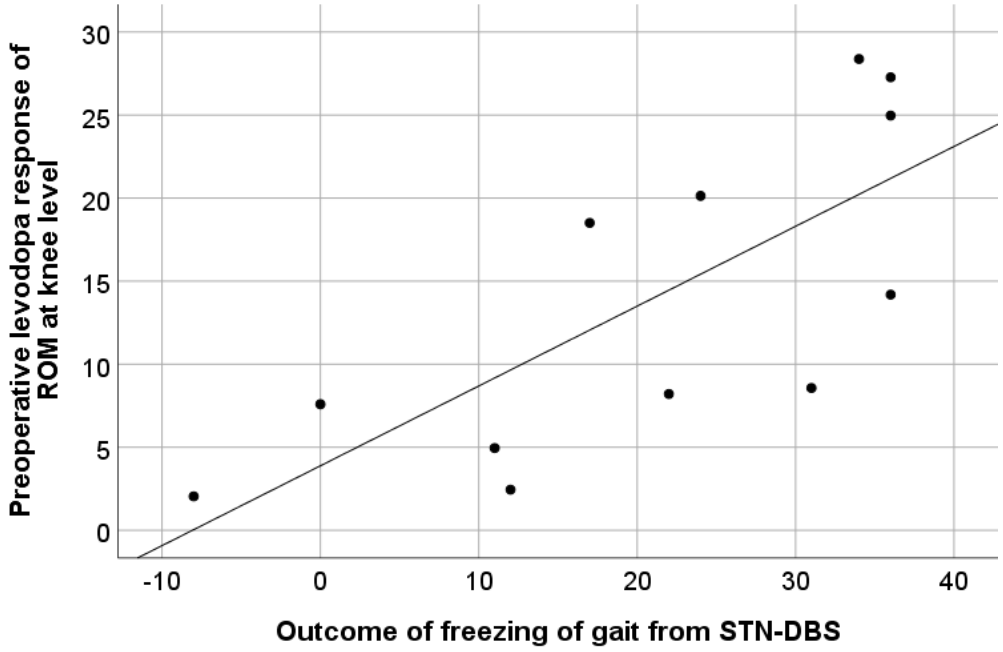

Figure 9: Correlation between FOG outcome and preoperative levodopa response of ROM at knee level (Cebi et al., 2020)

Preoperative levodopa response of ROM at knee level calculated as improvement of ROM at knee level from baseline medication off to baseline medication on condition. Postoperative FOG outcome, calculated as improvement of FOG-AC from baseline medication off to follow-up medication on/stimulation on condition (r=0.817; p=0.001).

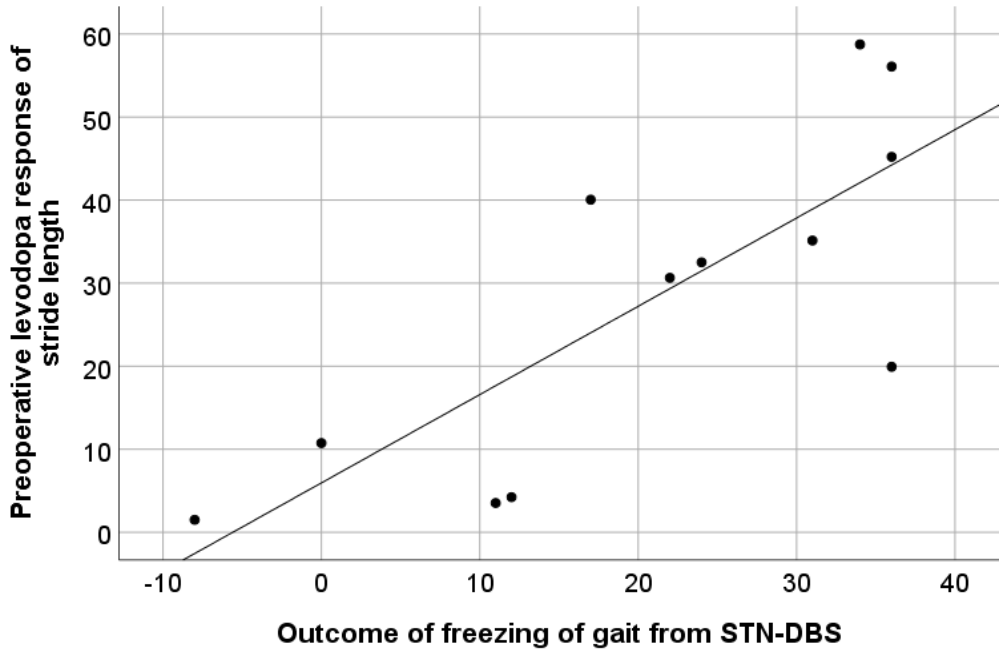

Figure 10: Correlation between FOG outcome and preoperative levodopa response of stride length (Cebi et al., 2020)

Preoperative levodopa response of stride length calculated as improvement of stride length from baseline medication off to baseline medication on condition. Postoperative FOG outcome calculated as improvement of FOG-AC from baseline medication off to follow-up medication on/stimulation on condition (r=0.761; p=0.004).

3.6. Prediction

For our prediction model, we used FOG outcome as the dependent value, which is calculated as the difference in FOG-AC score between six months follow-up and preoperative medication off condition. The clinical and kinematic variables which showed significant correlation to FOG outcome were used as independent values. These independent values were preoperative levodopa response of FOG-AC, preoperative FOG-AC severity in medication off condition, preoperative levodopa response of PIGD subscore, preoperative levodopa response of ROM shank, preoperative levodopa response of ROM knee and preoperative levodopa response of stride length. The prediction model showed that the preoperative levodopa response of FOG-AC predicted the postoperative FOG outcome (R^2=0.952, 95% CI: 0.95-1.29, p<0.001) (Figure 5). Other independent variables did not show significant predictive values (preoperative FOG-AC severity p=0.966, preoperative levodopa response of PIGD subscore p=0.086, preoperative levodopa response of ROM at shank p=0.508, preoperative levodopa response of ROM at knee p=0.666and preoperative levodopa response of stride length p=0.555) (Cebi et al., 2020).

4. Discussion

Due to variable outcomes of gait and FOG after STN-DBS implantation, it is important to stratify and counsel patients with predominant gait problems including FOG during the preoperative period about the expected outcomes. This consultation would be very helpful for the patients' decision towards an implantation by giving patients an opinion about what to expect from STN-DBS. Additionally, this may help prevent frustrations after implantation. Unfortunately, with our current knowledge the accuracy of such prediction is limited. Only a few meta-analyses or retrospective studies are available in literature, which point to different conclusions. Findings from these studies certainly provide valuable information, but they are not sufficient to consult patients optimally as mentioned above. Therefore, further insights into preoperative factors determining the gait and FOG outcome is need.

Our study has the novelty of being the first prospective study investigating these factors. Besides not only have we considered clinical scores such as UPDRS, but also took quantitative FOG assessment and kinematic measures into account. Similar to existing literature we showed that FOG severity was improved preoperatively by levodopa and postoperatively with STN-DBS eight weeks after STN-DBS implantation. The combination of both these therapies improved FOG at six months follow-up compared to preoperative medication off condition as well. Gait kinematics involving stride length, ROM at shank and at knee level were modulated preoperatively by levodopa and postoperatively with STN-DBS, as well as by combination of both therapies at six months. Stride velocity was only modulated preoperatively by levodopa but not modulated with STN-DBS postoperatively. After characterizing these important features related to FOG, we built correlations with these preoperative features and FOG outcome. Our study suggests that favorable FOG outcome correlates to the preoperative clinical and kinematic characteristics. Correlation has been observed in particular to levodopa response of the FOG-AC, the preoperative severity of FOG-AC in medication off condition, as well as levodopa response of PIGD subscore of the MDS-UPDRS part III (sum of items 3.10-3.12). Among kinematic gait parameters, preoperative levodopa response of ROM at shank and at knee level as well as preoperative

levodopa response of stride length are related to a better FOG outcome. Furthermore, our prediction model with exploratory approach showed that the preoperative levodopa response of FOG-AC predicts the FOG outcome. Other values which showed a correlation with FOG outcome did nor further improve the accuracy of the prediction model (Cebi et al., 2020).

4.1. Effects of levodopa, stimulation and combined therapy

Preoperatively, all of our patients had a clear levodopa response in their motor scores measured by the total MDS-UPDRS III (mean improvement of 45.1±13.9%). This is seen as a prerequisite towards the decision for STN-DBS (Defer et al., 1999). Most of our patients also had preoperatively levodopa sensitive gait and balance disorders, which was proven by a significant improvement of gait and balance measured by the PIGD subscore, Push and Release Test, Berg Balance Scale and number of steps as well as time in CAPSIT-PD. These results were similar to existing literature (Nova et al., 2004, Koller et al., 2004).

Focusing on gait kinematics after levodopa administration we were able to demonstrate an improvement of ROM of knee and ankle, stride length and stride velocity as in other previous studies (Faist et al., 2001, Stolze et al., 2001, Xie et al., 2001, Ferrarin et al., 2005, Krystkowiak et al., 2003). Gait cycle time and swing time asymmetry did not change between medication off and medication on condition. Other studies focusing on gait kinematics were mostly not able to show any improvements of temporal gait measures under levodopa (Collomb-Clerc and Welter, 2015). Absence of improvement of gait cycle time were concordant with these studies. We found only one existing study, which investigated the effect of levodopa on gait asymmetry. Similar to our results, this study did not find significant change in gait asymmetry after levodopa administration (Lubik et al., 2006). Previously, we reported that 13 out of 18 patients suffered from FOG preoperatively. In baseline medication off condition, five of 13 freezers (ID3, ID5, ID6, ID22, ID23) were not able to perform the FOG-AC, therefore they were rated with the highest value of the test (36 points). In medication on condition all 13

freezers, except one (ID3), received better scores in FOG-AC compared to medication off condition. Another patient (ID19) showed an insufficient levodopa response of FOG after levodopa administration (22 points in medication off condition and 20 points in medication on condition). An important annotation about our study is that most of our patients had levodopa sensitive gait problems including FOG. Only the previously mentioned two patients (ID3 and ID19) showed levodopa resistance or insufficiently responsive gait and FOG. Although gait and freezing were levodopa resistant, these two patients had levodopa sensitive general motor symptoms (bradykinesia and rigidity) and showed motor fluctuations under optimized medication accompanied by a reduced quality of life due to fluctuations. We should admit that the patients with levodopa resistant gait problems were underrepresented in our study, because as reported above we only had two non-responders regarding FOG within 13 freezers.

The rate of improvement in patients with levodopa responsive FOG differed between individual patients. After levodopa application, six patients did not demonstrate FOG anymore (ID9, 11, 12, 14, 15, 23), i.e. these patients showed only off- condition FOG. Remaining patients (including ID3) showed FOG in both off and on condition. None of our patients had levodopa induced FOG (Espay et al., 2012), which is a very rare phenomenon. In some cases, such patients might show a worsening of preexisting FOG after levodopa intake. In other cases, these patients do not show FOG in medication off condition, but it appears after levodopa intake (Espay et al., 2012).

Eight weeks after the operation, subthalamic stimulation alone (in medication off condition) led to a significant improvement of motor symptoms, measured by the total MDS-UPDRS III (mean improvement 32.5±15.0%) during interim assessment. This improvement was less than 41% on average (Deuschl et al., 2006), nevertheless over 30% in range. Only one patient (ID19), who predominantly had axial symptoms, showed no improvement in MDS-UPDRS III score (45 points in stimulation off condition and 46 points in stimulation on condition), although the patient had a good response to levodopa preoperatively respective to MDS-UPDRS III score (29% improvement). Retrospectively, we cannot rule out entirely that this patient may have suffered from a progressive

supranuclear palsy parkinsonism. However, at the timepoint of preoperative screening the patient already had PD for five years, showed a 29% levodopa response of total motor score (MDS-UPDRS III) and had motor fluctuations. Therefore, we decided for STN-DBS. In retrospect, we will discuss that this patient might have atypical PD. The main supporting argument in this case is the unaffected MDS-UPDRS III score after switching stimulation on.

PIGD subscore as well as number of steps and time in CAPSIT-PD improved after turning stimulation on. While Push and Release Test improved by levodopa at baseline, it did not improve with stimulation alone at interim assessment. Here we would like to discuss both therapies, levodopa and STN-DBS that may have different pathways (Welter et al., 2002, Lang and Obeso, 2004, Fasano et al., 2015).

Stimulation alone improved stride length, ROM at shank and at knee level concordant to previous studies (Allert et al., 2001, Stolze et al., 2001, Ferrarin et al., 2002). Improvement of stride velocity did not reach the significance level, although it was reported to have improved in previous publications (Ferrarin et al., 2005, Xie et al., 2001). The reason for not reaching the significance level maybe due to the small sample size. Gait cycle time and swing time asymmetry did not change between stimulation off and stimulation on condition. From most of the previous studies we know that the temporal parameters of gait would not be improved by STN-DBS (Collomb-Clerc and Welter, 2015), therefore unchanged gait cycle time was not an exception for our study. Some studies showed an improvement of asymmetry index under STN-DBS (Lubik et al., 2006, Johnsen et al., 2009) and others did not (Allert et al., 2001). One study focusing in particular on swing time asymmetry showed an improvement under STN-stimulation (Scholten et al., 2017). We were not able to reproduce these findings, perhaps again due to our small sample size.

Focusing on the freezer subgroup at interim assessment, all of 13 freezers showed FOG in medication off/stimulation off condition. Three patients (ID3, 11 and 22) were not able to perform FOG-AC in medication off/stimulation off condition similar to the case in preoperative medication off condition. Two

patients (ID9 and ID19) demonstrated more severe FOG in FOG-AC in medication off/stimulation off condition compared to preoperative medication off condition. Compared to preoperative medication off condition, remaining patients (ID5, 6, 12, 14, 15, 16, 29, 14) showed FOG at a lower extent in medication off/stimulation off condition eight weeks after operation. This could be associated to a micro lesioning effect or insufficiency of 30 minutes stimulation arrest or insufficient medication pause. One patient (ID6) achieved the same score (22 points) and one other (ID19) almost the same (32 vs 31 points) in FOG-AC after turning the stimulation on, which means they showed no response of FOG to STN-DBS. It is worth mentioning that ID19 showed also no levodopa response of FOG-AC preoperatively. Other patients showed an improvement of FOG-AC between two conditions. The extent of the improvements was again different in between the patients. Ten of 13 patients showed FOG also in medication off/stimulation on condition (FOG-AC scores between 3 and 36 points), only three of 13 patients showed no FOG in medication off/stimulation on condition. During baseline we had six patients showing no freezing after levodopa application in medication on condition. From these results we can conclude that stimulation was less efficient than levodopa to alleviate FOG alone, which was in accordance with the previous publications (Ferraye et al., 2008). However, we should admit that we did not make a head to head comparison of improvement levels at baseline and interim assessment. Another important point in our study was that none of the five non-freezers became a freezer at the time of interim assessment. Therefore, in our group we had no patient with stimulation induced FOG (Follett et al., 2010).

At follow-up assessment, the patients had a significant improvement of motor symptoms compared to preoperative medication off condition but not compared to medication on condition in accordance with existing literature (Schlenstedt et al., 2017). Looking at our clinical scores, MDS-UPDRS III, PIGD subscore, Push and Release Test, Berg Balance Scale, number of steps as well as time in CAPSIT-TD timed walking test improved with combined therapy compared to preoperative medication off condition. These findings were concordant to existing literature (Deuschl et al., 2006, Szlufik et al., 2018).

Among kinematic gait parameters; stride length, ROM at shank and at knee level were significantly better compared to preoperative medication off condition but not compared to medication on. Improvement of stride velocity again did not reach the significance level. However, as we have only analyzed the freezer subgroup; stride velocity reached the significance level. Therefore, we discuss that we have some outliers, who probably had tremor dominant PD, showing no gait impairment in medication off condition.

Seven of 13 freezers showed FOG at follow-up assessment, remaining six had no FOG. Statistically, a significant improvement of FOG severity is observed (FOG-AC score between 1 and 36) compared to preoperative medication off condition but not compared to medication on condition. In our cohort we did not have any patient, who did not suffer from FOG during baseline but did suffer from FOG during follow-up. Two patients showed no freezing in baseline medication on condition but showed freezing at follow-up. This is probably due to levodopa overshoot during levodopa challenge at baseline. To prevent such a levodopa overshoot, we decided to perform follow-up in regular on condition. As we focused on patients individually, three patients showed no FOG during interim assessment in medication off/stimulation on condition as well as during the follow-up assessment. All other patients except ID3, who could not perform FOG-AC, had better FOG-AC scores at follow-up compared to interim assessment in medication off/stimulation on condition (Cebi et al., 2020).

From baseline to follow-up we could reduce the LEDD (mean reduction 40±23%). Compared to preoperative assessment the motor complications assessed by MDS-UPDRS part IV was significantly improved, this is concordant with existing literature (Deuschl et al., 2006). Postoperative MDS-UPDRS part I and MDS-UPDRS part II scores did not differ from preoperative scores. Surprisingly, there were no improvements in PDQ39; also, not in mobility or activities of daily living subscores. These findings were discordant to existing literature, although we had a similar patient cohort with respect to disease duration and LEDD, only difference being the slightly higher ages of our patients (mean age 60.5±7.7 vs 66.9±6.9) (Deuschl et al., 2006, Cebi et al., 2020).

4.2. Features and predictors associated with a better freezing of gait outcome

In our study we have verified a significant improvement of FOG six months after STN-DBS in a regular daily relevant condition (medication on/stimulation on condition) compared to preoperative medication off condition. This finding was in line with previous publications (Ferraye et al., 2008, Bejjani et al., 2000, Schlenstedt et al., 2017, Barbe et al., 2019). However, we shall add that these studies mostly used the anamnestic FOG item 14 from old UPDRS. As mentioned in the introduction section, studies focusing primarily on FOG are rare and these mostly use specific questionnaires relying on patient reported information. Studies focusing on objectively assessed FOG severity as well as the studies searching for predictors are uncommon.

A meta-analysis from 2017 using UPDRS item 14 as one of the primary outcome parameters showed a significant correlation of this outcome to preoperative levodopa response of the UPDRS III total score in short and long time periods. In the discussion they admit that UPDRS gives only limited information about gait and FOG and they report that further specific features of gait related to FOG are needed. We could not verify this significant correlation of preoperative levodopa response of the MDS-UPDRS III total score with FOG outcome (Schlenstedt et al., 2017, Cebi et al., 2020).

Another recent publication using also UPDRS item 14 as an outcome measure for FOG showed a reduction in FOG for 1/3 of patients after STN-DBS implantation and found a correlation between preoperative FOG severity and residual postoperative FOG (Karachi et al., 2019). Our study could not confirm this finding as well, even though we found a correlation between preoperative FOG severity and better FOG outcome. This could be related to the lower mean age of the patient cohort compared to ours (mean age 57.7±8.4). Additionally, their follow-up assessment was one year after operation and their sample size was much larger than ours (total 331 patients) (Cebi et al., 2020).

A secondary analysis of the EARLYSTIM-trial focused on FOG by analyzing UPDRS item 14. 52% of the patients showed FOG preoperatively, which

decreased to 34% at 24 months follow-up. The patients showing freezing at 24 months follow-up had longer disease duration compared to those who did not have FOG at 24 months follow-up anymore. This finding is important and new in the field; however, it should be interpreted carefully. Compared to our study and most of the other existing studies, the EARLYSTIM cohort was younger (mean 52.6±6.3 years) and had a shorter disease duration (mean 7.5±2.8 years) (Barbe et al., 2019, Cebi et al., 2020).

We can see that the existing studies have different conclusions. One main reason for this is probably the heterogenic patient characteristics. Logically, the patients with shorter disease duration would have a better outcome and the patients with longer disease duration would have a worse outcome. Another reason might be that these scores and items used are not sufficient or adequate to assess FOG. Anamnestic scores as well as regular gait tests are not specific to FOG and they may be not be sufficient for evaluation. UPDRS gives information about many aspects of PD including an idea about gait and FOG. However, specific features related to gait, freezing and falls such as gait kinematics are not included in this score (Schlenstedt et al., 2017). From previous publications we know that some kinematic characteristics of gait are related to FOG. These are namely gait rhythmicity, gait asymmetry and bilateral coordination of stepping (Plotnik et al., 2008). Impairments of these features are shown in PD patients with FOG. Moreover, an increase in cadence and decrease in step length are monitored prior to FOG (Weiss et al., 2019). There are no existing studies or publications investigating the relation of gait kinematics and their levodopa response to freezing outcome. This is an important absence in the literature (Cebi et al., 2020).

In the light of all the information above we have investigated clinical as well as kinematic features and their relation to the FOG outcome. We have found a significant correlation between preoperative levodopa response of ROM at knee and at shank level, as well as of stride length. From clinical data, preoperative levodopa response of FOG-AC, preoperative severity of FOG-AC in medication off condition and preoperative levodopa response of PIGD subscore correlated to a beneficial outcome. Preoperative FOG severity was defined by FOG-AC

score. The levodopa responsivity has been suggested in many other studies as a good predictor for general outcome after STN- DBS (Welter et al., 2002). However, it is not specifically investigated focusing on FOG. Age, disease duration, LEDD at baseline, severity of MDS-UPDRS III in preoperative medication off condition and preoperative levodopa response of MDS-UPDRS III score did not correlate to a better outcome. The reason for analyzing these features were previous findings from other publications (Welter et al., 2002, Schlenstedt et al., 2017, Barbe et al., 2019). On the whole, these results should be interpreted carefully. This is further discussed together with the reasons in the limitations section.

4.3. Limitations

Our study was designed as a prospective one without a control group. Due to its explorative design, it has a relatively small sample size with a total of 24 subjects, among them 18 with STN-DBS and 13 freezers. The clinical assessments were not performed in a blinded way. Our study was not designed to cover long-term effects of STN-DBS on gait and FOG. Thus, we had a relatively short follow-up time at six months. This was chosen to minimize the bias due to the natural progression of the disease. At follow-up assessment we decided for the medication on/stimulation on condition, since we wanted to determine the gait and FOG outcome under a regular daily life condition. We argue that medication pause overnight and a reinsertion of levodopa would have been artificial as it would not necessarily reflect normal daily life conditions. Because such a challenge would lead to an under or overshoot of dopamine effect depending on intestinal resorption or metabolism. Instead, an ongoing continuous intake of levodopa would lead to a more stable dopaminergic effect. The downside of this choice was of course that we were not able to determine the pure stimulation effect at the postoperative 6-month follow-up (Cebi et al., 2020).

Given that we selected the candidate patients according to existing clinical criteria and the major component in this selection was the levodopa-responsive parkinsonism, one might discuss that the patents with preoperative unfavorable

levodopa response of FOG have been under-represented in this study. That is probably the reason why we have found a high rate of responders after STN-DBS.

4.4. Insights

This is the first prospective study, which primarily used an objective FOG assessment with a validated rating instrument (Ziegler et al., 2010) compared to previous studies measuring FOG with UPDRS item 14, which does not reflect the severity of FOG objectively (Schlenstedt et al., 2017) and portrays only limited information. Only few studies focused on FOG as the primary end point, using mostly the new freezing of gait questionnaire (NFOG-Q) that relies on reported and not observed data. Moreover, some studies rely on unspecific walking tasks such as walking straight forward for a couple of meters, which might not always provoke FOG.

Most of the studies assessing gait parameters cover only the postoperative status or analyze the data retrospectively. Only a few studies with prospective design covering both preoperative and postoperative status are available.

Our study has the novelty of being the first study investigating the relationship of FOG outcome with preoperative clinical and kinematic measures in a prospective manner. Despite the small sample size and exploratory intent, the findings from our study provide fundamental information for larger prospective studies. Our findings from this study provide a good basis that shall be investigated further. Features related to FOG outcome should be confirmed in larger prospective studies such as a multicenter study involving higher number of subjects, with the aim to confirm our findings and validate the candidate clinical and kinematic features identified in this study for their predictive value. Besides, a longer follow-up period could be considered. Further clinical measures of long-term response of FOG should be included such as FOG questionnaire. In addition to assessments in the clinic, home-used sensors may enable acquisition of even superior information on kinematic measures (Cebi et al., 2020).

5. Summary

Freezing of gait (FOG) is one of the most debilitating symptoms in Parkinson's disease (PD), resulting in falls, injuries and immobility. Although FOG usually responds well to therapy in earlier stages of PD, as the disease progresses it becomes increasingly resistant to therapy. Only some patients show an improvement in FOG after deep brain stimulation of nucleus subthalamicus (STN-DBS), while remaining patients still suffer from FOG. STN-DBS is also shown to aggravate or even trigger FOG in some patients.

There are no predictive factors to stratify FOG response to deep brain stimulation. In our study, we aimed to find clinical and kinematic variables that may affect FOG outcome. We characterized 18 PD patients, 13 of them with preoperative FOG, undergoing STN-DBS treatment, both preoperatively and postoperatively. As primary outcome we focused on FOG and its relation to certain clinical surrogates, as well as kinematic features. At the preoperative assessment we included examinations under both medication off and medication on condition. First postoperative evaluation was conducted eight weeks after operation in medication off condition, once with stimulation switched off, followed by stimulation switched on to evaluate its effect. We have reassessed the patients on the same measures six months after STN-DBS implantation on their best individual treatment (medication on/stimulation on condition) to evaluate the overall outcome of FOG.

FOG, evaluated by the FOG Assessment Course (FOG-AC), improved significantly at six-month follow-up compared with the preoperative medication off condition. We observed a positive postoperative FOG outcome, when FOG-AC responded well to levodopa preoperatively. Furthermore, preoperative severity of FOG-AC in medication off condition and preoperative levodopa response of PIGD subscore were linked to a better FOG outcome. Among kinematic gait parameters, preoperative levodopa response of range of motion at ankle and at knee level as well as stride length pointed to a better outcome. A further regression model showed that preoperative levodopa response of FOG-AC predicted the postoperative FOG outcome.

These findings need to be confirmed in further studies with a larger patient cohort, such as in a multicenter study. Our study delivers candidate parameters for this purpose, which can be used for the study design and a statistical data-based estimation of number of required cases.

6. Zusammenfassung

Gangblockaden, sogenannte „feezing of gait“ (FOG) Episoden, gehören zu den an den stärksten beeinträchtigenden Symptomen der Parkinsonerkrankung. Insbesondere führen sie Stürzen, Verletzungen und Immobilität. Obwohl FOG meistens in früheren Krankheitsphasen auf dopaminerge Therapie gut anspricht, nimmt im Krankheitsverlauf der Therapieeffekt ab. Nur ein Teil der Patienten mit FOG erlebt eine Verbesserung des Freezings nach der Tiefen Hirnstimulation des Nucleus subthalamicus (STN-DBS). Andere Patienten zeigen hingegen weiterhin beeinträchtigendes FOG.

Bislang fehlen präoperative Faktoren, die ein gutes Ansprechen des FOG nach STN-DBS vorhersagen könnten. Dies ist für optimale Therapieentscheidungen aber bedeutend. In dieser Studie explorierten wir klinische und kinematische Variablen, die einen positiven Effekt der STN-DBS auf FOG-Ansprechen anzeigen könnten. Dafür charakterisierten wir 18 Parkinsonpatienten vor und nach STN-DBS, 13 davon wiesen ein präoperatives FOG auf. Wir konzentrierten uns auf FOG, sowie dessen Zusammenhang zu den präoperativen klinischen und kinematischen Gangparametern. Präoperative Auswertungen erfolgten in den sogenannten dopaminergen Off- und On-Zuständen. Die erste postoperative Auswertung erfolgte acht Wochen nach der Operation in im dopaminergen Off mit ausgeschalteter und danach mit angeschalteter Stimulation. Eine erneute postoperative Auswertung nach sechs Monaten erfolgte im dopaminergen On und mit angeschalteter Stimulation, um das Outcome in der für die Patienten alltagsrelevanten Therapiekondition zu erfassen.

Klinisch besserte sich FOG signifikant anhand des FOG Assessment Course (FOG-AC), mit Tiefer Hirnstimulation in der sechs Monaten Kontrolle im Vergleich zum präoperativen dopaminergen Off-Zustand. Diese Verbesserung zeigte eine positive Korrelation zum präoperativen Ansprechen des FOG-AC auf Levodopa, zum präoperativen Ansprechen des PIGD Subscore auf Levodopa und zum perioperativen Schweregrad des FOG im dopaminergen Off-Zustand. Von den kinematischen Gangparameter zeigte die präoperative Verbesserung der Schrittlänge sowie des Bewegungsumfang (range of motion) des

Sprunggelenkes und der Knie nach Levodopa-Gabe eine positive Korrelation mit einer Verbesserung des FOG. Eine zusätzliche Regressionsanalyse zeigte, dass das postoperative FOG-Outcome durch präoperatives Levodopa Ansprechen de FOG-AC mit hoher Genauigkeit vorhergesagt wird.

Die Ergebnisse aus unserer Studie müssen in größeren Folgestudien bestätigt werden. Unsere Studie liefert hierfür Kandidatenparameter, die für das Studiendesign und eine Daten-basierte statistische Fallzahlschätzung herangezogen werden können.

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8. Declaration of Contributions

I declare that I have produced the work entitled: "Preoperative Stratification of Gait Outcome from Subthalamic Nucleus Stimulation" at the Neurological University Clinic in Tübingen in the Department of Neurodegeneration under the supervision of Prof. Dr. med. Daniel Weiß. The concept of the study is designed together with Prof. Dr. med. Daniel Weiß. I have carried out the measurements and data collection by myself after a training given by Prof. Dr. med. Daniel Weiß and Frau Dr. rer. nat. Marlieke Scholten. All statistical analyses as well as literature research were conducted by myself.
I confirm that I have written the dissertation without any help from others and have cited all the articles I have used.
The manuscript is written by me and Prof. Dr. med. Daniel Weiß and Frau Dr. rer. nat. Marlieke Scholten have proof read the manuscript.

Ich erkläre, dass ich die zur Promotion eingereichte Arbeit mit dem Titel: „Vorhersage von Gang- und Gleichgewichtsfunktion nach Tiefer Hirnstimulation“ in der Neurologischen Universitätsklinik Tübingen in der Abteilung für Neurodegeneration unter Betreuung von Prof. Dr. med. Daniel Weiß durchgeführt habe. Die Konzeption der Studie erfolgte in Zusammenarbeit mit Prof. Dr. med. Daniel Weiß. Sämtliche Versuche wurden von mir nach Einarbeitung durch Prof. Dr. med. Daniel Weiß und Frau Dr. rer. nat. Marlieke Scholten eigenständig durchgeführt und dokumentiert. Die Datenanalyse und statistische Auswertung erfolgten nach Einarbeitung durch mich. Die Literaturrecherche erfolgte ausschließlich durch mich.

Ich versichere, die Dissertationsschrift selbständig verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

Die Veröffentlichung wurde von mir verfasst und von Prof. Dr. med. Daniel Weiß und Frau Dr. rer. nat. Marlieke Scholten überarbeitet.

Tübingen, den

Idil Cebi

9. Publications

Parts of the dissertation presented here have already appeared in the following publications:

Cebi I, Scholten M, Gharabaghi A and Weiss D (2020) Clinical and Kinematic Correlates of Favorable Gait Outcomes From Subthalamic Stimulation. Front. Neurol. 11:212. Doi: 10-3389/fneur.2020.00212

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