Spring 2023

# Effects of Coordinated Reset Deep Brain Stimulation of Subthalamic Nucleus on Parkinsonian Gait in the Non-Human Primate Model

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An Honors Thesis Submitted to the Neuroscience Program

at Macalester College, Saint Paul, Minnesota, USA

April 13th, 2023

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**Abstract**

Parkinson's Disease (PD) is a neurodegenerative disorder that affects over 10 million people worldwide. Deep Brain Stimulation (DBS) has been a successful treatment for advanced PD, however, can be accompanied with current spread related side effects. Coordinated Reset (CR) DBS is a novel therapeutic approach that could reduce the risk of side-effects by using lower current. Previous research has shown therapeutic effects of CR DBS on PD motor symptoms including akinesia, bradykinesia, rigidity, and tremor that sustained after stimulation cessation (i.e., carryover effect), however its effect on gait dysfunction is unknown even though it can be one of the most difficult symptoms to treat. The goal of this study is to investigate the carryover effect of subthalamic CR DBS on PD gait. Two non-human primates (NHP) were rendered parkinsonian and implanted with a DBS lead in the subthalamic nucleus (STN). Each subject received STN CR DBS for 2 hours per day for 5 consecutive days. Gait was quantitatively assessed before and after the stimulation using a gait testing apparatus. A modified clinical rating scale (mUPDRS) was used to monitor carryover effects on other motor symptoms. Moreover, in one NHP, the differential effects of CR DBS using two additional burst frequencies were also explored. Our results showed that STN CR DBS induced carryover improvement in gait as well as in other symptoms. We also identified a significant impact of varying burst frequency on the effect of CR DBS in gait given that one burst frequency produced greater gait improvement than the others. Although preliminary, this study

encourages the further advancement of CR DBS and emphasizes the importance of customizing parameter settings of CR DBS to treat specific symptoms of PD.

# Effects of Coordinated Reset Deep Brain Stimulation of Subthalamic Nucleus on Parkinsonian Gait in a Non-Human Primate Model

Parkinson's Disease (PD) is a progressive neurodegenerative disorder with symptoms such as tremor, bradykinesia (slowness of movement) and akinesia (inability to produce voluntary movement), rigidity (limb stiffness), and gait and balance problems. Many of these symptoms are often identified and measured by the Unified Parkinson's Disease Rating Scale (UPDRS) (Ebersbach et al., 2006 & Poewe, 2009). The age of onset is between 50 and 65 years old on average but early or late onsets are also reported. In addition to motor symptoms, non-motor symptoms such as depression, anxiety, psychosis, apathy and anhedonia, impulse control disorder, sleep disorders, and cognitive dysfunction are commonly seen in PD patients. In particular, the prevalence of PD dementia (PDD) has been reported as high as 83% and the prevalence increases with age and duration of PD (Hely et al., 2008). PD is also the second most common neurodegenerative disorder, affecting more than 1 % of the population equal to or older than 65 years of age and with a prevalence set to double by 2030 (Dorsey et al., 2007).

## *History of Parkinson's Disease*

Components of PD can be found in very early texts. One of the earliest pieces of evidence of PD can be found in traditional Indian texts from about 1000 BC and ancient Chinese sources (Manyam, 1990 & Zhang et al., 2006). In Ayurveda, the ancient Indian medical system, the earliest reference to bradykinesia dates to 600 BC and a coherent

picture of parkinsonism that includes description of tremor, rigidity, bradykinesia, and gait disturbances was proposed in 300 BC by Charaka, one of the principal contributors to Ayurveda (Ovallath et al., 2013). In the 15th-century classic, “Bhasava rajyam, the term, “kampavata”, was introduced as an analogue of parkinsonism. As a primary therapy for kampavata, seed powder of mucuna pruriens, which contains 4~7 % levodopa (L-dopa), was used (Lampariello et al., 2012). In the modern era, L-dopa has become the most widely used medication to alleviate PD motor symptoms.

Franciscus Sylvius documented resting tremor, one of the most common symptoms in PD patients, in a book, *“Opera Medica”*, that was published in 1680. In 1817, PD was first described as a neurological syndrome in *“An Essay on the Shaking Palsy”* by an English surgeon named James Parkinson. In 1953, the most complete pathological analysis of PD and the clear delineation of the brainstem lesions was performed by Greenfield and Bosanquet (Greenfield et al., 1953). They examined the pigmented cells of the brainstem, especially those in the substantia nigra (SN) in 34 cases of Parkinsonism and 22 subjects with no signs of Parkinsonism. Then they reported that Lewy bodies and/or neurofibrillary tangles without plaques that are observed in Alzheimer’s were observed in pigmented cells of the brainstem in all parkinsonism cases except for one and that these changes were not observed in the healthy control group.

Lewy bodies were first described by Frederich H. Lewy in 1912 as intraneuronal inclusions in the substantia innominata and dorsal vagus nucleus in patients with parkinsonism (Lewy, 1912). In 1919, Tretiakoff recognized these inclusions in SN and called them corps de Lewy, which is when people started to refer to the inclusions as

Lewy bodies. Lewy bodies are spherical neuronal masses in cytoplasm that measure 8 μm to 30 μm in diameter. Occasionally, more complex, multilobar shapes exist (Lee et al., 2022).

Clinical progression and morbidity of PD was studied thoroughly by Hoehn and Yahr and their internationally recognized staging system was first introduced in 1967 (Hoehn et al., 1967). A practical classification of the types of parkinsonism (primary, secondary, and indeterminate) was presented along with a system to grade severity of PD into 5 stages. Stage I consists of minimal or unilateral symptoms, and bilateral symptoms start at stage II. As a key turning point, stage III includes the development of impairment in postural reflex.

### *Neural Circuits in Parkinson's Disease*

Studies have shown that histopathological hallmarks of PD are loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) associated with the presence of Lewy bodies and depletion of dopamine (DA) levels in the striatum. The loss of DA neurons in SNc occurs in a region-specific manner and the loss was greatest in the lateral ventral tier of SNc with an average loss of 91% (Fearnley et al., 1991). It is estimated that at least 50% of these DA neurons in SNc must degenerate to produce symptoms and in most cases at least loss of 80% is observed post-mortem (Lewy, 1912).

While the exact mechanism of DA neuronal loss in SNc is not well understood, PD primarily affects the cortico-basal ganglia-thalamo-cortical loop in the brain. The basal ganglia consists of neostriatum (caudate and putamen), globus pallidus interna

(GPi) and externa (GPe), subthalamic nucleus (STN), substantia nigra pars reticulata (SNr), and SNc. Within the cortico-basal ganglia-thalamo-cortical loop, there are direct, indirect, and hyperdirect pathways **(Fig. 1A)**. The direct pathway projects from the motor cortex to D1 receptors in neostriatum, mainly in putamen. The inhibitory signals are sent from there to GPi/SNr, and then to the centromedian (CM), ventral anterior (VA) and ventrolateral (VL) thalamic nuclei. From these nuclei, excitatory signals are sent back to the motor cortex, and down the spinal cord in order to produce movement. Due to the double negative (the inhibitory connections between putamen and GPi/SNr, and GPi/SNr and thalamus), excitation of the direct pathway results in excitation of the motor cortex. The indirect pathway runs from the motor cortex to D2 receptors on putamen. Inhibitory connections are present between putamen and GPe, and GPe and STN. STN neurons send down their axons to GPi/SNr to create excitatory connections, which cause GPi/SNr to send more inhibitory signals to thalamus. Thus, the indirect pathway produces a net inhibition of the motor cortex. In the hyperdirect pathway, neurons travel directly from the motor cortex to STN and the pathway continues onto GPi/SNr, thalamus, then back to the motor cortex. This pathway is able to deliver information with a shorter delay compared to the direct and indirect pathways (Nambu et al., 2002). In addition, glutamatergic excitatory inputs are sent to putamen from CM neurons (Smith et al., 2014). Although not shown in **Figure 1**, this neural circuit originates in somatosensory, motor, and premotor cortices, which innervate the postcommissural putamen (PCP) at the level of neostriatum.

**Figure 1**

*Motor Pathway of Cortico-Basal Ganglia-Thalamo-Cortical Loop*

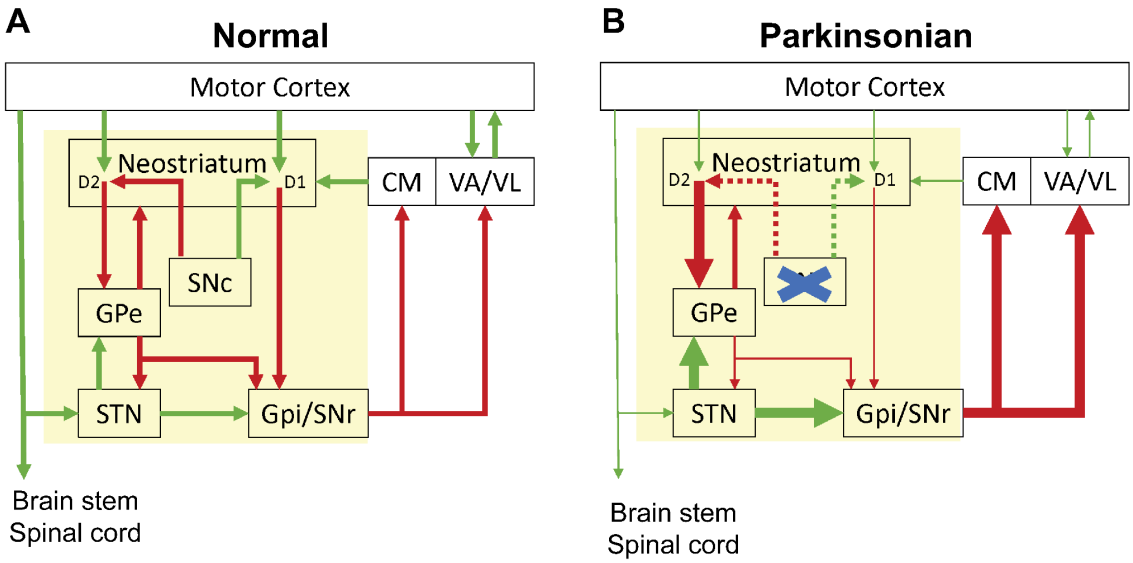


**Figure 1.** Motor pathway of cortico-basal ganglia-thalamo-cortical loop in **(A)** normal and **(B)** parkinsonian states. Only the connections of interest are shown. Thickness of the arrows correspond to the amount of signals received/sent. (i.e. thicker arrows indicate more intense signals whereas thinner arrows represent weaker signals.) Yellow box: basal ganglia; Red arrows: inhibitory connections; Green arrows: excitatory connections Abbreviations: CM, centromedian nucleus of thalamus; D1, dopamine receptor type 1; D2, dopamine receptor type 2; GPe, globus pallidus externa; GPi, globus pallidus interna; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VA, ventral anterior nucleus of thalamus; VL, ventrolateral nucleus of thalamus.

The nigrostriatal pathway degenerates progressively in PD. The DA projections to the sensorimotor striatum (putamen) are affected more strongly than those to the associative and limbic striatal regions, contributing to greater abundance of motor symptoms in PD (Kish et al., 1988 & Brooks et al., 1990). In the direct pathway, the loss of DA neurons in SNc causes less excitatory inputs to be sent to D1 receptors in putamen, which then leads to a decrease in inhibitory signals sent to GPi/SNr **(Fig. 1B)**. In the indirect pathway, the loss of DA neurons is first observed as less inhibitory inputs on D2

receptors in putamen. Having less inhibitory control, more inhibitory inputs are sent to GPe from putamen. This leads to a decrease in inhibitory signals received by STN, and GPi/SNr. Although more excitatory signals are sent to GPe due to STN having less inhibitory signals from GPe, it does not affect the circuit significantly. Despite receiving a reduced amount of excitatory inputs via hyperdirect pathway, reduced inhibitory control allows STN to send more excitatory signals to GPi/SNr. Receiving less inhibitory inputs and more excitatory inputs, GPi/SNr become capable of oversending inhibitory inputs to CM, VA, and VL. Therefore, the excitatory synapses onto the motor cortex and putamen are also reduced, thus weakening the excitatory connections from the motor cortex to skeletal muscle.

### *Gait Dysfunction in Parkinson's Disease*

In PD, gait dysfunction is a debilitating symptom that is frequently observed in patients from an early stage (Galna et al., 2015; Del Din et al., 2019). It also significantly impacts their quality of life and puts them at increased risk of falls and reduced mobility with more severe symptoms with further PD progression (Balash et al., 2005; Bloem et al., 2004; Curtze et al., 2016; Pickering et al., 2007; Bloem et al., 2016). It has been reported that PD patients step shorter and slower with less overall number of steps compared to healthy individuals most likely due to a reduced ability to initiate movements and difficulties with motor planning and execution (Morris et al., 2016; Zanardi et al., 2021). Freezing of gait (FoG) is another common gait impairment in PD with the prevalence of 39.9 % (Ge et al., 2020). It is characterized by a sudden inability

to initiate or continue walking, particularly when perceiving tight surroundings (Nutt et al., 2011). Atypical gait patterns such as shuffling gait, festinating gait and stooped posture are also observed in PD patients. Shuffling gait is described as short, shuffling steps with reduced arm swing and decreased foot clearance whereas festinating gait is characterized by a short, quick, and shuffling gait pattern with a tendency to fall forward (Morris et al., 2000; Nonnekes et al., 2019). Unlike these gait patterns, stooped posture is characterized by a forward flexion of the trunk, which results in reduction of stride length (Jacobs et al., 2009; Tolosa et al, 2021). These gait disturbances may exhibit asymmetrically across the body, where, for instance, the patients may exhibit symptoms with more severity in one side of the body than the other. Previous studies have reported that greater asymmetry in gait parameters such as balance and stride length was observed in PD patients (Boonstra et al., 2014; Fling et al., 2018). Gait parameters used to study these gait impairments include stride speed, stride length, and swing time as shown in **Figure 2**. Longer stride length, faster swing speed, and shorter stance time are generally considered the characteristics of improved gait as they show that the subjects were able to travel in longer steps in shorter time periods and reduced FoG.

**Figure 2**

*Gait Parameters*

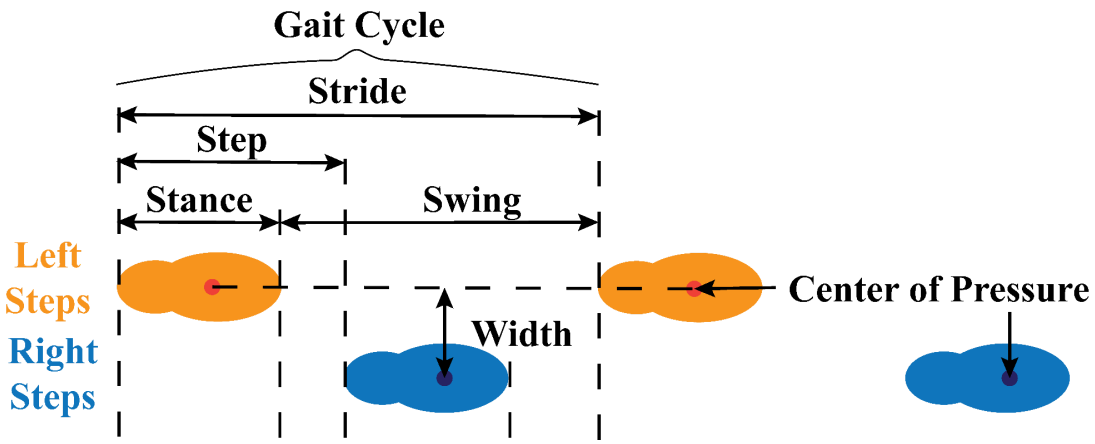


**Figure 2.** Gait pattern showing the definition of stance, swing, and stride. Stride Length: distance between successive points of initial contact of the same foot; Swing Time: time in which the paw is completely off the ground and in the air; Stance Time: time during which the paw is in contact with the ground; Swing Speed: the total stride length divided by the swing time; Width: the difference in x coordinates of the center of left paw and that of corresponding right paw.

### *Traditional Treatments*

Although there is no cure for PD, pharmacological and surgical treatments as well as other therapies are available to alleviate PD symptoms, with the most common treatment being the carbidopa/L-dopa therapy which was approved by FDA in 1975 (Ovallath et al., 2017). L-dopa serves as the precursor to DA and carbidopa is a decarboxylase inhibitor that prevents L-dopa from converting to DA outside of the central nervous system (Zhu et al., 2017). In addition to carbidopa/L-dopa therapy, DA agonists and enzyme inhibitors such as monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) inhibitors are also added to augment therapeutic effects of treatment. L-dopa is highly effective at the early stage of PD as it is able to

significantly ameliorate motor impairments, however as the PD stage advances and the motor symptoms get more severe, it becomes insufficient to control the symptoms even with the assistance of DA agonists and enzyme inhibitors (Lewitt, 2008; PD Med Collaborative Group 2014). After a prolonged use of L-dopa, motor complications often develop in PD patients. A study has reported that dyskinesia and motor fluctuations were barely experienced by PD patients during the first year of L-dopa therapy but were experienced after 4-6 years of treatment by slightly less than 40% and approximately 40% of the patients respectively (Ahlskog et al., 2001). Moreover, even though the severity of FoG is thought to lessen with L-dopa, it has been reported that the prevalence of FoG may be smaller in patients that were not treated with L-dopa and that the use of DA agonists may induce FoG or lead to an increased risk of falling (Garcia-Ruiz, 2011; Koehler et al., 2019; Nonnekes et al., 2020; Serrao et al., 2015). However, it must be noted that age-related changes significantly affect motor and gait impairments in PD. For example, changes created by loss and atrophy of muscle strength, level of physical inactivity, and other age-related conditions such as arthritis can produce rigidity and pain during movement (Busch et al., 2015; Chen et al., 2013; Kiesmann et al., 2021; Song and Geyer, 2018; Zhang & Jordan, 2010). Due to the complex nature of motor impairments in PD created by the combination of disease-specific and age-related factors, the long-term effectiveness of pharmacological treatment in PD has yet to be fully identified (Wilson et al., 2020). Before the introduction of L-dopa, neurosurgical approaches such as pallidotomy and thalamotomy had been extensively offered as treatment options for patients with severe PD symptoms in the 1950s (Chao et al., 2007; Laitinen et al., 1992;

Ponce, 2014). Pallidotomy intentionally creates a lesion in GPi to alleviate rigidity and dyskinesia whereas thalamotomy involves destroying thalamus to treat tremor. Significant therapeutic improvement by these treatments had been observed, however side effects such as facial weakness and exacerbated gait and speech disorders from unintended lesioning of other areas of the brain were observed in as many as 50% of the patients (Hariz & Salles, 1997; Laitinen et al., 1992). Due to high prevalence of these side effects, these treatments are typically performed only in the hemisphere that is contralateral to the side of the body on which the effects should be observed. Although these surgical treatments became less frequent with the rise of medical therapy and high morbidity and mortality associated with them, recent advancement in technology such as focused ultrasound, computational tomography-based stereotaxis, and microelectrode recording techniques has allowed them to be performed with more accuracy to reduce the side effects and created renewed interest in them (Chao et al., 2007; Kelly et al., 1987).

### *Deep Brain Stimulation*

The discovery of long-term motor complications with L-dopa caused regained interests in surgical therapies, which led to the invention of the novel Deep Brain Stimulation (DBS) paradigm. Nowadays, DBS is offered as a treatment option to those who experience medication-related side effects or those who experience severe motor impairments that cannot be controlled by pharmacological therapies. The traditional DBS (tDBS) is a therapeutic approach originally developed in 1987, and has been used to improve PD symptoms since 1997 (Gardner, 2013). It received FDA approvals for

advanced PD symptoms in 2002 and even for earlier PD stages (minimum of 4 years with PD required) in 2016. tDBS uses continuous high frequency pulse-train stimulation (often >100 Hz) through one lead contact on surgically implanted DBS leads in specific areas of the brain (GPi, STN, etc).

**Figure 3**

*Deep Brain Stimulation in a human subject*

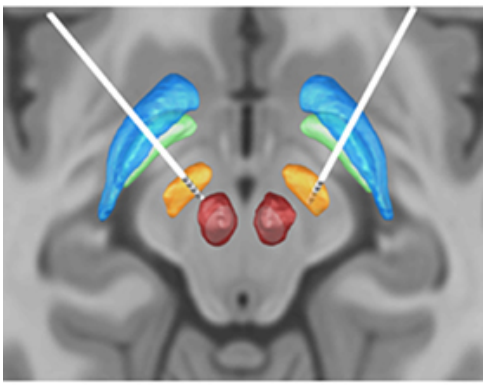

**Figure 3.** Bilateral STN lead location, the STN (orange), globus pallidus internus (light green), globus pallidus externus (light blue), and red nucleus (red) are shown for reference. From "New Onset On-Medication Freezing of Gait After STN-DBS in Parkinson's Disease" by Mei, S., Li, J., Middlebrooks, E. H., Almeida, L., Hu, W., Zhang, Y., Ramirez-Zamora, A., & Chan, P., 2019, June 19, Frontiers in Neurology, 10, 659. Copyright 2019 by Mei, Li, Middlebrooks, Almeida, Hu, Zhang, Ramirez-Zamora, & Chan.

In order to study effects of tDBS, non-human primates (NHP), especially rhesus macaque (*Macaca mulatta*), have often been used as subjects. NHP models are heavily selected in neuroscience, neurology, or neuromuscular research for various reasons including their close phylogenetic relationships and physiologic similarities to humans (Lankau et al., 2014). In the NHP model of PD, a neurotoxin, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), is used to produce PD symptoms in subjects. The toxicity of MPTP was first reported in *Science* in 1983 after accidental

self-administration of the compound by people who tried to ingest MPPP, an opioid drug with effects similar to morphine, which produces MPTP (1-methyl-4-phenyl-4-propanoypiperidine) as a byproduct during its synthesis (Langston., 2017). In primates, MPTP produces damage to the dopaminergic neuronal systems in the SNc and the striatum, thus reproducing essential symptoms of PD with high similarity to human PD patients (Liu et al., 2014 & Ashkan et al., 2007). In order to assess the severity of PD symptoms in NHP subjects, a version of the UPDRS (mUPDRS) which rate bradykinesia, akinesia, and tremor as well as other motor features such as balance, defense reaction, food retrieval, gait, posture, and turning has been used (Vitek et al., 2012, Wang et al., 2016, & Wang et al., 2017).

It has been reported that STN DBS can result in a 60% mean reduction of PD motor symptoms even after 5 years of DBS if the patients are off dopaminergic medications and that, in patients on dopaminergic medications, the dosage could be significantly reduced, which produces as much as 60% reduction in dyskinesia (Krack et al., 2003). A large scale, randomized study has also shown a 41 % improvement in UPDRS ratings of advanced PD patients who received STN CR DBS 6 months postoperatively (Deuschl et al., 2006). Despite showing significant motor benefits, tDBS has been associated with side effects due to the spread of current into unintended areas of the brain (Deuschl et al., 2006; Odekerken et al., 2012). The reported side effects include but are not limited to worsening of the speech abnormality, postural stability, cognitive functions, akinesia, FoG and resistance to treatment over time (Deuschl et al, 2006; Krack et al., 2003; Saint-Cyr et al., 2000). In fact, a study reported that about 42% of PD

patients who received bilateral STN DBS experienced worsened gait (van Nuenen et al., 2008).

After over 35 years since its invention, tDBS has barely changed from its original form despite the advancement in the knowledge of neurophysiology such as the reported persistent side effects and limitations as a clinical treatment. Consideration such as this prompted more research in the novel DBS paradigms, which studied topics including but are not limited to multi-site stimulation of STN, waveforms of energy efficient neural stimulation, and closed-loop strategy of DBS in order to increase accuracy in targeting the specific region of interest, and/or to reduce the overall stimulation delivered to the brain (Guo et al., 2011; Rosin et al., 2011; Wongsarnpigoon et al., 2010).

### *Coordinated-Reset Deep Brain Stimulation*

Coordinated-Reset DBS (CR DBS) is an innovative therapeutic approach that may be able to reduce the risk of side-effects by delivering burst electric pulse trains at a greatly reduced current level through multiple DBS lead contacts on DBS leads in a pseudo-randomized order **(Fig. 4A-B)**. A significant advantage of using CR DBS compared to tDBS is that it is able to achieve its effects with lower pulse amplitudes and frequencies. CR DBS was developed as numerous stimulation protocols were studied as part of computational modeling research by Peter Tass group in order to counteract excessive synchronization which is observed in PD patients by desynchronization (Tass, 2001; Tass et al., 2003; Tass et al., 2006). In CR DBS, the pulse trains reset the phase of the targeted neurons rather than blocking neuronal firings. By delivering the stimulation

from different depths at different times, the target population of neurons is divided into subpopulations, which cause network desynchronization (Hauptmann et al., 2007). It has been reported that CR DBS with low intensity delivered to STN induced improvement in mUPDRS scores during the stimulation as well as carryover improvement which sustained for over a month after the last stimulation was given in the NHP model (Tass et al., 2012; Wang et al., 2016). STN CR DBS has also been found to be effective in human subjects with 58% mean reduction in motor dysfunction measured by UPDRS immediately after the third day of stimulation (Adamchic et al., 2014). These studies, however, have mainly shown improvement in general motor symptoms of PD and the effect of STN CR DBS on PD gait has not been explored even though gait can be one of the most difficult symptoms to treat among all motor impairments of PD (Bohnen et al., 2011; Collomb-Clerc & Walter, 2015).

**Figure 4**

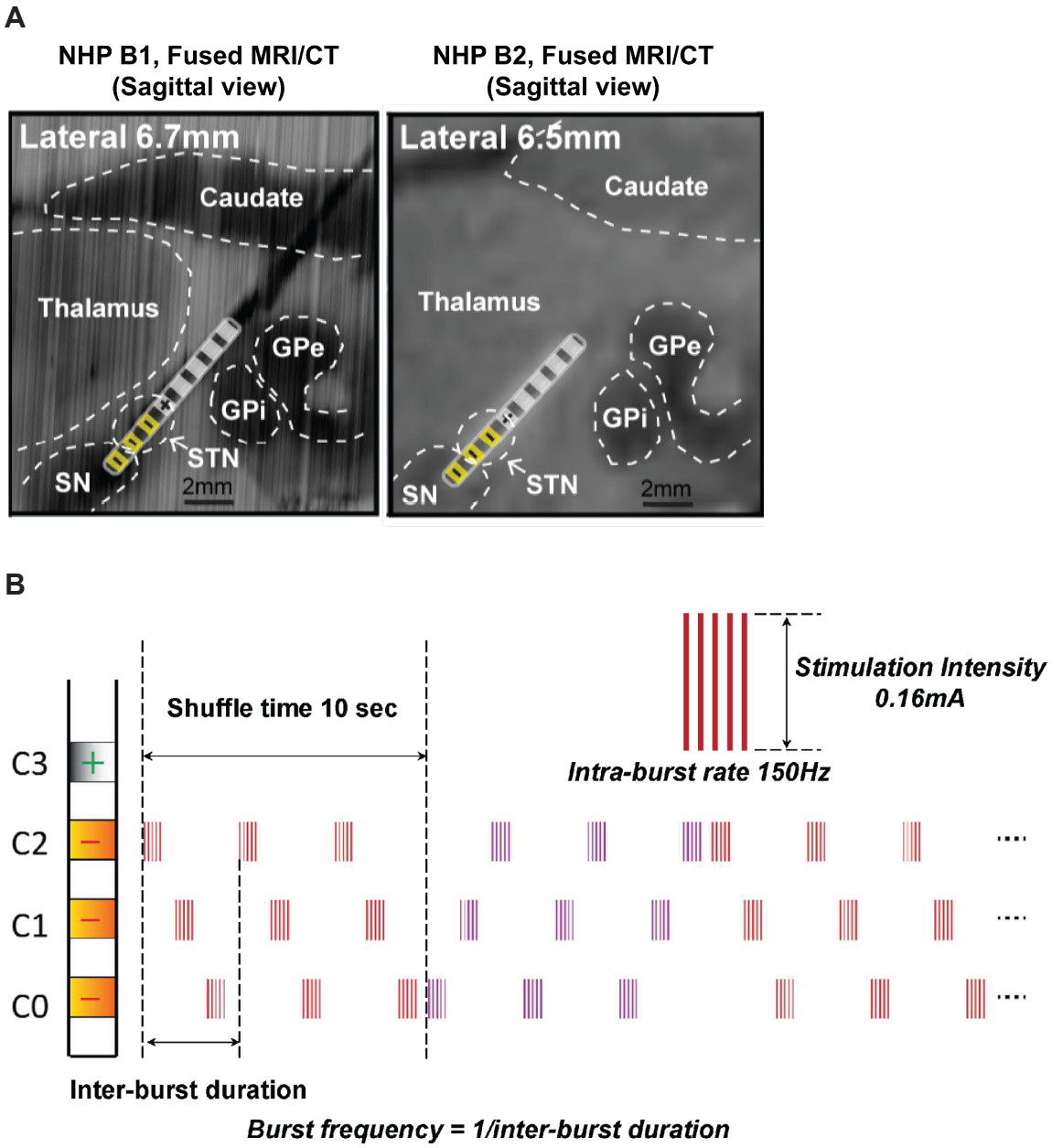


**Figure 4. (A)** Merged MRI/CT showing the location of the DBS lead in STN in NHP B1 (left) and B2 (right). Stimulation contacts used to deliver CR DBS are indicated in yellow. **(B)** Stimulation pattern in CR DBS showing the definition of shuffle time (10 s), stimulation intensity (0.16 mA), inter-burst duration, and burst frequency.

### *Present Study*

Despite the lack of research in the effects of CR DBS on PD gait, the prevalence of PD is projected to be more than 1.6 million by 2037 just in the U.S. (Yang et al., 2020). Given the complex nature of PD motor impairments and the high prevalence of gait dysfunction in PD patients, an effective, sustainable therapeutic approach that is capable of treating PD gait will be required in forms that are accessible to those in need. In the present study, we hypothesized that CR DBS stimulation can produce therapeutic effects on PD gait as well as on general motor symptoms, and that variation in burst stimulation frequency of CR DBS would lead to differential effects on these symptoms of interest. In order to test these hypotheses, CR DBS was delivered to STN in two Parkinsonian NHP subjects at the same burst stimulation frequency and measured gait pattern and general motor symptoms to evaluate the effects of CR DBS on gait. Subsequently, additional two different stimulation frequencies were explored in NHP B1 to investigate the effects of differential frequencies of STN CR DBS on gait.

## Method

### *Animals and Surgical Procedures*

Animal care complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and all procedures were performed under a protocol approved by the Institutional Animal Care and Use committee of the University of Minnesota. Two adult female rhesus macaque (*macaca mulatta*) (NHP B1, 8.2 kg, 26 y.o. and NHP B2 10.5 kg, 25 y.o.) were used. Approximate equivalent ages of subjects in

human years are 78 years old in NHP B1 and 75 years old in NHP B2. They received long-term positive reinforcement training to become familiar with the laboratory setting and passive limb manipulation.

Presurgical CT and 10.5 T MRI scans were used to determine STN location in each NHP. Then both NHPs received surgical implantation of a cephalic chamber and a head restraint post. During the surgery, microelectrode recording and stimulation techniques were used to map the sensorimotor region and borders of the STN, followed by an implantation of a smaller version of the DBS lead (0.63 mm diameter, 0.5 mm contact height, and 0.5 mm space between contacts; NuMed Inc., TX, USA) in STN (Hutchison et al., 1998) **(Fig. 4A)**. The lead placement depth was determined from a final recording track of the implanted DBS lead. The implanted DBS lead was routed to the chamber and connected to an omnetics connector which enables access for DBS. Stimulation was delivered using an implantable pulse generator (Boston Scientific). Unrestricted food and water access and appropriate infection and pain management were incorporated after surgery. After complete recovery from surgery, NHPs were rendered Parkinsonian via intramuscular injections, which produced Parkinsonian symptoms on both sides of the body. The severity of these motor symptoms were rated by using mUPDRS. On a 4-point scale (0-3; 0 = unimpaired), it was used to assess akinesia, bradykinesia, rigidity and tremor for upper and lower limbs and food retrieval for upper limbs (maximum score = 27 points; most severe). Before CR DBS assessment, both animals reached mild to moderate parkinsonian state (mUPDRS (mean±STD): 10.4±0.4

in NHP B1 and 7.6±0.2 in NHP B2). In NHP B2, gait was more impaired compared to NHP B1.

### *Experiment Protocol*

Each NHP received STN CR DBS for 2 hours per day for five consecutive days. In NHP B1, different burst frequencies, 21 Hz, 24 Hz, and 27 Hz, were explored whereas, in NHP B2, only 21 Hz burst stimulation was employed. CR DBS parameter settings are shown in **Table 1**. Three sessions were collected from NHP B1 in total with at least a two week interval between each of them. The stimulation was delivered via four ventral DBS lead contacts (Cathodes: C0, C1, C2-, and C3+) in STN. One cycle is the time needed for the burst stimulation to be delivered across all stimulation contacts and a burst frequency is the frequency of burst stimulation. The stimulation intensity was determined as 1/2 (in B1) and 1/3 (in B2) of the intensity used for tDBS. The shuffle time is the time duration in which the stimulating contact order is kept the same before this order is pseudo-randomly shuffled.

**Table 1**. *Parameter settings used in STN CR DBS*

| Parameters | NHP | |
|---|---|---|
| | B1 | B2 |
| Intensity (mA) | 0.16 | 0.1 |
| Pulse Width (μs) | 120 | 120 |
| Pulses/Bursts | 6 | 6 |
| Intra-burst Rate (Hz) | 150 | 150 |
| Burst Frequency (Hz) | 21, 24, 27 | 21 |
| Shuffle Time (s) | 10 | 10 |
| Stimulation Duration (hr/day) | 2 | 2 |

Each session was followed by a post-treatment observation period of at least five days in order to examine carry-over effects. mUPDRS scores were obtained prior to CR

DBS (baseline), on stimulation days, and once daily on post-CR days. The initiation of a new session was not allowed until mUPDRS score was back to baseline. The exact timelines of mUPDRS and gait assessments for each session are illustrated in **Figure 5C**.

Gait patterns were assessed using the Gait Testing Apparatus (GTA), which consists of a high-resolution pressure walkway mat (HR Walkway 4 VersaTek system, Tekscan, Inc.) in a plexiglass fixture **(Fig. 5A)**. The system recorded temporal and spatial features of NHP's gait pattern and plantar pressures from footprints for each complete walk across the walkway mat. Gait data was collected prior to stimulation (baseline), on the last day of stimulation session (CR 5), and post-CR days.

**Figure 5**

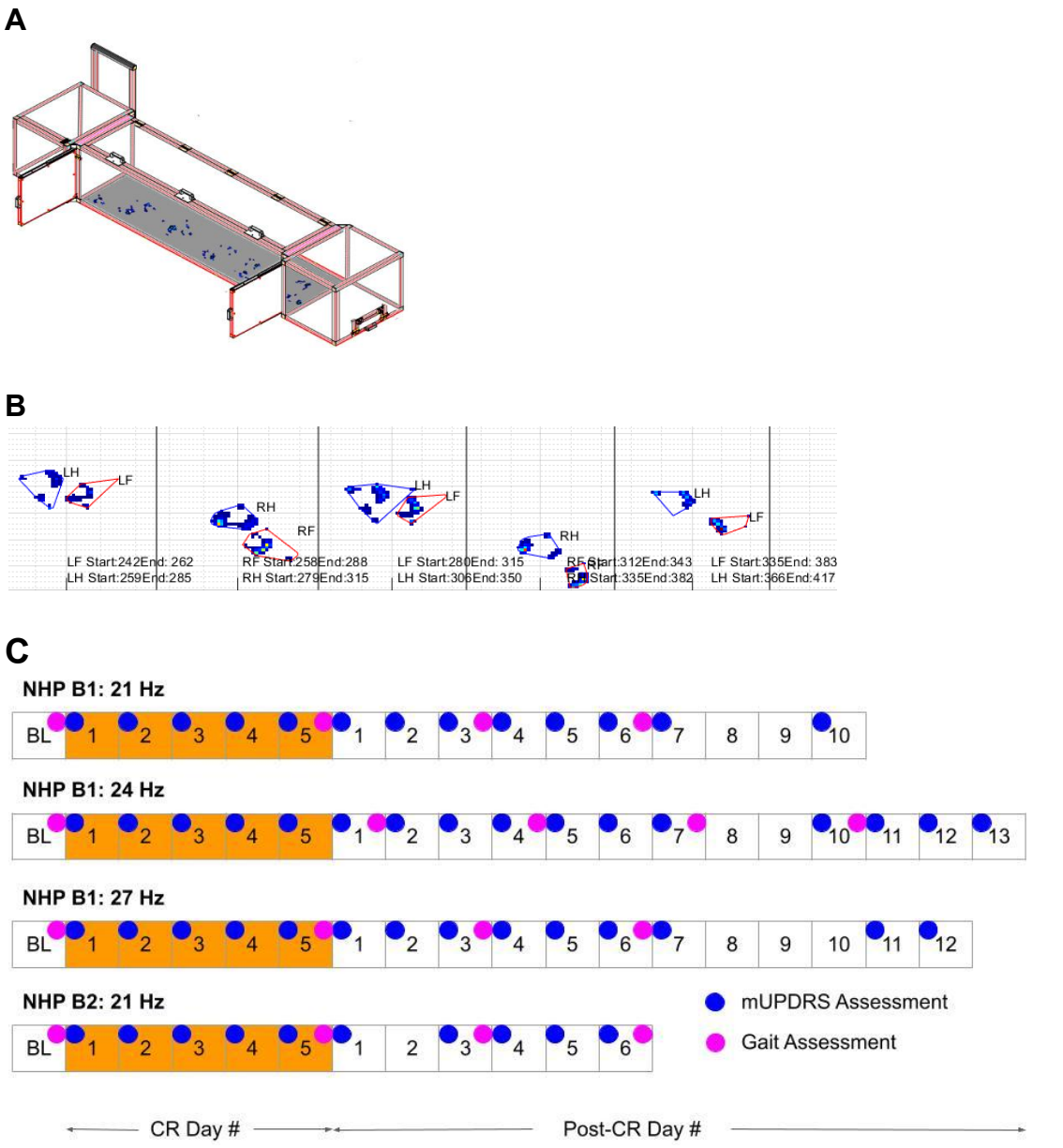


**Figure 5. (A)** Gait Testing Apparatus (GTA) and **(B)** plantar pressure visualized using a customized MATLAB GUI. GTA was enclosed by plexiglass and contained a pressure walkway mat which collected plantar pressure data. **(C)** Schematic of the experiment protocol including the timeline of mUPDRS and gait assessment. Orange panels: STN CR DBS 2 hours/day. mUPDRS was assessed at the beginning of the day and gait was assessed at the end of the day.

### *Data Analysis*

Collected mUPDRS score was converted to a percentage of improvement compared to the score at baseline using the following formula:

$$\frac{Change\ in\ subscores\ from\ baseline}{Total\ mUPDRS\ score} \times 100 = Percentage\ Improvement\ in\ mUPDRS$$

The percentage improvement in each subscore was then added together to compute the total percentage improvement. The median of the scores obtained prior to CR DBS sessions were considered as the baseline score. The carryover effect was considered to be present until the total mUPDRS improvement reached below 15% during post-CR days.

A custom MATLAB (MathWorks) Graphical User Interface was used to label NHP's footprints and process their pressure data after which the cleaned and processed data was analyzed using additional custom MATLAB codes to calculate gait parameters (stride length, swing time, swing speed, mean plantar pressure, width between left and right paws for both front and hind limbs, and balance index) **(Fig. 5B)**. The average coordinates of the center of plantar pressure were used to determine paws' locations from which stride length, swing time, and width were derived. Swing speed was calculated via division of stride length by swing time. The equation below was used to calculate the balance index, which represents how balanced the weight distribution between the left and right sides of the body is.

$$\left|1 - \frac{Mean\ plantar\ pressure\ of\ left\ front/hind\ paw}{Mean\ plantar\ pressure\ of\ right\ front/hind\ paw}\right| = Balance\ Index$$

Smaller balance index is an indication that the mediolateral weight distribution was more balanced in comparison to baseline in the subject.

JMP (SAS Institute Inc., NC, USA) was used to perform statistical analysis. The non-parametric Wilcoxon test ($p < 0.01$) with Steel With Control test ($p < 0.01$) was performed to examine statistical significance of any changes after stimulation from baseline. In NHP B1, baseline data from each session was combined to create one baseline dataset in order to account for daily differences observed in pre-stimulation conditions.

## Results

Impact of STN CR DBS on motor symptoms rated by mUPDRS are presented first. Due to the difference in stimulation parameters and the number of assessments, changes in gait parameters following CR DBS are demonstrated by frequency setting for each animal.

### *mUPDRS Ratings Improved in All STN CR DBS Sessions*

General motor symptoms measured by mUPDRS improved significantly in both animals after CR DBS using all burst frequencies examined in the study. In NHP B1 at 21 Hz, carryover improvement was observed in rigidity, food retrieval, akinesia, and bradykinesia **(Fig. 6A)**. Gradual increase in improvement of mUPDRS was observed during the 5 days of STN CR DBS and eventually reached a total improvement of 25.63% from baseline on post-CR day 3. The carryover improvement was sustained for 5 days before returning to baseline. In NHP B1 at 24 Hz, unlike the result with 21 Hz burst frequency, carryover effect in mUPDRS was observed for 10 days after stimulation cessation with the maximum total percent change of 23.11% on 4th and 5th post-CR days **(Fig. 6B)**. The improvement was observed in all subscores but food retrieval. It did not

show a gradual increase during the first five days of stimulation and instead showed a significant total improvement starting on CR day 2. At 27 Hz in NHP B1, carryover effect was observed with a maximum total improvement of 32.14% on the first day after stimulation cessation. The improvement was observed in all subscores except for the tremor similarly to 21 Hz and sustained for 11 days. During the acute phase, improvement was observed but followed a similar pattern as 24 Hz with the largest improvement of this period being observed on CR day 2 **(Fig. 6C)**. In NHP B2 at 21 Hz, the carryover effect in mUPDRS sustained for 5 days after stimulation cessation **(Fig. 6D)**. Consistent improvement in rigidity was present from CR day 2 until post-CR day 6. Improvement in bradykinesia, akinesia, and food retrieval was observed between CR day 4 and post-CR day 3. A maximum total improvement of 56.41% was achieved on post-CR days 1 and 3.

### *Gait Improved after 21Hz STN CR DBS*

### *NHP B1: 21 Hz*

Gait improvement was observed immediately after 5 days of CR DBS and on post-CR day 3. Increase in swing speed and mean pressure as well as decreased balance index were observed on CR day 5 **(Fig. 7A, C and E)**. Longer stride length and increased width between front/hind limbs were observed on both CR day 5 and post-CR day 3 **(Fig. 7B and D)**. Statistics are provided in **Table 2**.

***NHP B1: 24 Hz***

Limited changes in gait parameters were observed immediately after CR DBS with only reduced balance index and larger mean pressure at front limb observed on post-CR day 1 **(Fig. 8A)**. Longer stride length and increased width were observed on post-CR day 4 **(Fig. 8B and D)**. Additional reduction in mean pressure and increased width and balance index were observed in hind limb on post-CR days 7 and/or 10 **(Fig. 8C, D and E)**. Statistics are provided in **Table 3**.

***NHP B1: 27 Hz***

No significant change was observed in gait parameters immediately after CR DBS. On post-CR day 3, we observed increased stride length in hind limb and decreased mean pressures in both limbs **(Fig. 9B-C)**. On post-CR day 6, reduced swing speed, longer stride length, decreased mean pressure, and longer width were observed in both limbs **(Fig. 9A-D)**. No change was observed in the balance index throughout the whole CR session **(Fig. 9E)**. Statistics are provided in **Table 4**.

***NHP B2: 21 Hz***

Limited changes in gait parameters were observed after STN CR DBS, however, the swing speed in the front limb increased on CR day 5 **(Fig. 10A)**. Shorter width between hind limbs compared to baseline was also observed on CR day 5 and post-CR day 3 **(Fig. 10D)**. Reduced mean pressure was observed in the front limb on post-CR day 3 **(Fig. 10C)**. No statistically significant changes were observed in stride length and balance index **(Fig. 10B and 10E)**. Statistics are provided in **Table 5**.

**Figure 6**

*Carryover Effect in mUPDRS ratings*

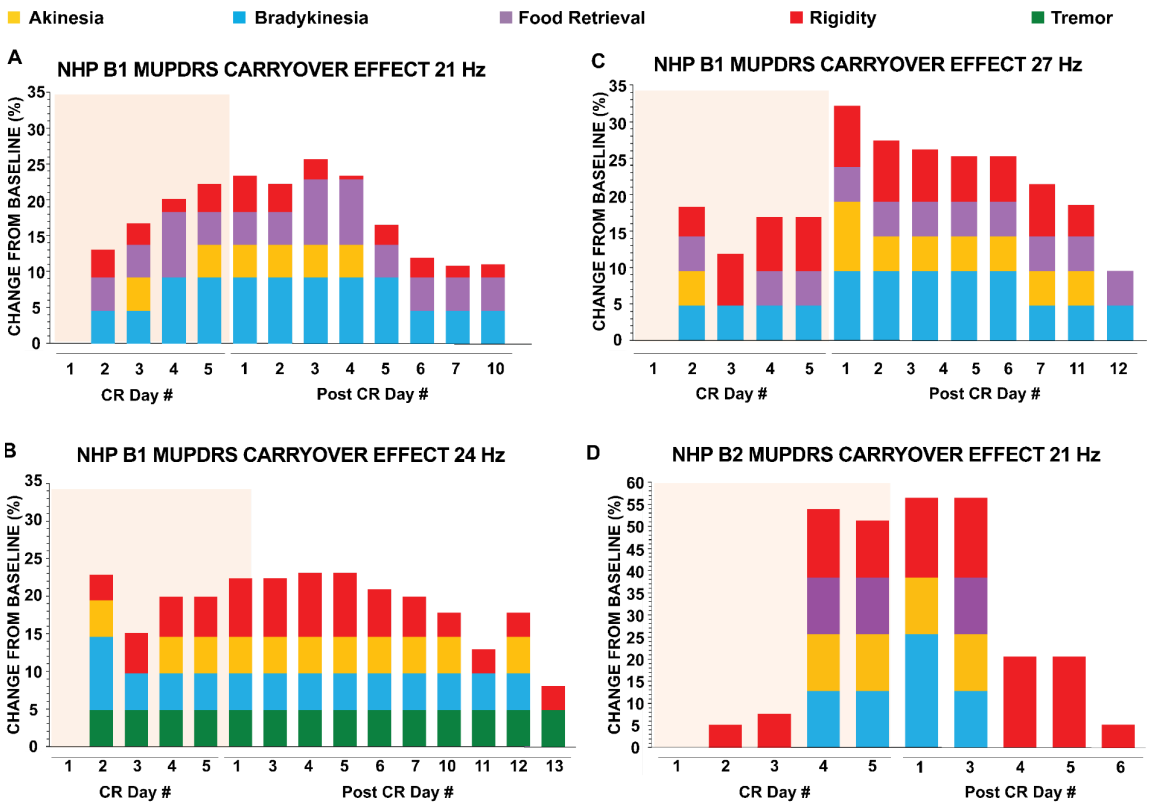


**Figure 6.** Changes in the mUPDRS from baseline in NHP B1 with burst frequencies of **(A)** 21 Hz, **(B)** 24 Hz, and **(C)** 27 Hz, and **(D)** in NHP B2 with burst frequency set at 21 Hz. The composite mUPDRS is further broken down to reveal the changes in individual subscores.

**Figure 7**

*Effect of **21 Hz** STN CR DBS on Parkinsonian Gait in NHP B1*

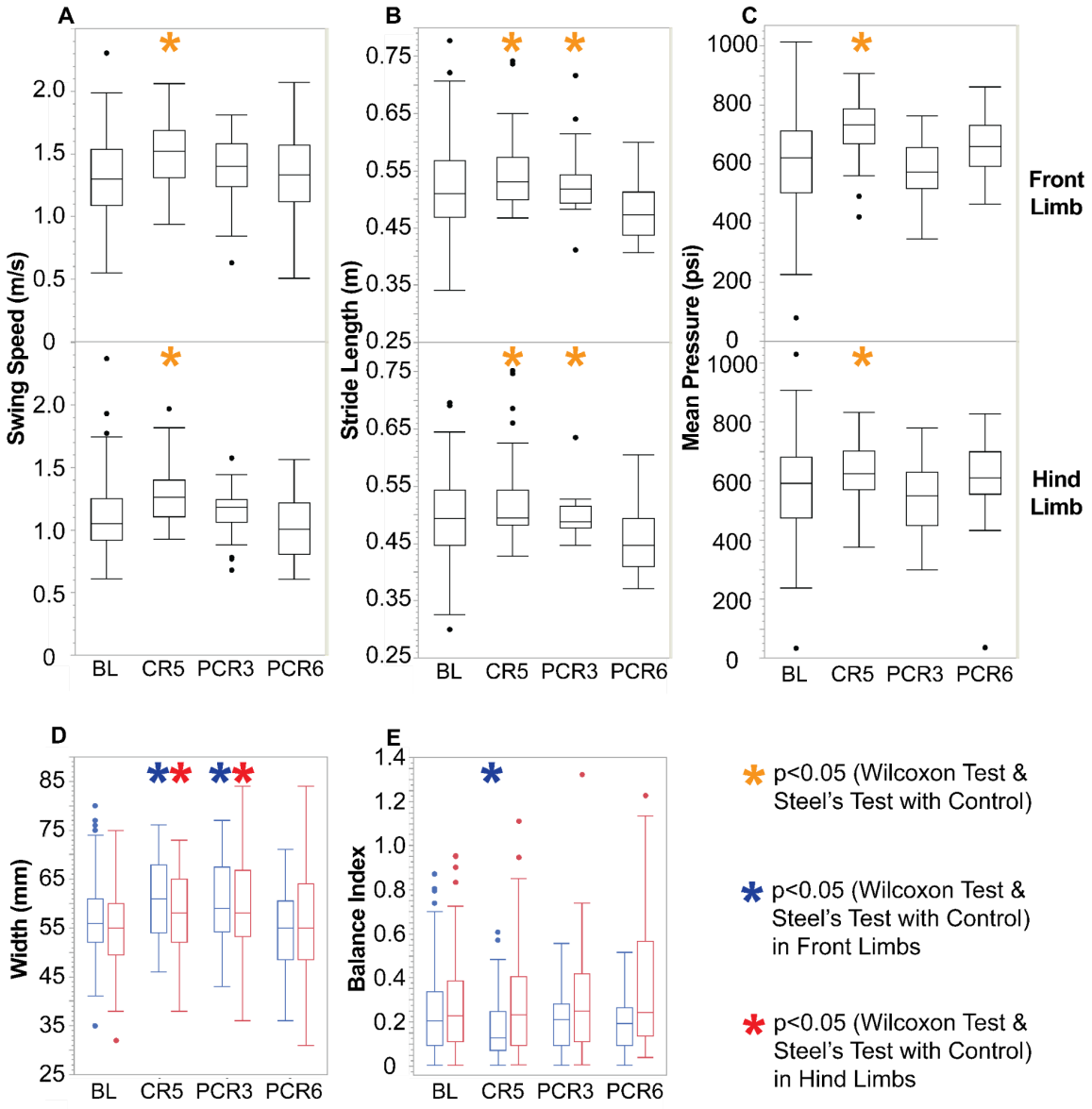


**Figure 7.** Effect of CR DBS on gait parameters in NHP B1 with burst frequency at 21 Hz. Changes in **(A)** the swing speed, **(B)** the stride length, and **(C)** the mean plantar pressure in the left front and hind limbs. Changes in **(D)** the width and **(E)** the balance index between the front/hind limbs from the baseline. Blue and red box plots represent front and hind limbs respectively.

**Figure 8**

*Effect of **24 Hz** STN CR DBS on Parkinsonian Gait in NHP B1*

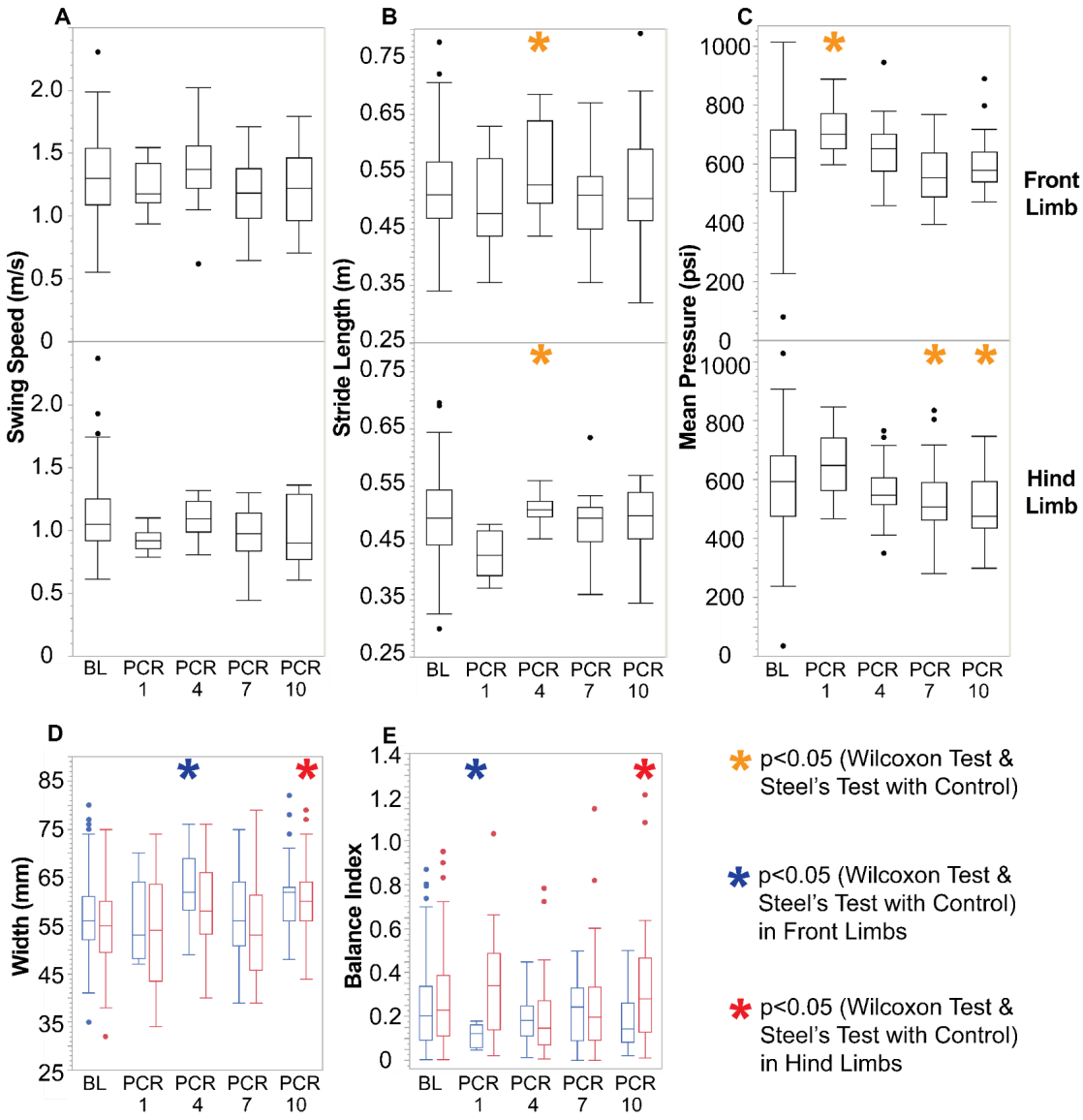


**Figure 8.** Effect of CR DBS on gait parameters in NHP B1 with burst frequency at 24 Hz. Changes in **(A)** the swing speed, **(B)** the stride length, and **(C)** the mean plantar pressure in the left front and hind limbs. Changes in **(D)** the width and **(E)** the balance index between the front/hind limbs from the baseline. Blue and red box plots represent front and hind limbs respectively.

**Figure 9**

*Effect of **27 Hz** STN CR DBS on Parkinsonian Gait in NHP B1*

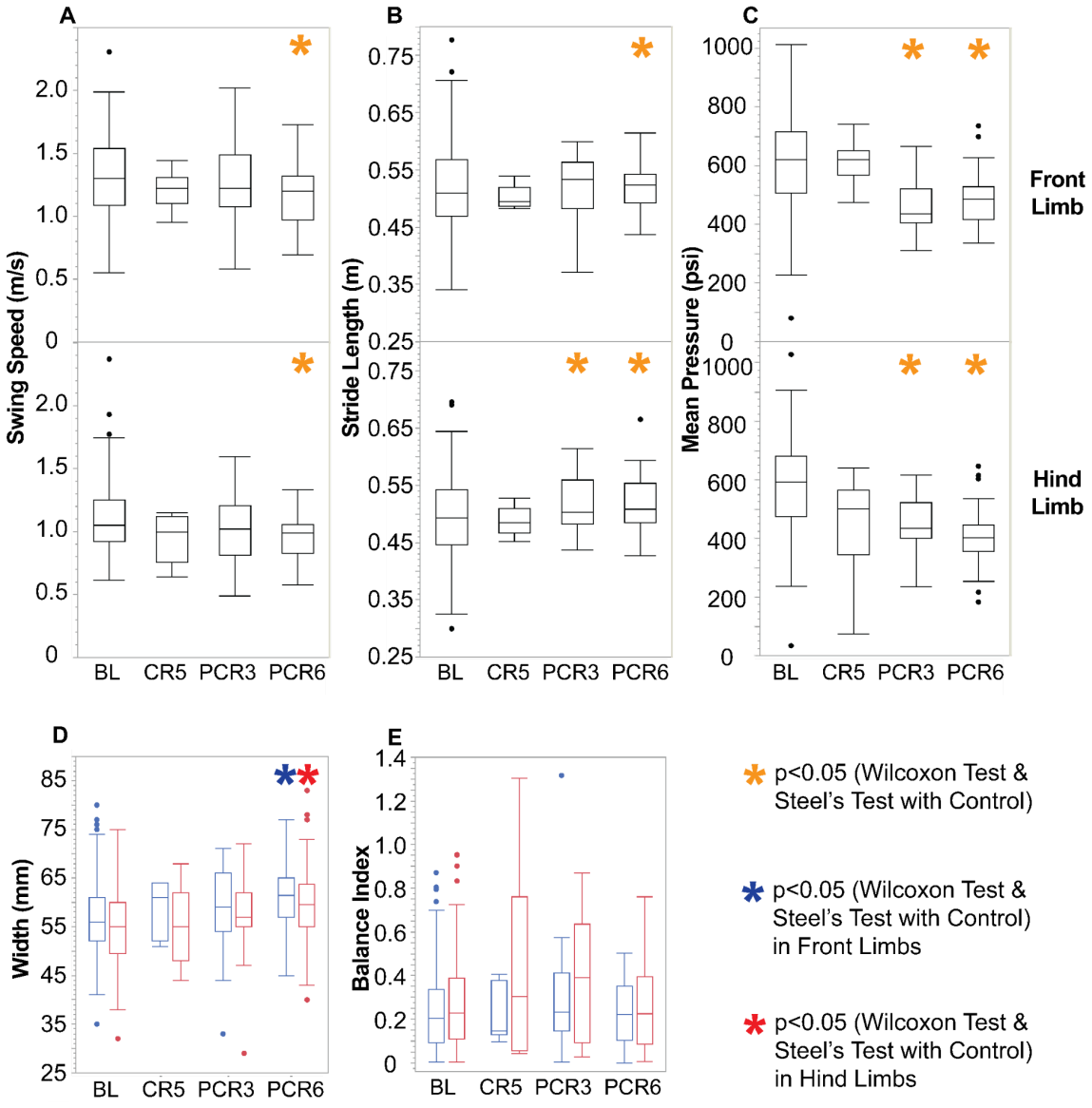


**Figure 9.** Effect of CR DBS on gait parameters in NHP B1 with burst frequency at 27 Hz. Changes in **(A)** the swing speed, **(B)** the stride length, and **(C)** the mean plantar pressure in the left front and hind limbs. Changes in **(D)** the width and **(E)** the balance index between the front/hind limbs from the baseline. Blue and red box plots represent front and hind limbs respectively.

**Figure 10**

*Effect of 21 Hz STN CR DBS on Parkinsonian Gait in NHP B2*

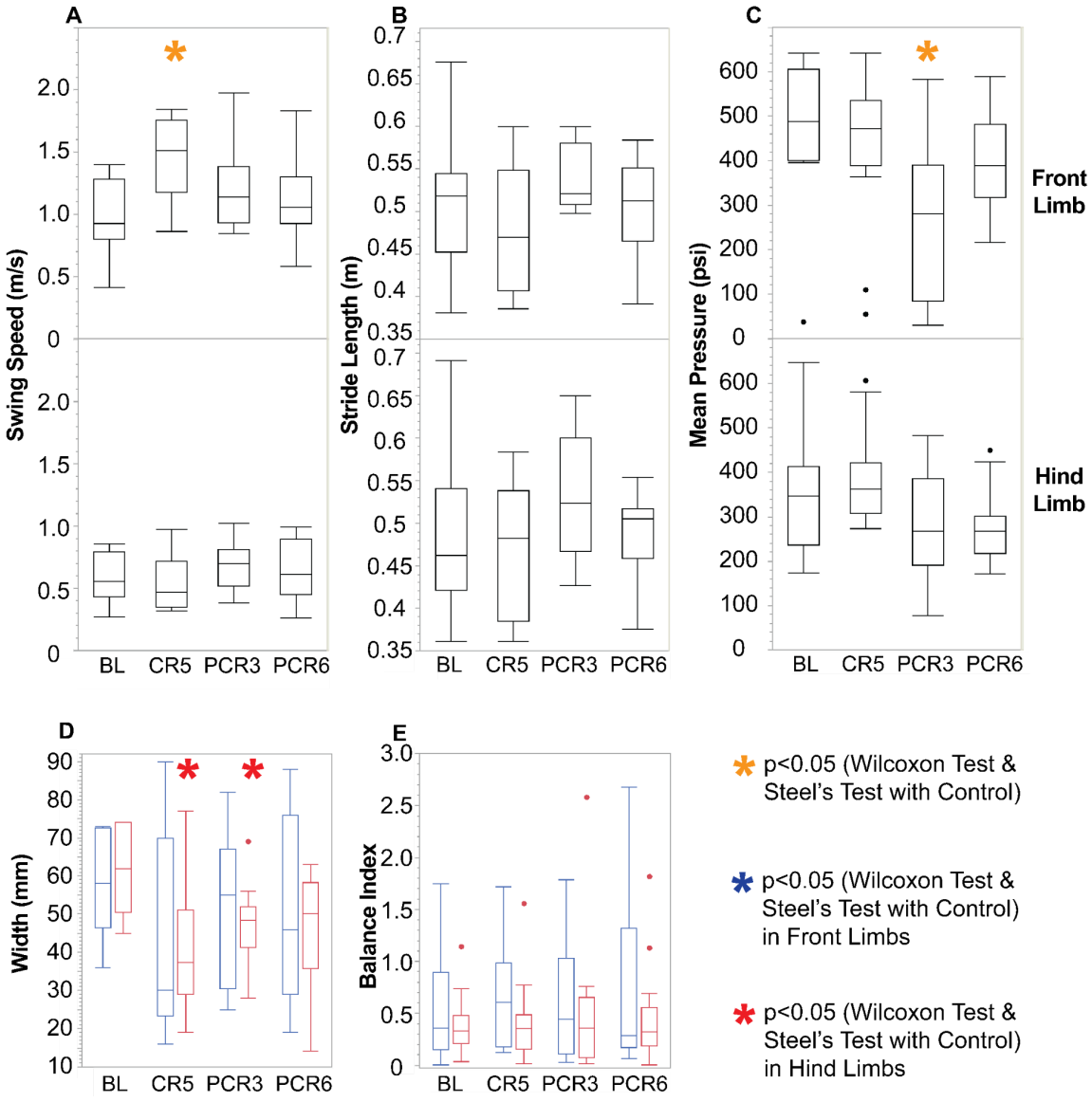


**Figure 10.** Effect of CR DBS on gait parameters in NHP B2 with burst frequency at 21 Hz. Changes in **(A)** the swing speed, **(B)** the stride length, and **(C)** the mean plantar pressure in the left front and hind limbs. Changes in **(D)** the width and **(E)** the balance index between the front/hind limbs from the baseline. Blue and red box plots represent front and hind limbs respectively.

**Table 2**.

*Statistical analysis on gait parameters in NHP bl at 21 Hz burst frequency*

| [NHP B1, 21 Hz] | | Wilcoxon Test | | | P value of Steel's Test with Control = BL | | |
|---|---|---|---|---|---|---|---|
| | | $X^2$ | DoF, N | p | CR Day 5 | Post CR Day 3 | Post CR Day 6 |
| Swing Speed | Left Front | 12.7880 | 3, 221 | 0.0051 | 0.0025 | 0.3876 | 1.0000 |
| | Left Hind | 25.2396 | 3, 221 | <0.0001 | 0.0001 | 0.1164 | 0.5591 |
| Stride Length | Left Front | 32.6634 | 3, 221 | <0.0001 | <0.0001 | 0.0057 | 0.5223 |
| | Left Hind | 30.6595 | 3, 216 | <0.0001 | 0.0003 | 0.0123 | 0.2171 |
| Mean Pressure | Left Front | 59.5620 | 3, 321 | <0.0001 | <0.0001 | 0.0552 | 0.0816 |
| | Left Hind | 21.8006 | 3, 321 | <0.0001 | 0.0202 | 0.2932 | 0.0583 |
| Width | Front | 18.8119 | 3, 297 | 0.0003 | 0.0065 | 0.0284 | 0.5167 |
| | Hind | 10.3346 | 3, 297 | 0.0159 | 0.0187 | 0.0384 | 0.8508 |
| Balance Index | Front | 6.5687 | 3, 297 | 0.087 | 0.0407 | 0.9692 | 0.6792 |
| | Hind | 3.2591 | 3, 297 | 0.3534 | 0.9992 | 0.7530 | 0.2574 |

**Table 3**.

*Statistical analysis on gait parameters in NHP B1 at 24 Hz burst frequency*

| [NHP B1, 24 Hz] | | Wilcoxon Test | | | P value of Steel's Test with Control = BL | | | |
|---|---|---|---|---|---|---|---|---|
| | | $X^2$ | DoF, N | p | Post CR Day 1 | Post CR Day 4 | Post CR Day 7 | Post CR Day 10 |
| Swing Speed | Left Front | 7.0721 | 4, 175 | 0.1321 | 0.8172 | 0.8731 | 0.1484 | 0.9018 |
| | Left Hind | 9.9297 | 4, 175 | 0.0416 | 0.1359 | 0.9974 | 0.1380 | 0.5308 |
| Stride Length | Left Front | 10.3151 | 4, 176 | 0.0354 | 0.9960 | 0.0107 | 0.9212 | 0.5418 |
| | Left Hind | 16.8629 | 4, 176 | 0.0021 | 0.1757 | 0.0124 | 0.6690 | 0.5631 |
| Mean Pressure | Left Front | 20.7551 | 4, 258 | 0.0004 | 0.0392 | 0.5291 | 0.0695 | 0.9222 |
| | Left Hind | 22.0217 | 4, 258 | 0.0002 | 0.2536 | 0.7955 | 0.0305 | 0.0067 |
| Width | Front | 14.3939 | 4, 242 | 0.0061 | 0.9477 | 0.0061 | 0.9970 | 0.0796 |
| | Hind | 15.3375 | 4, 242 | 0.0041 | 0.9906 | 0.2257 | 0.8331 | 0.0035 |
| Balance Index | Front | 9.3782 | 4, 242 | 0.0523 | 0.0500 | 0.7530 | 1.0000 | 0.4370 |
| | Hind | 6.8495 | 4, 242 | 0.1441 | 0.5698 | 0.3124 | 0.9593 | 0.7448 |

**Table 4**.

*Statistical analysis on gait parameters in NHP B1 at 27 Hz burst frequency*

| [NHP B1, 27 Hz] | | Wilcoxon Test | | | P value of Steel's Test with Control = BL | | |
|---|---|---|---|---|---|---|---|
| | | $X^2$ | DoF, N | p | CR Day 5 | Post CR Day 3 | Post CR Day 6 |
| Swing Speed | Left Front | 6.8022 | 3, 162 | 0.0785 | 0.6657 | 0.9437 | 0.0346 |
| | Left Hind | 7.1228 | 3, 162 | 0.0681 | 0.5277 | 0.7923 | 0.0408 |
| Stride Length | Left Front | 10.7208 | 3, 163 | 0.0133 | 0.8859 | 0.0541 | 0.0290 |
| | Left Hind | 19.3177 | 3, 163 | 0.0002 | 0.7205 | 0.0050 | 0.0012 |
| Mean Pressure | Left Front | 56.3867 | 3, 237 | <0.0001 | 0.9992 | <0.0001 | <0.0001 |
| | Left Hind | 65.8019 | 3, 237 | <0.0001 | 0.0813 | <0.0001 | <0.0001 |
| Width | Front | 12.1855 | 3, 215 | 0.0068 | 0.8339 | 0.2874 | 0.0027 |
| | Hind | 10.6252 | 3, 215 | 0.0139 | 0.9964 | 0.2505 | 0.0074 |
| Balance Index | Front | 1.7585 | 3, 214 | 0.624 | 0.9987 | 0.5246 | 0.9997 |
| | Hind | 6.3796 | 3, 214 | 0.0945 | 0.7354 | 0.1041 | 0.8975 |

**Tab1e 5**.

*Statistical analysis on gait parameters in NHP B2 at 21 Hz burst frequency*

| [NHP B2, 21 Hz] | | Wilcoxon Test | | | P value of Steel's Test with Control = BL | | |
|---|---|---|---|---|---|---|---|
| | | $X^2$ | DoF, N | p | CR Day 5 | Post CR Day 3 | Post CR Day 6 |
| Swing Speed | Left Front | 7.9529 | 3, 38 | 0.0470 | 0.0336 | 0.5049 | 0.4454 |
| | Left Hind | 7.1228 | 3, 42 | 0.4816 | 0.9544 | 0.7112 | 0.7469 |
| Stride Length | Left Front | 2.3995 | 3, 38 | 0.4937 | 0.8172 | 0.8607 | 0.9783 |
| | Left Hind | 2.7636 | 3, 42 | 0.4295 | 1.0000 | 0.4176 | 0.8360 |
| Mean Pressure | Left Front | 12.4914 | 3, 59 | 0.0059 | 0.9618 | 0.0121 | 0.0591 |
| | Left Hind | 9.7485 | 3, 63 | 0.0208 | 0.7823 | 0.5247 | 0.1559 |
| Width | Front | 5.8055 | 3, 59 | 0.1215 | 0.0638 | 0.3491 | 0.4129 |
| | Hind | 13.9343 | 3, 59 | 0.0030 | 0.0033 | 0.0204 | 0.0716 |
| Balance Index | Front | 0.5326 | 3, 59 | 0.9117 | 0.8650 | 0.9949 | 0.9808 |
| | Hind | 0.0095 | 3, 59 | 0.9998 | 1.0000 | 1.0000 | 1.0000 |

## Discussion

The purpose of this study is to investigate effects of STN CR DBS on PD gait and the impact of using different burst frequencies in STN CR DBS. STN CR DBS was delivered for five consecutive days at 21 Hz in both subjects and additionally at 24 Hz and 27 Hz in NHP B1. While improvement in mUPDRS ratings was observed in all CR DBS sessions, significant gait improvement associated with STN CR DBS was observed

in NHP B1 after CR DBS using 21 Hz burst frequency. Limited improvement in gait was observed in NHP B1 after 24 Hz CR DBS and in NHP B2 after 21 Hz CR DBS.

### *STN CR DBS as an Effective Treatment for PD Gait*

Previous studies have shown that STN CR DBS is an effective therapeutic approach to alleviate Parkinsonian akinesia, bradykinesia and tremor at preclinical and clinical levels (Adamchic et al., 2014; Hammond et al., 2007; Oswal et al., 2013; Tass et al., 2012; Wang et al., 2016). This present study demonstrated carryover therapeutic effects of STN CR DBS on gait in NHP B1 after 21 Hz CR DBS. However, in NHP B2, even though the same burst frequency was used when delivering CR DBS, limited improvement was observed in gait. This may be due to the fact that at the baseline gait was more severely impaired in NHP B2 compared to NHP B1. For the same reason, limited sample size in the gait data was available for NHP B2, which also contributed to the limited changes in gait we observed in this animal. Although preliminary, the results support the hypothesis that STN CR DBS can induce improvement in PD gait in the preclinical model in addition to its therapeutic benefits in akinesia, bradykinesia, rigidity, and tremor. Despite some immediate improvement in gait with tDBS, past studies have reported worsened gait symptoms over time (Krack et al., 2003; Ravi et al., 2021; Volkmann et al., 2004). Given that CR DBS is promising at improving gait function, this study highlights the importance of additional research to confirm our findings and the significance of the further advancement in the CR DBS paradigm.

### *Exploration of New Gait Parameters*

In order to accurately assess PD gait improvement by STN CR DBS, new gait parameters, mean plantar pressure, balance index, and width, were explored in addition to traditional gait parameters such as swing speed and stride length. Significant decrease in balance index was observed when swing speed and stride length were improved in NHP B1 after 21 Hz CR DBS **(Fig. 7E)**. As asymmetrical weight distribution results in unbalanced coordination of gait leading to additional gait dysfunction in PD patients, reduced asymmetry in balance reflected by lower balance index can be considered a significant improvement (Boonstra et al., 2014; Park et al., 2015). Although further research to investigate its validity as a functional gait parameter and its relationship with other traditional gait parameters will be required, balance index may be utilized as another promising gait parameter in the future. Both increased and decreased mean pressures were observed after CR DBS **(Fig. 7C, 8C, 9C and 10C)**. Although past studies have suggested that increased plantar pressure can be an indication of FoG, we did not observe any FoG during the data collection on these days (Pardoel et al., 2022; Shalin et al., 2021). Therefore, further research is needed to examine the validity of mean pressure as an appropriate gait parameter in the NHP model. Longer width in comparison with baseline was observed in NHP B1 at all three frequencies whereas NHP B2 exhibited width shorter than baseline **(Fig. 7D, 8D, 9D, and 10D)**. This may be due to innate individual differences in gait pattern, which can only be assessed with gait data collected during the pre-MPTP conditions. As gait scissoring is observed as a compensatory behavior due to dysfunction of mediolateral stability in patients with PD,

increased width may indicate improvement in gait stability associated with less gait scissoring (Galena et al., 2013; Nonnekes & Bloem, 2018). Further research in width is required to determine whether this increase in width could indicate an improvement in PD gait.

### *Effects of Different Burst Frequencies on PD Motor Symptoms and Gait*

Previous research on variation in stimulation parameters in the CR DBS paradigm have discovered that variation in parameters such as stimulation intensity, frequency, number of DBS lead contacts, and stimulation patterns can produce significant changes in the desynchronization effect of CR DBS (Manos et al, 2018; Manos et al, 2018; Tyulmankov et al., 2018). In NHP B1, 21 Hz burst frequency produced greater gait improvement while 24 Hz and 27 Hz burst frequencies produced longer carryover improvement in mUPDRS **(Fig. 6A-C, 7C, 8C, 9C, and 10C)**. This may indicate that different burst frequencies may be required to maximize CR DBS effect on different PD symptoms. Since a specific STN CR DBS parameter that allows maximized therapeutic effects on both PD gait and other symptoms has yet to be identified, it is possible that in clinical settings severity of different PD symptoms should be considered in the selection of CR stimulation parameters. Given the different phenotypes of PD, customizations of CR DBS parameters based on each patient's primary symptom would be crucial in providing subject-specific and symptom-specific treatment to PD patients.

### *Limitations and Future Directions*

Although preliminary results that support our hypothesis have been shown, some limitations were present in this study. The different burst frequencies were evaluated only in NHP B1 and not in NHP B2 due to availability of subjects and length of time required for data collection and analysis. In addition, the number of samples of gait data was significantly smaller in NHP B2 than in NHP B1. This is largely due to the difference in severity of PD symptoms between the subjects; NHP B2 exhibited more pronounced gait impairment which did not allow it to carry out the gait task as well as NHP B1. This small sample size led to decreased statistical power, increased variability, and limited generalizability in NHP B2's gait data. In addition, only one session was collected per frequency setting and per animal. In order to maximize the accuracy and to account for variability produced by these limitations throughout the research process in the future, gait evaluation should be performed in a more systematic manner with more repetitions of each CR DBS parameter setting in all animals.

The opposite results that were observed in width between NHP B1 and B2 could not be determined whether that was due to innate individual differences in gait pattern as pre-MPTP gait data was not available, which highlights the importance of comparison of data not only between pre- and post-CR DBS stimulation but also between healthy and parkinsonian states.

In spite of the limitations, this study offers meaningful observations in the effects of STN CR DBS on PD gait and has also identified a significant impact of varying burst frequency on the effect of STN CR DBS given that one burst frequency produced greater

gait improvement than the others. Although preliminary, this study encourages further advancement of CR DBS and emphasizes the importance of customizing CR DBS parameter settings to treat specific PD symptoms. In the future, further research in the personalized approach of CR DBS may also lead to deeper understanding of between-subject variance in the pathophysiology and response to therapeutic DBS, which will be crucial not only in realizing subject-specific CR DBS therapy but also in the development of other PD treatments.

**Acknowledgements**

I would like to thank Dr. Jing Wang, my mentor and principal investigator and all the researchers at the Neuromodulation Research Center at University of Minnesota for their continuous, generous support since the summer of 2021. Without the resources and support, it would have never been possible to conduct this project. I would also like to thank Dr. Darcy Burgund for supporting me throughout my journey at Macalester as a wonderful academic advisor and mentor, and Dr. Elizabeth Jansen and Dr. Jaine Strauss for serving on my honors committee. Last but not least, I am very humbled to have very supportive friends who uplifted me in difficult moments.

**References**

Aarsland, D., Batzu, L., Halliday, G. M. et al. (2021). Parkinson disease-associated cognitive impairment. *Nature Reviews: Disease Primers, 7*(47). https://doi.org/10.1038/s41572-021-00280-3

Adamchic, I., Hauptmann, C., Barnikol, U. B., Pawelczyk, N., Popovych, O., Barnikol, T. T., Silchenko, A., Volkmann, J., Deuschl, G., Meissner, W. G., Maarouf, M., Sturm, V., Freund, H. J., & Tass, P. A. (2014). Coordinated reset neuromodulation for Parkinson's disease: proof-of-concept study. Movement disorders : official journal of the Movement Disorder Society, 29(13), 1679–1684. https://doi.org/10.1002/mds.25923

Ahlskog, J. E., & Muenter, M. D. (2001). Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Movement disorders : official journal of the Movement Disorder Society*, *16*(3), 448–458. https://doi.org/10.1002/mds.1090

Ashkan, K., Wallace, B. A., Mitrofanis, J., Pollo, C., Brard, P. Y., Fagret, D., & Benabid, A. L. (2007). SPECT imaging, immunohistochemical and behavioural correlations in the primate models of Parkinson's disease. Parkinsonism & related disorders, 13(5), 266–275. https://doi.org/10.1016/j.parkreldis.2006.10.009

Balash, Y., Peretz, C., Leibovich, G., Herman, T., Hausdorff, J. M., & Giladi, N. (2005). Falls in outpatients with Parkinson's disease: frequency, impact and identifying factors. *Journal of neurology*, *252*(11), 1310–1315. https://doi.org/10.1007/s00415-005-0855-3

Bloem, B. R., Hausdorff, J. M., Visser, J. E., & Giladi, N. (2004). Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. *Movement disorders : official journal of the Movement Disorder Society*, *19*(8), 871–884. https://doi.org/10.1002/mds.20115

Bloem, B. R., Marinus, J., Almeida, Q., Dibble, L., Nieuwboer, A., Post, B., Ruzicka, E., Goetz, C., Stebbins, G., Martinez-Martin, P., Schrag, A., & Movement Disorders Society Rating Scales Committee (2016). Measurement instruments to assess posture, gait, and balance in Parkinson's disease: Critique and recommendations. *Movement disorders : official journal of the Movement Disorder Society*, *31*(9), 1342–1355. https://doi.org/10.1002/mds.26572

Bohnen, N. I., Albin, R. L., Müller, M. L., & Chou, K. (2011). Advances in Therapeutic Options for Gait and Balance in Parkinson's Disease. US neurology, 7(2), 100–108. https://doi.org/10.17925/usn.2011.07.02.100

Boonstra, T. A., van Vugt, J. P., van der Kooij, H., & Bloem, B. R. (2014). Balance asymmetry in Parkinson's disease and its contribution to freezing of gait. *PloS one*, *9*(7), e102493. https://doi.org/10.1371/journal.pone.0102493

Brooks, D. J., Salmon, E. P., Mathias, C. J., Quinn, N., Leenders, K. L., Bannister, R., Marsden, C. D., & Frackowiak, R. S. (1990). The relationship between locomotor disability, autonomic dysfunction, and the integrity of the striatal dopaminergic system in patients with multiple system atrophy, pure autonomic failure, and Parkinson's disease, studied with PET. Brain : a journal of neurology, 113 ( Pt 5), 1539–1552. https://doi.org/10.1093/brain/113.5.1539

Busch, T.deA., Duarte, Y. A., Pires Nunes, D., Lebrão, M. L., Satya Naslavsky, M., dos Santos Rodrigues, A., & Amaro, E., Jr (2015). Factors associated with lower gait speed among the elderly living in a developing country: a cross-sectional population-based study. *BMC geriatrics*, *15*, 35. https://doi.org/10.1186/s12877-015-0031-2

Camprodon, J. A., Chou, T., Testo, A. A., Deckersbach, T., Scharf, J. M., & Dougherty, D. D. (2021). Case Report: Deep Brain Stimulation to the Ventral Internal Capsule/Ventral Striatum Induces Repeated Transient Episodes of Voltage-Dependent Tourette-Like Behaviors. *Frontiers in human neuroscience*, *14*, 590379. https://doi.org/10.3389/fnhum.2020.590379

Chao, Y., Gang, L., Na, Z. L., Ming, W. Y., Zhong, W. S., & Mian, W. S. (2007). Surgical management of Parkinson's disease: update and review. *Interventional neuroradiology : journal of peritherapeutic neuroradiology, surgical procedures and related neurosciences*, *13*(4), 359–368. https://doi.org/10.1177/159101990701300407

Chen, P.-H., Wang, R.-L., Liou, D.-J., & Shaw, J.-S. (2013). Gait disorders in parkinson's disease: assessment and management. *International Journal of Gerontology*, *7*(4), 189–193. https://doi.org/10.1016/j.ijge.2013.03.005

Collomb-Clerc, A., & Welter, M. L. (2015). Effects of deep brain stimulation on balance and gait in patients with Parkinson's disease: A systematic neurophysiological review. Neurophysiologie clinique = Clinical neurophysiology, 45(4-5), 371–388. https://doi.org/10.1016/j.neucli.2015.07.001

Curtze, C., Nutt, J. G., Carlson-Kuhta, P., Mancini, M., and Horak, F. B. (2016). Objective gait and balance impairments relate to balance confidence and perceived mobility in people with Parkinson disease. *Phys. Ther.* 96, 1734–1743. doi: 10.2522/ptj.20150662

Del Din, S., Elshehabi, M., Galna, B., Hobert, M. A., Warmerdam, E., Suenkel, U., et al. (2019a). Gait analysis with wearables predicts conversion to parkinson disease. *Ann. Neurol.* 86, 357–367. doi: 10.1002/ana.25548

Deuschl, G., Herzog, J., Kleiner-Fisman, G., Kubu, C., Lozano, A. M., Lyons, K. E., Rodriguez-Oroz, M. C., Tamma, F., Tröster, A. I., Vitek, J. L., Volkmann, J., & Voon, V. (2006). Deep brain stimulation: postoperative issues. *Movement disorders : official journal of the Movement Disorder Society*, *21 Suppl 14*, S219–S237. https://doi.org/10.1002/mds.20957

Deuschl, G., Schade-Brittinger, C., Krack, P., Volkmann, J., Schäfer, H., Bötzel, K., Daniels, C., Deutschländer, A., Dillmann, U., Eisner, W., Gruber, D., Hamel, W., Herzog, J., Hilker, R., Klebe, S., Kloss, M., Koy, J., Krause, M., Kupsch, A., Lorenz, D., … German Parkinson Study Group, Neurostimulation Section (2006). A randomized trial of deep-brain stimulation for Parkinson's disease. *The New England journal of medicine*, *355*(9), 896–908. https://doi.org/10.1056/NEJMoa060281

Dorsey, E. R., Constantinescu, R., Thompson, J. P., Biglan, K. M., Holloway, R. G., Kieburtz, K., Marshall, F. J., Ravina, B. M., Schifitto, G., Siderowf, A., & Tanner, C. M. (2007). Projected number of people with Parkinson disease in the most populous

nations, 2005 through 2030. *Neurology*, 68(5), 384–386. https://doi.org/10.1212/01.wnl.0000247740.47667.03

Ebersbach, G., Baas, H., Csoti, I., Müngersdorf, M., & Deuschl, G. (2006). Scales in Parkinson's disease. *Journal of neurology,* 253 Suppl 4, IV32–IV35. https://doi.org/10.1007/s00415-006-4008-0

Fearnley, J. M., & Lees, A. J. (1991). Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain : a journal of neurology, 114 ( Pt 5), 2283–2301. https://doi.org/10.1093/brain/114.5.2283

Fling, B. W., Curtze, C., & Horak, F. B. (2018). Gait asymmetry in people with parkinson's disease is linked to reduced integrity of callosal sensorimotor regions. *Frontiers in Neurology*, *9*, 215–215. https://doi.org/10.3389/fneur.2018.00215

Galna, B., Lord, S., Burn, D. J., and Rochester, L. (2015). Progression of gait dysfunction in incident Parkinson's disease: impact of medication and phenotype. *Mov. Disord.* 30, 359–367. doi: 10.1002/mds.26110

Galna, B., Murphy, A. T., & Morris, M. E. (2013). Obstacle crossing in parkinson's disease: mediolateral sway of the centre of mass during level-ground walking and obstacle crossing. Gait & Posture, 38(4), 790–794. https://doi.org/10.1016/j.gaitpost.2013.03.024

Garcia-Ruiz P. J. (2011). Gait disturbances in Parkinson disease. Did freezing of gait exist before levodopa? Historical review. *Journal of the neurological sciences*, *307*(1-2), 15–17. https://doi.org/10.1016/j.jns.2011.05.019

Gardner, J. (2013). A history of deep brain stimulation: Technological innovation and the role of clinical assessment tools. Social Studies of Science, 43(5), 707–728. http://www.jstor.org/stable/43284202

Ge, HL., Chen, XY., Lin, YX. et al. The prevalence of freezing of gait in Parkinson's disease and in patients with different disease durations and severities. Chin Neurosurg Jl 6, 17 (2020). https://doi.org/10.1186/s41016-020-00197-y

GREENFIELD, J. G., & BOSANQUET, F. D. (1953). The brain-stem lesions in Parkinsonism. *Journal of neurology, neurosurgery, and psychiatry*, *16*(4), 213–226. https://doi.org/10.1136/jnnp.16.4.213

Guo, Y., & Rubin, J. E. (2011). Multi-site stimulation of subthalamic nucleus diminishes thalamocortical relay errors in a biophysical network model. *Neural networks : the official journal of the International Neural Network Society*, *24*(6), 602–616. https://doi.org/10.1016/j.neunet.2011.03.010

Hammond, C., Bergman, H., & Brown, P. (2007). Pathological synchronization in Parkinson's disease: networks, models and treatments. Trends in neurosciences, 30(7), 357–364. https://doi.org/10.1016/j.tins.2007.05.004

Hariz, M. I., & De Salles, A. A. (1997). The side-effects and complications of posteroventral pallidotomy. *Acta neurochirurgica. Supplement*, *68*, 42–48. https://doi.org/10.1007/978-3-7091-6513-3_8

Hauptmann, C., Popovych, O., & Tass, P. A. (2007). Desynchronizing the abnormally synchronized neural activity in the subthalamic nucleus: a modeling study.

*Expert review of medical devices*, *4*(5), 633–650. https://doi.org/10.1586/17434440.4.5.633

Hely, M.A., Reid, W.G.J., Adena, M.A., Halliday, G.M. and Morris, J.G.L. (2008), The Sydney multicenter study of Parkinson's disease: The inevitability of dementia at 20 years. *Movement Disorders: Official Journal of the Movement Disorder Society*, 23: 837-844. https://doi.org/10.1002/mds.21956

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: onset, progression and mortality. *Neurology*, *17*(5), 427–442. https://doi.org/10.1212/wnl.17.5.427

Hutchison WD, Allan RJ, Opitz H, Levy R, Dostrovsky JO, Lang AE, et al. Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease. Ann Neurol. (1998) 44:622–8. doi: 10.1002/ana.410440407

Jacobs, J. V., Nutt, J. G., Carlson-Kuhta, P., Stephens, M., & Horak, F. B. (2009). Knee trembling during freezing of gait represents multiple anticipatory postural adjustments. *Experimental neurology*, *215*(2), 334–341. https://doi.org/10.1016/j.expneurol.2008.10.019

Kelly, P. J., Ahlskog, J. E., Goerss, S. J., Daube, J. R., Duffy, J. R., & Kall, B. A. (1987). Computer-assisted stereotactic ventralis lateralis thalamotomy with microelectrode recording control in patients with Parkinson's disease. *Mayo Clinic proceedings*, *62*(8), 655–664. https://doi.org/10.1016/s0025-6196(12)65215-x

Kiesmann, M., Sauleau, E., Perisse, J., Jehl, C., Konrad, S., Karcher, P., Fleury, M. C., Rohmer, D., Sauer, A., Ehret, M., Vogel, T., Kaltenbach, G., & Schmitt, E. (2021). Parkinsonian gait in elderly people: significance of the threshold value of two and more

falls per year. *Revue Neurologique*, *177*(4), 385–393. https://doi.org/10.1016/j.neurol.2020.06.012

Kish, S. J., Shannak, K., & Hornykiewicz, O. (1988). Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. The New England journal of medicine, 318(14), 876–880. https://doi.org/10.1056/NEJM198804073181402

Koehler, P. J., Nonnekes, J., & Bloem, B. R. (2021). Freezing of gait before the introduction of levodopa. *The Lancet. Neurology*, *20*(2), 97. https://doi.org/10.1016/S1474-4422(19)30091-2

Krack, P., Batir, A., Van Blercom, N., Chabardes, S., Fraix, V., Ardouin, C., Koudsie, A., Limousin, P. D., Benazzouz, A., LeBas, J. F., Benabid, A. L., & Pollak, P. (2003). Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *The New England journal of medicine*, *349*(20), 1925–1934. https://doi.org/10.1056/NEJMoa035275

Laitinen, L. V., Bergenheim, A. T., & Hariz, M. I. (1992). Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. *Journal of neurosurgery*, *76*(1), 53–61. https://doi.org/10.3171/jns.1992.76.1.0053

Lampariello, L. R., Cortelazzo, A., Guerranti, R., Sticozzi, C., & Valacchi, G. (2012). The Magic Velvet Bean of Mucuna pruriens. *Journal of traditional and complementary medicine*, 2(4), 331–339. https://doi.org/10.1016/s2225-4110(16)30119-5

Langston J. W. (2017). The MPTP Story. Journal of Parkinson's disease, 7(s1), S11–S19. https://doi.org/10.3233/JPD-179006

Lankau, E. W., Turner, P. V., Mullan, R. J., & Galland, G. G. (2014). Use of nonhuman primates in research in North America. Journal of the American Association for Laboratory Animal Science : JAALAS, 53(3), 278–282.

Lee, J. Y., Martin-Bastida, A., Murueta-Goyena, A., Gabilondo, I., Cuenca, N., Piccini, P., & Jeon, B. (2022). Multimodal brain and retinal imaging of dopaminergic degeneration in Parkinson disease. Nature reviews. Neurology, 18(4), 203–220. https://doi.org/10.1038/s41582-022-00618-9

Lewy, F. H. (1912). Paralysis agitans. *Handbuch der neurologie*, *3*, 920-958.

Lewitt P. A. (2008). Levodopa for the treatment of Parkinson's disease. *The New England journal of medicine*, *359*(23), 2468–2476. https://doi.org/10.1056/NEJMct0800326

Liu, Y., Yue, F., Tang, R. et al. Progressive loss of striatal dopamine terminals in MPTP-induced acute parkinsonism in cynomolgus monkeys using vesicular monoamine transporter type 2 PET imaging ([18F]AV-133). Neurosci. Bull. 30, 409–416 (2014). https://doi.org/10.1007/s12264-013-1374-3

Manos, T., Zeitler, M., & Tass, P. A. (2018). Short-Term Dosage Regimen for Stimulation-Induced Long-Lasting Desynchronization. *Frontiers in physiology*, *9*, 376. https://doi.org/10.3389/fphys.2018.00376

Manos, T., Zeitler, M., Tass, P. A., & Battaglia, F. P. (2018). How stimulation frequency and intensity impact on the long-lasting effects of coordinated reset stimulation. Plos Computational Biology, 14(5). https://doi.org/10.1371/journal.pcbi.1006113

Manyam B. V. (1990). Paralysis agitans and levodopa in “Ayurveda”: Ancient Indian medical treatise. *Movement Disorders: Official Journal of the Movement Disorder Society*, *5*(1), 47–48. https://doi.org/10.1002/mds.870050112

Mei, S., Li, J., Middlebrooks, E. H., Almeida, L., Hu, W., Zhang, Y., Ramirez-Zamora, A., & Chan, P. (2019). New Onset On-Medication Freezing of Gait After STN-DBS in Parkinson's Disease. Frontiers in neurology, 10, 659. https://doi.org/10.3389/fneur.2019.00659

Morris M. E. (2000). Movement disorders in people with Parkinson disease: a model for physical therapy. *Physical therapy*, *80*(6), 578–597.

Morris, R., Lord, S., Bunce, J., Burn, D., & Rochester, L. (2016). Gait and cognition: Mapping the global and discrete relationships in ageing and neurodegenerative disease. *Neuroscience and biobehavioral reviews*, *64*, 326–345. https://doi.org/10.1016/j.neubiorev.2016.02.012

Nambu, A., Tokuno, H., & Takada, M. (2002). Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway. Neuroscience research, 43(2), 111–117. https://doi.org/10.1016/s0168-0102(02)00027-5

Nonnekes, J., Giladi, N., Guha, A., Fietzek, U. M., Bloem, B. R., & Růžička, E. (2019). Gait festination in parkinsonism: introduction of two phenotypes. *Journal of neurology*, *266*(2), 426–430. https://doi.org/10.1007/s00415-018-9146-7

Nonnekes, J., Bereau, M., & Bloem, B. R. (2020). Freezing of Gait and Its Levodopa Paradox. *JAMA neurology*, *77*(3), 287–288. https://doi.org/10.1001/jamaneurol.2019.4006

Nonnekes, J., & Bloem, B. R. (2018). Deliberate gait scissoring to overcome freezing of gait in parkinson disease. Neurology, 91(2), 97–97. https://doi.org/10.1212/WNL.0000000000005780

Nutt, J. G., Bloem, B. R., Giladi, N., Hallett, M., Horak, F. B., & Nieuwboer, A. (2011). Freezing of gait: moving forward on a mysterious clinical phenomenon. *The Lancet. Neurology*, *10*(8), 734–744. https://doi.org/10.1016/S1474-4422(11)70143-0

Odekerken, V. J., van Laar, T., Staal, M. J., Mosch, A., Hoffmann, C. F., Nijssen, P. C., Beute, G. N., van Vugt, J. P., Lenders, M. W., Contarino, M. F., Mink, M. S., Bour, L. J., van den Munckhof, P., Schmand, B. A., de Haan, R. J., Schuurman, P. R., & de Bie, R. M. (2013). Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial. *The Lancet. Neurology*, *12*(1), 37–44. https://doi.org/10.1016/S1474-4422(12)70264-8

Oswal, A., Brown, P., & Litvak, V. (2013). Synchronized neural oscillations and the pathophysiology of Parkinson's disease. Current opinion in neurology, 26(6), 662–670. https://doi.org/10.1097/WCO.0000000000000034

Ovallath, S., & Deepa, P. (2013). The history of parkinsonism: descriptions in ancient Indian medical literature. *Movement Disorders: Official Journal of the Movement Disorder Society*, 28(5), 566–568. https://doi.org/10.1002/mds.25420

Ovallath, S., & Sulthana, B. (2017). Levodopa: History and Therapeutic Applications. *Annals of Indian Academy of Neurology*, *20*(3), 185–189. https://doi.org/10.4103/aian.AIAN_241_17

Pardoel, S., Nantel, J., Kofman, J., & Lemaire, E. D. (2022). Prediction of Freezing of Gait in Parkinson's Disease Using Unilateral and Bilateral Plantar-Pressure Data. Frontiers in neurology, 13, 831063. https://doi.org/10.3389/fneur.2022.831063

Park, J. H., Kang, Y. J., & Horak, F. B. (2015). What Is Wrong with Balance in Parkinson's Disease?. *Journal of movement disorders*, *8*(3), 109–114. https://doi.org/10.14802/jmd.15018

PD Med Collaborative Group, Gray, R., Ives, N., Rick, C., Patel, S., Gray, A., Jenkinson, C., McIntosh, E., Wheatley, K., Williams, A., & Clarke, C. E. (2014). Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial. *Lancet (London, England)*, *384*(9949), 1196–1205. https://doi.org/10.1016/S0140-6736(14)60683-8

Pickering, R. M., Grimbergen, Y. A., Rigney, U., Ashburn, A., Mazibrada, G., Wood, B., Gray, P., Kerr, G., & Bloem, B. R. (2007). A meta-analysis of six prospective studies of falling in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society*, *22*(13), 1892–1900. https://doi.org/10.1002/mds.21598

Poewe W. (2009). Clinical measures of progression in Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*, 24 Suppl 2, S671–S676. https://doi.org/10.1002/mds.22600

Ravi, D. K., Baumann, C. R., Bernasconi, E., Gwerder, M., Ignasiak, N. K., Uhl, M., Stieglitz, L., Taylor, W. R., & Singh, N. B. (2021). Does Subthalamic Deep Brain Stimulation Impact Asymmetry and Dyscoordination of Gait in Parkinson's Disease?.

*Neurorehabilitation and neural repair*, *35*(11), 1020–1029. https://doi.org/10.1177/15459683211041309

Saint-Cyr, J. A., Trépanier, L. L., Kumar, R., Lozano, A. M., & Lang, A. E. (2000). Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. *Brain : a journal of neurology*, *123 ( Pt 10)*, 2091–2108. https://doi.org/10.1093/brain/123.10.2091

Serrao, M., Ranavolo, A., Conte, C., Davassi, C., Mari, S., Fasano, A., Chini, G., Coppola, G., Draicchio, F., & Pierelli, F. (2015). Effect of 24-h continuous rotigotine treatment on stationary and non-stationary locomotion in de novo patients with Parkinson disease in an open-label uncontrolled study. *Journal of neurology*, *262*(11), 2539–2547. https://doi.org/10.1007/s00415-015-7883-4

Shalin, G., Pardoel, S., Lemaire, E. D., Nantel, J., & Kofman, J. (2021). Prediction and detection of freezing of gait in Parkinson's disease from plantar pressure data using long short-term memory neural-networks. Journal of neuroengineering and rehabilitation, 18(1), 167. https://doi.org/10.1186/s12984-021-00958-5

Smith, Y., Galvan, A., Ellender, T. J., Doig, N., Villalba, R. M., Huerta-Ocampo, I., Wichmann, T., & Bolam, J. P. (2014). The thalamostriatal system in normal and diseased states. Frontiers in systems neuroscience, 8, 5. https://doi.org/10.3389/fnsys.2014.00005

Song, S., & Geyer, H. (2018). Predictive neuromechanical simulations indicate why walking performance declines with aging. *The Journal of physiology*, *596*(7), 1199–1210. https://doi.org/10.1113/JP275166

Tass P. A. (2001). Desynchronizing double-pulse phase resetting and application to deep brain stimulation. *Biological cybernetics*, *85*(5), 343–354. https://doi.org/10.1007/s004220100268

Tass, P. A. (2003). A model of desynchronizing deep brain stimulation with a demand-controlled coordinated reset of neural subpopulations. Biological Cybernetics, 89(2), 81–88. https://doi.org/10.1007/s00422-003-0425-7

Tass, P. A., & Majtanik, M. (2006). Long-term anti-kindling effects of desynchronizing brain stimulation: a theoretical study. *Biological cybernetics*, *94*(1), 58–66. https://doi.org/10.1007/s00422-005-0028-6

Tass, P. A., Qin, L., Hauptmann, C., Dovero, S., Bezard, E., Boraud, T., & Meissner, W. G. (2012). Coordinated reset has sustained aftereffects in Parkinsonian monkeys. Annals of neurology, 72(5), 816–820. https://doi.org/10.1002/ana.23663

Ponce, F.A. (2014) Thalamotomy. *Encyclopedia of the Neurological Sciences (second edition)*. Academic Press. Retrieved 2023, from https://doi.org/10.1016/B978-0-12-385157-4.00794-6.

Tolosa, E., Garrido, A., Scholz, S. W., & Poewe, W. (2021). Challenges in the diagnosis of Parkinson's disease. *The Lancet. Neurology*, *20*(5), 385–397. https://doi.org/10.1016/S1474-4422(21)00030-2

Tyulmankov, D., Tass, P. A., Bokil, H., & Gross, R. E. (2018). Periodic flashing coordinated reset stimulation paradigm reduces sensitivity to on and off period durations. Plos One, 13(9). https://doi.org/10.1371/journal.pone.0203782

Vitek JL, Zhang J, Hashimoto T, Russo G, Baker KB. External pallidal stimulation improves parkinsonian motor signs and modulates neuronal activity throughout the basal ganglia thalamic network. Exp Neurol. (2012) 233:581–6. doi: 10.1016/j.expneurol.2011.09.031

Volkmann, J., Allert, N., Voges, J., Sturm, V., Schnitzler, A., & Freund, H. J. (2004). Long-term results of bilateral pallidal stimulation in Parkinson's disease. *Annals of neurology*, *55*(6), 871–875. https://doi.org/10.1002/ana.20091

Wang J, Nebeck S, Muralidharan A, Johnson MD, Vitek JL, Baker KB. Coordinated reset deep brain stimulation of subthalamic nucleus produces long-lasting, dose-dependent motor improvements in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine non-human primate model of Parkinsonism. Brain Stimul. (2016) 9:609–17. doi: 10.1016/j.brs.2016.03.014

Wang J, Johnson LA, Jensen AL, Baker KB, Molnar GF, Johnson MD, et al. Network-wide oscillations in the parkinsonian state: alterations in neuronal activities occur in the premotor cortex in parkinsonian nonhuman primates. J Neurophysiol. (2017) 117:2242–9. doi: 10.1152/jn.00011.2017

Wilson, J., Alcock, L., Yarnall, A. J., Lord, S., Lawson, R. A., Morris, R., Taylor, J.-P., Burn, D. J., Rochester, L., & Galna, B. (2020). Gait progression over 6 years in parkinson's disease: effects of age, medication, and pathology. *Frontiers in Aging Neuroscience*, *12*, 577435–577435. https://doi.org/10.3389/fnagi.2020.577435

Wongsarnpigoon, A., & Grill, W. M. (2010). Energy-efficient waveform shapes for neural stimulation revealed with a genetic algorithm. *Journal of neural engineering*, *7*(4), 046009. https://doi.org/10.1088/1741-2560/7/4/046009

Yang, W., Hamilton, J. L., Kopil, C., Beck, J. C., Tanner, C. M., Albin, R. L., Ray Dorsey, E., Dahodwala, N., Cintina, I., Hogan, P., & Thompson, T. (2020). Current and projected future economic burden of Parkinson's disease in the U.S. *NPJ Parkinson's disease*, *6*, 15. https://doi.org/10.1038/s41531-020-0117-1

Zanardi, A.P.J., da Silva, E.S., Costa, R.R. *et al.* Gait parameters of Parkinson's disease compared with healthy controls: a systematic review and meta-analysis. *Sci Rep* 11, 752 (2021). https://doi.org/10.1038/s41598-020-80768-2

Zhang, Z. X., Dong, Z. H., & Román, G. C. (2006). Early descriptions of Parkinson disease in ancient China. *Archives of neurology*, *63*(5), 782–784. https://doi.org/10.1001/archneur.63.5.782

Zhang, Y., & Jordan, J. M. (2010). Epidemiology of osteoarthritis. *Clinics in geriatric medicine*, *26*(3), 355–369. https://doi.org/10.1016/j.cger.2010.03.001

Zhu, H., Lemos, H., Bhatt, B., Islam, B. N., Singh, A., Gurav, A., Huang, L., Browning, D. D., Mellor, A., Fulzele, S., & Singh, N. (2017). Carbidopa, a drug in use for management of Parkinson disease inhibits T cell activation and autoimmunity. PloS one, 12(9), e0183484. https://doi.org/10.1371/journal.pone.0183484