Quantification of Gait and Time Perception in Parkinson's Disease



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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor dysfunctions because of death of dopaminergic cells in the basal ganglia (BG). It is usually treated with the dopamine precursor levodopa and/or deep brain stimulation (DBS) where electrical stimulus pulses are delivered to parts of the BG.

Despite much research into potential biomarkers, current diagnosis and disease staging remain reliant on the clinical assessment of motor symptoms using rating scales. This causes several problems: assessments are subject to inter-observer variability; rating scales are nonlinear; and the scales only enter their working range once more than half of the dopamine producing cells in the brain have died.

New treatments, and in particular disease modifying drugs (DMDs), are desperately needed. Only around one in 10 newly developed drugs survives rigorous assessment in trials, which are both time consuming and very costly. Failures must be recognized quickly so that resources can be transferred to the next candidate agent. When evaluating DMDs investigators are usually looking for small changes in disease trajectory. The more sensitive a biomarker, and the less affected it is by noise, the sooner a difference will be seen after treatment commences. A sensitive and noise resistant measure is therefore critical to minimizing resource consumption in the evaluation of doomed drugs. An additional problem arises when the measurement is affected by background symptomatic medication, which the great majority of PD patients are treated with. Symptomatic treatment can obscure progression in motor scales almost completely, rendering them completely insensitive to changes in disease trajectory.

Thanks to novel technology we are now able to quantify motor disturbances rapidly, accurately, noninvasively, and objectively using wearable sensors. Due to its portable and easily operable nature, wearable sensors are replacing motion detection systems and force plates to give quick clinical measurements. This thesis examines the usefulness of precise measurements of gait and balance as a means of quantifying PD. The aim is to identify and characterize features that change significantly over periods of months rather than years, are not noisy, and are relatively unaffected by the presence of symptomatic medication. Gait measurements will be taken from both PD patients and age-match controls every three months for two years. In addition, cross-sectional studies will be conducted to examine gait in patients' on- and off- medication and DBS states to allow rapid evaluation of which features show the greatest change and thus warrant the closest examination from inducing abrupt shifts in parkinsonian state.

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Related Publications

Journal Articles

- Su ZH, Patel S, Gavine B, Buchanan T, Bogdanovic M, Sarangmat N, Green AL, Bloem BR, FitzGerald JJ, Antoniades CA. Deep Brain Stimulation and Levodopa Affect Gait Variability in Parkinson Disease Differently. Neuromodulation 2022.
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- Su ZH, Brezezick M, Fitzgerald J, Antoniades C. Quantifying eye and gait abnormalities in Parkinson's patients after Deep Brain Stimulation. Abstract. *Movement Disorders 2019*

Online Presence

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Abbreviations

AADC	aromatic L-amino acid decarboxylase
ABC	Activities-specific Balance Confidence
ACC	acceleration
Ach	acetyl choline
ADL	Activities of Daily Living
ALH	aldehyde dehydrogenase
ANOVA	Analysis of Variance
AP	anterior-posterior
APA	anticipatory postural adjustments
BBB	blood-brain barrier
BG	basal ganglia
CNS	central nervous system
COM	centre of mass
COMT	catechol-O-methyltransferase
COP	centre of pressure
CoV	co-variance
CST	corticospinal tract
CV	Coefficient of variation
DA	dopamine
DA-R	dopamine receptor
DAT	dopamine transporters
DBS	Deep Brain Stimulation
deg	degrees
DLPFC	dorsal lateral pre-frontal cortex
DMD	Disease modifying drugs
DOPA	L-3,4-dihydroxyphenylalaminie
DOPAC	3,4-dihydroxyphenylacetic acid
DOPAL	3,4-dihydroxyphenylacetaldehyde
DOPET	3,4-dihydroxyphenylethanol
EMG	electromyography
EQ-5D	EuroQol-5 Dimension
FAD	flavin adenine dinucleotide
FES	Falls Efficacy Scales
FOG	freezing-of-gait
GABA	gamma-aminobutyric acid
GCT	gait cycle time
Glut	glutamate
GPe	external globus pallidus
GPi	internal globus pallidus
HC	Healthy control
HD	Huntington's disease
HVA	homovanillic acid

IIV	Intraindividual variability
IMU	inertial measurement unit
LEU	levodopa equivalent units
LID	levodopa-induced-dyskinesia
LRRK2	leucine rich repeat kinase 2
LTD	long-term depression
LTP	long-term potentiation
MAO	monoamine oxidase
MDS	Movement Disorder Society
MDS-UPDRS	Movement Disorder Society--Unified Parkinson's Disease Rating Scale
ML	mediolateral
MLR	midbrain locomotor region
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MPTP	1-methyl-4-phenol-2,3,6-tetrahydropyridine
MSN	medium spiny neurons
NMDA	N-methyl D-aspartate
OHDA	hydroxydopamine
OxQUIP	Oxford Quantification in Parkinsonism
PD	Parkinson's disease
PDQ39	Parkinson's Disease Questionnaire
PET	positron emission tomography
PFC	pre-frontal cortex
PPN	pedunculopontine nucleus
PSL	prosaccadic latency
rTMS	Repetitive transcranial magnetic stimulation
RN	red nucleus
ROM	root-mean-square
ROM	range of motion
SC	superior colliculus
SD	Poincare standard deviations
SMA	supplementary motor area
SN	substantia nigra
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
Std	standard deviation
STN	subthalamic nucleus
TUG	Timed Up and Go test
Vim	ventralis intermediate
WSRT	Wilcoxon signed rank test

Chapter 1 Introduction

1.1 Parkinson's Disease is a Basal Ganglia Disorder

PD was first identified and described in *An Essay on the Shaking Palsy*[1] in 1817, so named due to patients' most obvious motor symptom, an uncontrollable and involuntary shaking of the limbs. It is a slowly progressive neurodegenerative disease in which there is gradual death of dopaminergic cells in the BG. The causes are poorly understood: only a small portion (around 10%) of PD is caused by genetics, suggesting that environmental factors have a key role in disease pathogenesis and progression[2].

The BG are situated at the base of the forebrain and connect to brain regions including the cortex, thalamus, and brain stem. Anatomically, the BG consist of four interconnected and uniquely functioning nuclei, substantia nigra (SN), the striatum (caudate nucleus and putamen), the globus pallidus (separated into internal and external regions based on location and function), and the subthalamic nucleus (STN). The BG receive sensory and motor information from the cortex, integrate it with information fed back from regions including the thalamus and limbic system, and send the processed information and selected decision to the cortex and brain stem to elicit action on a subconscious level.

The SN is located dorsal to the cerebral peduncle, composed of mostly dopaminergic cells that contain high levels of neuromelanin. It is named after the dark appearance of these cells from neuromelanin that appears black[3]. The SN is composed of substantia nigra pars compacta (SNc), involved in motor control, and pars reticulata (SNr), involved in information

integration and inhibitory control[4]. In PD there is degeneration of the dopaminergic cells in the SNc.

The striatum is made up of the putamen and caudate nuclei, consisting of mostly medium spiny neurons (MSN) that produces gamma-aminobutyric acid (GABA) and usually quiet[5]. The caudate and putamen play different roles in decision-making with the caudate encoding object choice[6] and the putamen action choice[7]. PD patients are found to have a more active striatum. The striatal MSN usually fires at low rates at around 0.5-2Hz, which is significantly increased in PD to around 25-30 Hz. This increase in firing has been found to be suppressed by levodopa, the most common treatment for PD, and the low firing rate has been suggested to be the key for faithful information transfer in the BG[8].

The globus pallidus is a key player in information transfer within the BG involved in regulation of voluntary movements[9]. It receives input from the cortex via the striatum and sends output directly to the thalamus and SN. It is divided by the medial medullary lamina intro the internal (GPi) and external (GPe) globus pallidum.

The STN is located ventral to the thalamus and is a common target for deep brain stimulation (DBS) treatment for PD. How STN stimulation affects gait and posture will be the subject of examination in Chapter 4 of this thesis.

As a collection of these nuclei, the BG is responsible for relaying information across different regions in the brain, specifically to the thalamus and cortex. The five BG-thalamocortical circuits[10] include the motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and

anterior cingulate circuits. This thesis focuses on quantifying motor symptoms of PD, so we will focus on the motor BG-thalamocortical circuit. In the motor circuit, motor and somatosensory cortices, arcuate premotor area and the supplementary motor area (SMA), project to the spinal cord and putamen, and the latter then projects to the SN and GP. The GPi then projects to the ventrolateral nucleus of the thalamus, closing the loop by projection to the SMA. The SMA plays a vital role in motor programming and initiating movements. SMA lesions show similar characteristics to PD[11, 12]. Death of SNc cells decrease dopaminergic input to the striatum. Striatal DA deficiency reduces SMA activity and lead to akinesia in PD[13].

The commonly accepted model of BG function features two parallel neural pathways, the 'direct' pathway via the GPi and the 'indirect' pathway via GPe, which have largely opposite effects. In the direct pathway, striatal MSNs send GABAergic projections to the SNr and GPi, reducing activity in the inhibitory neurons that project from GPi/SNr to the thalamus and superior colliculus (SC), leading to action. In the indirect pathway, a separate group of MSNs send inhibitory projections to the GPe; activity in these reduces the inhibitory influence of the GPe on the STN, leading to net activation of the STN and thus increased activity of the inhibitory neurons that project from GPi/SNr to the thalamus. Dopaminergic projection to the MSNs of the indirect pathway is lost first in early stages of PD before those of the direct pathway are affected. The balanced interplay between the two pathways normally acts as a filter and decision maker for a single precise movement to be carried out by selecting the correct movement through the direct pathway and inhibiting all other inappropriate movements through the indirect pathway. Interruption to this balance causes abnormal BG function that can either result in hypokinetic disorders like PD, or hyperkinetic disorder like Huntington's disease (HD). Excessive suppression to the neurons in the motor thalamus in PD

leads to freezing-of-gait or (FOG) paucity of spontaneous movement. On the other hand, an overpowered direct pathway from neuronal degeneration of the indirect pathway in HD reduces normal inhibition on the thalamus, resulting in excessive and unwanted movements.

As the only glutamatergic projection in the BG, STN activation activates GPi and SNr to inhibit thalamic activity to prevent movement. The SNr receives input from the caudate and projects to the SC for oculomotor control while the GPi receives input from the putamen and sends out thalamocortical projection for motor control. At the centre of the two opposing pathways, the SNr oversees information processing and decision making of the BG while the SNc of motor control[4]. The SNc functions to activate the striatum and the direct pathway via dopamine receptor D1 receptors and inhibits the striatum and the indirect pathway via dopamine receptor D2 receptors, resulting in a net activation signal for movement from the thalamus. Loss of SNc cells in PD reduces dopamine (DA) levels in the brain, changing the balance where the indirect pathway becomes stronger leading to a strong inactivation signal while the direct pathway becomes weaker, resulting in an overall increased inhibition of movement initiation and other motor symptoms.

PD is primarily a movement disorder and current clinical assessments are based on rating motor abilities. This thesis focuses on idiopathic PD cases and specifically the features of the Parkinsonian gait.

1.2 Motor Symptoms in PD

The three cardinal PD motor symptoms are tremor, rigidity, and bradykinesia[14-16]. Motor symptom onset is typically asymmetrical with symptoms manifesting on only one side of the body in the initial stages. As PD progresses, symptoms usually spread to involve the other side. Perhaps the most well-known symptom of PD is rest tremor[17]. Resting tremor can affect any part of the body and has a frequency of 4-6 Hz. Postural and kinetic hand tremor, when the hand is held in a specific position or during motion respectively, often accompany rest tremor. Muscular rigidity can usually be felt by the patient and clinicians as resistance during active and passive flexion and extension of the limb[18]. Typically, PD patients exhibit "cogwheel rigidity" that can be felt by clinicians as intermittent resistance when they are testing passive full extension or flexion movement in the limbs[19]. Rigidity also increases trunk inflexibility during postural changes, raising the fear and likelihood of falling[20]. Bradykinesia, or akinesia, is a reduction of automatic movement and decreased amplitude and speed of voluntary movements[21]. This is reflected in PD as reduced arm and hand gestures and the Parkinsonian mask, a lack of facial expression during conversations. In walking, bradykinesia causes patients to walk in small shuffling steps with reduced foot lifting [22], reduced stride length [23, 24], and reduced arm swing. Bradykinesia in PD can be a neural adaptation to allow more time to perceive, plan and adjust during walking[25]. Rigidity combined with bradykinesia also causes FOG symptoms during walking and more often during turning in the later stages of the disease. During FOG episodes, patients experience extreme difficulty lifting the foot off the ground to start walking due to muscle hypertonicity and bradykinesia[26, 27]. All these symptoms contribute to gait and balance impairments. Tremor adds high frequencies to postural sway[28], rigidity results in flexed posture, bradykinesia slows all postural responses, reducing gait speed and turn velocity, and akinesia and FOG prolong step initiation[29]. Clinical symptoms also include

decrease in dexterity and arm swing, soft voice, and decreased facial expression (otherwise known as the Parkinsonian mask)[14]. These motor symptoms affect gait and posture in patients, making daily activities more difficult[30, 31] and are also the basis of current clinical assessment of PD.

1.2.1 Gait and posture control in PD

Gait and posture disturbance is one of the most prominent features of PD[29, 32-34]. PD patients show a distinctive gait, that may interfere with their abilities to engage in daily activities including walking and turning. PD patients also exhibit the heel-to-toe characteristic, where the entire foot touches the ground at the same time as opposed to the heel touching the ground first in normal walking[35]. Gait abnormalities increase the tendency for PD patients to fall and attract unwanted attention which can be frustrating and demoralizing to patients. In addition, PD patients usually have a stooped posture with the head and neck protruded forward accompanying flexion at the knees. This results from impaired postural reflexes in patients where they are unable to correct sudden shifts of the normal upright position, where the more stooped the posture, the higher risk of falls.

Human locomotion is primitive[36, 37]. Gait is controlled by the spinal cord, brainstem, cerebellum and forebrain in bipedal primates[38]. Gait pathway involves the premotor and motor areas of the frontal cortex sending projections to the BG, then to the locomotor control centres in the brainstem and cerebellum before sending to the spinal pattern generators[39]. We have yet to establish a good understanding of the specific neural circuits involved in each aspect of the balance and gait control[40]. Locomotion and PD-specific gait and balance metrics can be separated into three categories based on neural control systems[41]: gait (walking at a self-

directed pace), postural sway, and postural transition (turning during walking and changing between seated and standing positions). These will be the foundation of how gait parameters are examined in this thesis.

1.2.2 The Gait Cycle

Walking can be easily overlooked as an entirely automatic process innate to all human beings, but gait control requires a well-organized integration of the motor, sensorial, and cognitive systems[42]. During walking, the person needs to constantly pay attention to surrounding environmental features while recovering from postural perturbation to avoid stumble and falls. It requires a good level of cognition and is mediated by frontal subcortical circuits also responsible for mediating executive functions[43]. Lower integrity of prefrontal-subcortical networks is related to slower gait and increased fall risk[44, 45]. Domains of executive functions such as having the mental flexibility to detect errors and modify motor behaviour, self-control to filter out irrelevant stimulus and distractions, and planning to carry out the desired intentions are all crucially important in gait performance.

Broadly speaking, gait can be defined as the method to move from one point to another, which includes both walking and running. This thesis focuses on walking alone and all mentions of gait in this thesis refer to walking. All gait evaluations require at least one complete gait cycle, composed of a foot strike of the observed leg, followed by foot strike of the contralateral leg, and another foot strike of the observed leg. Gait cycles are used for gait analysis to better understand gait disturbances in patients.

The gait cycle can be broken down into two phases, the stance phase, and the swing phase. The stance phase, usually making up around 60% of the gait cycle time (GCT), begins when the observed foot first touches the ground and ends when it leaves the ground. The swing phase begins when the foot first leaves the ground and ends when it touches the ground again, making up around 40% of the GCT.

The stance phase is when gait problems typically appear when the foot is loaded and is composed of three support phases. As the observed foot hit the ground and stance phase begins, the time between the foot strike and the contralateral foot-off is the initial double support phase, making up 14-20% of the stance phase. As the contralateral foot travels in the air, only the observed foot is in contact with the ground and this is called the single support phase, consisting of 60-72% of the stance phase. As the contralateral foot descends and touches the ground, the terminal double support begins and lasts until the observed foot is off the floor, making up another 14-20%. Initial and terminal double support phases can be combined and represented as total double support.

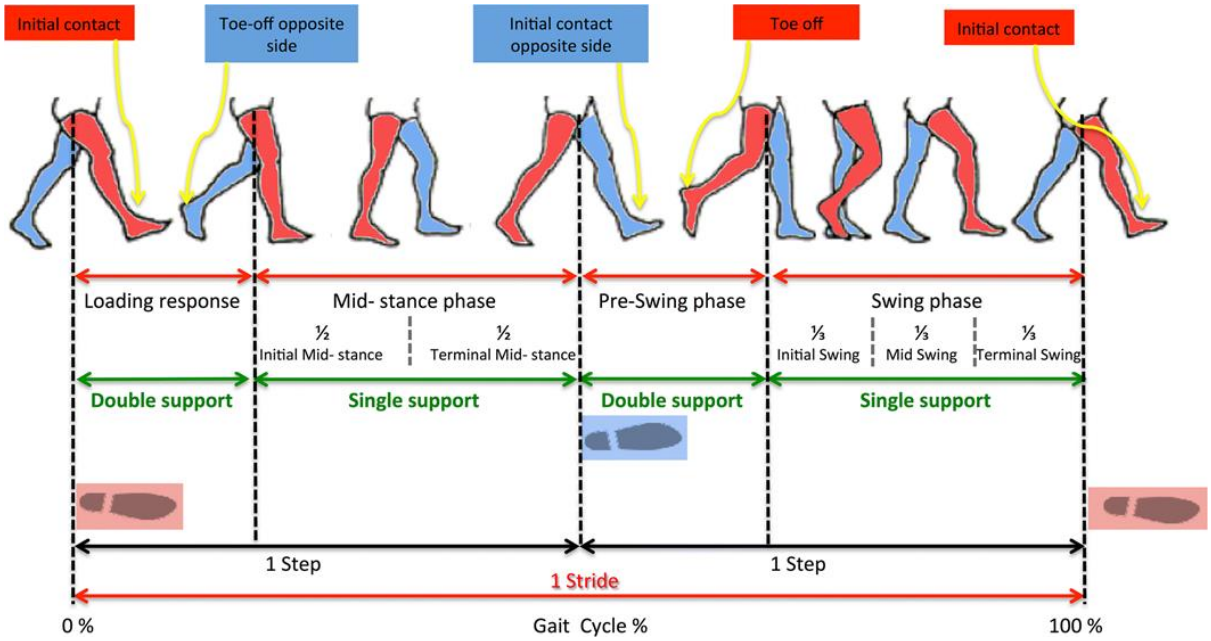


Figure 1.1. Components of a gait cycle. Taken from Camathias et al.2020[46].

The interaction between the foot and the ground, or heel to toe characteristic, is indicative of gait disturbances. The stance phase can be further broken down to subphases based on the position of the foot to the ground. The stance phase begins as the heel strikes the ground. This is called the contact phase and the angle of the foot at the initial contact is called the foot strike angle. As the foot comes into full contact with the ground, the foot-flat phase starts where the body weight is transferred to the observed leg and ends at when the contralateral foot leaves the ground, when the mid-stance phase begins. This is where the support limb moves from shock absorption function to stability function and ends when the heel of the observed limb leaves the ground. As the heel leaves the ground, the foot act like a lever to help propel the body forward in the propulsive phase, and the angle of the foot as it leaves the ground is the toe off angle.

In addition to having reduced stride length and arm swing during gait due to rigidity and bradykinesia/akinesia[23, 24, 47, 48], durations of constituents in the gait cycle are also disrupted by

PD. PD patients spend less time during the single support phase[48, 49] where only one foot is on the ground and have a longer double support phase[24, 50, 51] where they are in a more stable position. The total duration of gait cycles is also prolonged due to a slower cadence, or steps per minute[47-49, 52, 53]. These changes in gait cycle compositions reflects a lack in competency in maintaining balance on one leg as well as a lack in confidence to do so in PD patients. Furthermore, it is likely a result of the distinctive heel-to-toe characteristic of PD. PD patients have a reduced foot strike angle and toe off angle[49]. At the beginning of the double support phase, the observed foot contacts the ground at a lesser angle, reducing load or the amount of shock absorbed by the observed leg. At the end of the double support phase, PD patients have a smaller toe off angle and reduced propulsion force when the foot leaves the ground. This causes less foot lifting, shorter distance the foot travels in the air, and as a result a shorter single support duration and increased likelihood to stumble and fall. Parameters of gait will be examined in detail in Chapters 2, 3, and 4.

1.2.3 Postural balance in stance

Standing balance, or physiological sway during quiet standing, is the ability to maintain and control the body's centre of mass (COM) during quiet upright standing, and is reflected as slow drift in space over time accompanied by occasional rapid corrections[54]. Humans exhibit spontaneous sway with continual oscillation in the anterior-posterior (AP) and mediolateral (ML) planes during quiet standing[55]. The upright human body is naturally unstable with a narrower base of support (smaller distance between the feet compared to shoulder width when standing) and a high COM, where two-thirds of the body mass (head, arms, and trunk) is located in the top two-thirds of body height above ground. It is often described by the Inverted Pendulum model[56]. Constant muscle activations are required to combat rotational forces to

equalize all translational and torque forces to maintain equilibrium. The gravitational torque exerted by the body on the ankle is counteracted by the ankle restoring torque that can be divided into two components[57]: the stiffness component from the intrinsic ankle stiffness through muscles and connective tissue that provides stabilizing effects, complemented by the neural commands sending both tonic and phasic top-down commands.

Postural control system consists of four components[58] : the posture made up of the orientation of the head, neck, trunk, pelvis, and legs, the orientational senses including proprioception, vision, and vestibular sensation, the tone of muscles involved in maintaining stance, and the central nervous system integrating sensory information and sending out coordinated commands to make adjustments that prevent falls. During quiet standing the muscles act as springs to cause the centre of pressure (COP) to move in phase with the COM. Somatosensory information from the feet, leg and trunk is the most critical sensory information for postural control during stance[59-61].

Sway is traditionally assessed based on the displacement of COP measured by force plates where the COP is defined as the point of origination of ground reaction forces and is closely related to the sway of the COM during quiet stance[62]. COP controls the position of COM and keeps it within the limits of the base of support in a reverse manner (COP ahead of COM accelerates COM backwards)[63]. However, COM is a more meaningful measure because when it moves outside the base of support, falls occur.

The neural postural control of maintaining balance during quiet stance is affected by PD. Parkinson's patients are known to have jerkier[64-66] sway with higher sway area[67-69] and

velocity[65, 66, 69-71]. Higher sway velocity can be interpreted as an increased amount of neural control activity required by PD patients to maintain balance during stance. Patients with PD have been found to have difficulties reorganising sensory priorities for postural control[72]. The BG are involved in information integration and execution of commands, and it could be that pathologies in the BG affects normal integration required for postural control. Despite the more frequent neural control during sway, PD patients still have a larger sway area, reflecting the ineffectiveness of postural control and fine-tuning abilities. This ineffectiveness is likely the result of poor integration of somatosensory information, where PD patients have been found to have difficulties in detecting kinaesthetic and proprioceptive information[73-76]. As peripherally delayed somatosensory feedback can cause larger root-mean-square (RMS), ellipse area, and mean velocity of the COP[59, 77, 78], the larger sway area may reflect delayed somatosensory feedback and inaccurate, noisy detection of the position of the COM. In addition to more frequent neural control, PD patients also have more stiffness in the ankle joints, more muscle contraction in the legs and larger background electromyographic muscle activity during stance[79, 80]. Rigidity and muscle stiffness in PD contributes to jerky movements of the COP. Stiffness also contributes to sway at faster velocities and higher frequencies. PD tremor of 4-5Hz can also be observed from the power spectral density plots of sway[79]. The increase in sway could mean two things: imbalance[81], and or an exploratory attempt[82]. How standing sway progresses in PD over a two-year period will be examined in Chapter 2, and its response to levodopa medication in Chapter 3.

1.2.4 Postural transition

Recent changes in technological advancements with accelerometers and gyroscopes have allowed them to be used as wearable sensors in gait measurement to measure tilt signal of the

trunk[83, 84], making possible the measurement of postural transitions. Three key components of posture transition include anticipatory postural adjustments (APA) at the initiation phase of walking, turning during walking and changing between sitting and standing positions.

Gait initiation to transition from standing posture to cyclic walking is divided into three phases. The first phase is APA, coordinated muscular activities that precede the voluntary movements to counteract the associated postural perturbations. During APA, the COP moves backward to the swing foot before any detectable foot movement. The second phase is the swing foot unloading phase followed by the support foot unloading phase. The APA phase has been the phase of interest in gait and balance impairment as COP displacements in the APA has been shown to be a sensitive indicator of balance dysfunction[85, 86], decreased in older adults. In PD patients, the COP is much further ahead of the ankle joint due to the stooped posture, which contributes to prolonged APA durations and reduced COP backward displacements. It is well known that PD makes movement initiation harder with the lowered DA level. A study on the effect of dopaminergic medication indicated that it restored the level of force production for step initiation in PD patients[87]. Acceleration of the APA is indeed found to be slower in PD patients compared to healthy controls[86-88], and APA magnitude found to be hypometric in untreated PD patients in early stages of PD[86]. Progression of APA during a two-year period will be examined in Chapter 2.

Turning while walking is essential to daily mobility and requires the integration of gait and control for dynamic balance[89]. Compared to walking, turning requires more complex cognitive control to maintain stability while the body is reoriented to a new travel direction. Deficits in turning are often used to identify cognitive deficits[25]. PD patients experience difficulty in

turning from early disease stages[90] where they experience slower turn speed, longer turn durations, more steps required[91-93], narrower base of support[94] and decreased stability[95]. PD patients are found to have less directional asymmetry in turning compared to controls[91]. Turning problems are an indicator of the likelihood of falling, which can significantly impact the patients' quality of life. Turning characteristics during daily life (unprescribed) is more sensitive to fall risk than prescribed turning tasks. One study found that it differentiates fallers[96] where fallers turn with larger angles[97]. In daily monitoring, quantification of turning features (turn velocity, steps in turn and variability) better characterized PD than the number of turns taken alone[98]. Parameters of turning such as turn velocity and number of steps required to complete a turn strongly correlate with PD severity[29], suggesting turning parameters to be potential markers of PD disease states and progression. Progression of turning over a two-year period will be examined in Chapter 2, and its response to dopaminergic treatment in Chapter 3.

The Timed Up and Go (TUG) test has been widely used to assess balance and mobility in both older people[99-101] and PD[102-105]. This task tests the ability to stand up from a chair, walk a few meters (usually 3-7m), turn around and sit back into the chair. TUG was originally measured with a single component of time required for completion, which lacked specific information concerning which component of the whole sequence of movement is abnormal. To overcome this shortcoming, techniques such as optoelectronic systems, electromyography (EMG) and force plates[106] have been used. The ability to transition between seated and standing positions requires adequate neuromuscular function and the ability to integrate vestibular information and counteract unexpected external forces. It is more cognitively demanding than walking or turning. Features of sit-stand transitions including transition duration and number of attempts

are associated with falls risk in older adults[83]. Parkinsonian patients often display problems completing transition sequences in TUG[107, 108], and one item in the Movement Disorder Society—Unified Parkinson's Disease Rating Scale (MDS—UPDRS) part-III motor score is dedicated to the ability to arise from a chair. The most distinguishing factors of PD in the TUG task are mainly gait parameters rather than that related to sit-stand transitions itself[83]. Studies examining PD patients in advanced stages showed the TUG task suitable for discriminating PD patients[104, 105]. However, this function seems to be affected in later stages of PD, as studies on early and untreated PD showed no significant difference in transition duration[90] or lean angle of the body[83] from controls. This suggest that sit-stand transitions may be more useful in characterising more severe stages of PD.

1.3 PD Treatments

There is currently no disease-modifying treatment for PD. The focus of current PD treatment is to improve patients' quality of life through controlling symptoms for as long as possible while minimizing adverse effects from the treatment itself. The two main treatments for PD are medication and surgical DBS. Most cases are treated symptomatically with the DA precursor levodopa[109, 110]; other drugs include DA receptor (DA-R) agonists[109]. Response to levodopa is a key component of PD diagnosis[111]. Levodopa treatment has several potential complications. These include development of medication-induced motor complications with prolonged intake[112], absorptive fluctuations of levodopa levels, dyskinesia, decreased of drug-effective window with PD progression, and emotional and sleep disturbances. Around half of the patients developed medication-induced motor complications after five years of L-dopa medication use[112]. Levels of levodopa also fluctuates in the body, due to the absorptive nature of orally-taken drugs, leading to fluctuation of both motor and non-motor symptoms[112]. This fluctuation is further exacerbated with prolonged use of levodopa medication and PD progression. Dopaminergic medications are also known to disrupt sleep[113-116], in addition to PD itself[117], as another adverse treatment effect. Understanding the mechanism behind medication's therapeutic and adverse effects requires basic knowledge on DA biosynthesis and metabolism in the brain. This will be discussed in detail in Chapter 3.

Because of limitations and side effects of the current medication, DBS can be used in combination with dopaminergic medication. DBS is most often used to treat more advanced PD, with current evidence suggesting it is appropriate to consider surgery at the point when a patient is developing troublesome motor fluctuations despite optimal medical treatment[118]. It involves stimulating electrodes implanted in specific locations in the BG, that provide

electrical stimulation to the target site. For akinetic-rigid PD this is usually either the STN or the GPi. Studies have shown these are equivalent in effect for most symptoms, although the STN is commonly preferred as STN stimulation usually lowers medication requirements substantially. Other DBS targets include the ventralis intermediate (Vim) nuclei of the thalamus, used in the less common tremor dominant form of PD. Although DBS has been effective in treating motor symptoms of PD, its mechanism of action is not fully understood. One suggestion is that the electrical stimulation reduces the GPi neuron's electrical activity and synaptic transmission [119].

All the current treatments are effective for the motor symptoms in most cases, but relatively ineffective for the non-motor symptoms, and none of them slow progression. Treatment for PD is currently exclusively symptomatic, and discovery of disease-modifying treatments is needed.

1.4 PD Diagnosis and its Limitations

There is no disease-modifying treatment for PD, and the heterogeneous nature of PD, late and inaccurate diagnosis using motor-symptom based diagnostic scales, and the lack of sensitive markers to help study drug effects and disease progression make this effort more difficult.

Symptoms of PD are diverse and vary among patients, making its diagnosis and differentiation from other neurodegenerative disease with similar symptoms difficult. Diagnostic criteria used today are mostly reliant on the motor symptoms of tremor, rigidity, FOG, and slowness in walking[120, 121]. The current clinical rating scale used to diagnose and measure PD severity in a standardized fashion is the MDS-UPDRS[120]. This was introduced in 2008[121] as a revision of its predecessor scale, the UPDRS, which dated from 1987[122]. The use of an abbreviated form of the MDS-UPDRS in the Covid-19 era with home monitoring was assessed recently[123]. The MDS-UPDRS consists of four parts including Behaviours and Mood, Activities of Daily Living (ADL), Motor Performance, and Complications of Therapy. As a multidimensional non-linear scale, it is susceptible to inter-observer variability, depends on clinical expertise, and is time consuming[124]. It is also subject to floor effect, since motor rating scales are only useful once motor symptoms have developed, by which time more than half the dopaminergic neuronal population of the SN is already lost[125-128].These problems greatly affect the sensitivity and accuracy of the scale. Accuracy of clinical diagnosis is typically 80-90% when compared with pathological findings[129]. Due to the lack of laboratory biomarkers and dependency on clinical ratings, clinical diagnoses for all living patients are ‘possible’ or ‘probable’ PD and a definite diagnosis can only be made post-mortem based on neuronal loss and depigmentation of the SN, and presence of Lewy bodies in the brain stem[129]. A study has found only 58% of early PD diagnosis were confirmed to have PD at autopsy (defined by loss of SN DA neurons in the

presence of Lewy bodies)[130]. Similarly, current diagnostic imaging of the DAT lacks specificity for PD [131] and many patients with progressive supranuclear palsy and multiple system atrophy are misdiagnosed as PD. Other diagnostic tools are also non-specific, including cerebrospinal fluid alpha-synuclein level, positron emission tomography, cardiac imaging with radiation, and polygenic risk scores [130]. Prodromal phase of PD can last for 15 years or more[132]. This is problematic as many PD patients are misdiagnosed[133] and not given the most suitable treatment in a timely manner[134].

The lack of sensitivity of rating scales to small changes in disease state also makes it difficult to assess the effectiveness of novel treatments at early stages in the trial process, decreasing the efficiency of resource use[135, 136]. As would be expected, clinical rating scales based on motor function are strongly affected by symptomatic PD treatment[137, 138]. In fact, the presence of DA medication can completely obscure the progression in the scale that would otherwise be observed[139]. Yet the assessment of potential DMDs in trials is still mainly dependent on these scales. A search of the trial registry www.clinicaltrials.gov shows four current phase III trials of new drugs. All are reliant on clinical assessment of motor symptoms as the primary outcome. For potentially DMDs in particular, evaluation of effect is not easy, because the change in disease trajectory may be small, while standard scales based on motor assessment may be affected greatly by background symptomatic medication.

There is a pressing need for markers that can provide an early signal in clinical trials. Trials of new therapeutic agents usually fail[140-145] , in the process of which they consume vast quantities of both time and money. Efficacy of new PD drugs is hard to predict[146] because of the lack of good biomarkers of disease state to detect change within the timeframe of clinical trials[147, 148].

A sensitive biomarker would be able to terminate the development of drugs that are doomed to failure as early as possible in the discovery process so that resources could be diverted to more promising targets.

In response to this need, inertial measurement units (IMUs) have been suggested to quantitatively measure real physical variables of PD motor impairments[136]. More quantitative and objective assessment tools will allow better disease progression tracking, make more accurate and timely diagnosis, and facilitate discovery of DMDs.

1.5 Gait Quantification

Gait can be quantified using kinetic (force), kinematic (spatial/temporal), EMG, or infrared emitting diode[149, 150] sensors to collect objective and quantitative measurements rapidly. Gait studies have typically been via video-based motion analysis instruments, force plates and gait mats that measure ground-reaction force, and EMG. Such instrumentation provides detailed analysis of whole-body movement but might not be readily accessible due to its expensive, analysis-intensive, and non-portable nature. Force plates have been used in a laboratory setting to measure fluctuations of the COP which reflects postural sway integrity. However, it is not a viable solution for clinical or home-based assessments due to its cost and setup intensity, and provide no direct upper body measurement[90]. Likewise, video-based analysis and force plate are non-portable, expensive, and many times unsuitable for clinical use[151] or tracking daily activities[152]. For gait assessment to be clinically relevant, it needs to give quick results (minimal analysis), and be inexpensive, non-invasive, easy to use, portable, and scientifically proven[153-156].

Measuring gait has become much easier in the past few years with technological advances such as portable wearable IMUs[136] that are replacing motion detection camera systems, video recording analysis, and force sensitive mats in many gait laboratories. IMUs are composed of 3-axis accelerometers, 3-axis gyroscopes, and 3-axis magnetometers to measure force, angular velocity, and orientation. Body-worn IMUs can be easily used and provide an objective, accurate and convenient alternative to traditional gait labs[157, 158]. Wearable sensors can also be worn at home for home monitoring which alleviates the "white coat effect"[159] and gives a more accurate picture on the daily living activities of the patients. While studies conducted previously often analysed only a few measures, or even just one, modern systems

including the one used here usually report on dozens of variables. Which ones are the most clinically relevant is an important question to answer before the devices can be used for clinical assessment. Comparison of traditional gait lab systems and wearable IMU systems is summarised in the table below[151, 160-162]:

Table 1.1. Summary of advantages and disadvantages of traditional gait lab systems and wearable IMU systems.

Type of equipment	Advantages	Disadvantages
Non-wearable gait labs with optical motion measurement systems and forces plates linked to a computer	• Widely accepted as "gold standard"[163-165] • Good at measuring position • Well-quantified and accurate results over short distances • Simultaneous analysis of multiple parameters captured from different approaches • Non-intrusive systems (no need to attach sensors to the body) • More prevision and more measurement capacity • Not restricted to power consumption	• Limited measuring time • Limited measuring environment • Poor at measuring acceleration • Requires camera and visible marker • Long set-up times • Expensive and cumbersome equipment • Cannot monitor real life gait outside the lab
Wearable IMUs attached to parts of the body that can record and transmit data to a central signal processing system	• Portable, low-cost, and light-weight • Good at measuring acceleration • Does not require controlled environments • Continuous monitoring of daily activities possible • Usability enhanced by wireless systems • Promotes autonomy and active role of patients	• Poor at measuring position • Validation required to demonstrate real-world performance • Limited by power consumption and battery duration • Requires complex algorithms to calculate parameters • Analysis of limited number of gait parameters • Susceptible to noise and interference from uncontrolled external factors

Metrics from wearable sensors can be used in identifying PD biomarkers which track and characterize progression[65], help diagnose presymptomatic disease state[166], stratify heterogeneous PD phenotypes and serve as a surrogate endpoint in clinical assessment of

new treatments[41]. Biomarkers are measurable characteristics that indicate specific biological processes[41]. Clinical use of biomarkers in quantitative gait assessment[167] is summarized in *Table 1.2*.

Table 1.2. Summary of potential PD-specific biomarkers, their indication, responsiveness to levodopa, and changes with disease progression adapted from Mirelman, 2019[167]. Type of measurement used indicated in brackets.

Feature	Potential indication	Responsiveness to levodopa	Changes with disease progression	Comments
Gait velocity (m/s)	Bradykinesia, amplitude control	Yes *(inertial)*[168, 169] *(force)*[170-172]	Yes *(force)*[173]	Not PD-specific, affected by age. Progression might not be monotonic
Stride length (cm)	Bradykinesia, amplitude control	Yes *(inertial)*[168, 169] *(force)*[170-172, 174] *(infrared)*[175]	Yes *(force)*[173]	Unclear if independent from gait velocity
APA Duration (s)	Planning of gait, force generation, bradykinesia	Yes *(inertial)*[168] *(force)*[87, 176]	Data not available	Impacted by non-motor symptoms; unclear how it changes with progression
Turning	Susceptibility to falling, planning of gait, postural stability, disability	Pilot data	Yes *(inertial)*[97]	Response to medication not fully established
TUG duration (s)	Transitions, fall risk, bradykinesia	Yes (for completion time)	Yes *(motion-capture)*[177]	Not PD-specific
Step time (s) and cadence (steps/min)	Timing control	Inconsistent findings *(inertial)*[168, 169, 178]	Inconsistent findings	Further study required for medication response and progression
Stance duration (s)	Timing control	Inconsistent findings	Inconsistent findings	Further study required for medication response and progression
Stride time/width variability (%)	Fall susceptibility, planning and conscious control of gait, postural stability	Yes *(inertial)*[178] *(force)*[170]	Yes *(force)*[179]	Need further investigation of impact of age and disease severity
Double support (s)	Postural stability, proprioceptive sampling	Inconsistent findings *(inertial)*[168, 178] *(force)*[171, 172]	Data not available	Unclear if it is independent from timing aspects of gait
limb coordination	Early detection of disease and disease progression	Arm swing and leg ROM improve *(inertial)*[168, 180]	Pilot studies suggest a change with disease progression *(motion-capture)*[181]	insufficient information on coordination of upper and lower extremities

With increased computing power and rapid data collection from wearable sensors, hundreds of features can be computed from a simple walking task. A key challenge is to find a specific protocol or list of metrics to measure PD-sensitive and PD-specific balance and gait features, especially those that reflect functional integrity of underlying neural control systems, among many other redundant features. As current PD treatments are symptomatic and greatly improves gait and balance, how these features respond to PD treatments should also be understood to distinguish those that reflect PD severity and not masked by treatment effect.

For optimal evaluation, we need to identify a minimal dataset necessary for gait assessments. To enable the usability and acceptance of quantitative gait biomarkers in future disease-modifying clinical trials, establishing clear links between specific gait impairments, their underlying mechanisms, and disease progression is of utmost importance[167].

In this study we used the MobilityLab System[182] (APDM Wearable Technologies Inc., Portland, Oregon), which has been validated and used in previous studies to assess PD gait[183-187], with six synchronized IMU sensors each comprised of triaxial accelerometers, gyroscopes and magnetometers. These IMU sensors will be used to quantify changes in PD gait due to progression over a two-year period (Chapter 2), due to dopaminergic medication (Chapter 3), and due to DBS (Chapter4).

1.6 Time Perception in PD

1.6.1 Rhythmicity and disrupted time perception in PD

PD patients are known to have more variable gait[49] even from the de novo stage before any treatment is taken[24, 50, 170, 188]. They also tend to speed up during repetitive movements[189-191] and show less accurate and more variable-paced finger tapping than controls[192-194], which is associated with decreased activation in the medial frontal striatal circuit (dorsal putamen, ventrolateral thalamus, SMA)[190]. PD and other BG disorders have been studied to understand how the BG is involved in time perception. PD causes excessive inhibitory pallidal outflow associated with a lack of adequate frontal activation and reliance on the cerebellum for motor timing. Motor timing has been found to be disrupted in PD patients[195]. Dopaminergic medication alters gait rhythmicity[170, 196, 197] and ameliorates motor- and perceptual-timing difficulties by increasing striatal-frontal connectivity between the caudate nucleus and the pre-frontal cortex (PFC) during motor timing[198]. PD patients also exhibit a migration effect in double-duration reproduction task where participants are asked to reproduce two durations (usually 8s and 21s). PD patients are found to over-reproduce the shorter duration and under-reproduce the longer duration[199-202]. The extent of migration has also been found to correlate with akinesia[203] and corrected by STN-DBS[204]. As temporal perception is already altered in denovo patients, it is a potential early disease marker[205]. On visual temporal tasks, PD patients have impaired seconds-range perception but none in the subseconds range. This impairment is not significantly improved by either levodopa medication or DBS[205], despite the BG having a central role in timekeeping in the seconds to minutes range that is directly modulated by DA[199, 206-208].

The impairment in central rhythm mechanism is demonstrated through increased variability in gait and finger-tapping, which increases with UPDRS severity independent of age, disease duration or cognitive test performance. It is unclear whether PD-induced rhythm disorder is a primary deficit or compensating mechanism. Difficulties in rhythmic modulation in gait and speech may be due to inability to control step length and inter-pause speech duration. However, levodopa medication and DBS stimulation does not significantly improve rhythmicity measured by walking cadence and speech index of rhythmicity[209]. As PD affects both rhythm production and perception, timekeeping functions of PD patients are crucial in understanding the underlying mechanism behind arrhythmicity and variability in PD gait.

1.6.2 Timekeeping function

Timekeeping is an integral function of mammalian survival. It allows organisms to adjust behavioural and physiological processes to adapt to the ever-changing environment. Timekeeping function can be categorized into four timescales based on interval duration: the microseconds range, milliseconds range, seconds range, and hours range[210]. The mechanism of time perception in each of these ranges differs[210]. Animals use microseconds time perception for sound localization through neurons using coincidence detection to detect the intersection point of action potentials resulting from inputs for the left and right ears simultaneously. The biological clock responsible for circadian rhythm is not reliant on neurons at all; this is reflected in the fact that plants also have circadian rhythm. Rather, it relies on auto-inhibitory translation-transcription feedback loops where interaction of the *tim* and *per* proteins in the suprachiasmatic nucleus set the time and duration of the circadian cycle. Time keeping on the circadian scale is very precise with period variability of only 2% in absence of external cues[211]. Circadian clocks are also difficult to reset, as seen in the common

phenomenon of jet lag. In contrast, time perception in the sub and supra seconds range can be rapidly set to a new phase (flexible) but is less precise, with a variability of around 10%[212]. Milliseconds and seconds time perception are required for complex sensory and motor processing like motor coordination, speech recognition, playing music, and decision making[212, 213]. Despite its crucial importance in daily living, mechanisms behind discriminating durations are poorly understood with several proposed models.

1.6.3 Neurological basis of Time Perception

The BG act as a pacemaker that is regulated by DA to perceive time. Dopaminergic projections from the SNc to the striatum are crucial for both estimation and reproduction of time durations[214, 215]. DA is well-known for its effect on altering subjective time perception in the seconds to minutes range in both animals[215-218] and humans[219] where antagonists' receptor affinities negatively correlate with subjective clock speed and perceived duration can be increased or decreased by activation or deactivation of dopaminergic neurons respectively[220]. Cholinergic activity in the frontal cortex and cholinergic drugs are known to alter memory storage[214, 216, 221]. These two systems are connected through the frontal-striatal loop and play an interactive role in duration discrimination of time intervals. In addition to regulating the speed of the internal clock, DA also modulates attentional processing of temporal information[222]. Patients with disorders that affect the dopaminergic pathways, PD[195, 216], HD[223], and Schizophrenia[224-228] all show impaired supra second time processing. Electrophysiology studies have identified activation of two distinct subsets of striatal neurons during timing tasks, dissociating motor responses from temporal coding in the striatum. Functional imaging studies found that thalamo-cortical-striatal circuits (BG, PFC, posterior parietal cortex) are also activated during interval timing tasks[229, 230].

The BG threshold model hypothesizes that activation threshold for working memory update is regulated by DA, where suppression of DA through DA deficiency or DA antagonist raises the threshold leading to less frequent updates and a slower internal clock [213]. The results of studies looking at the effect of dopaminergic medication on time perception are inconsistent, with some showing further impairment[191, 231] and others improvement[232]. In addition to changing the threshold, DA depletion also introduces noise to the threshold setting[213], leading to threshold fluctuation that makes perceptual judgements more variable and adds variability to repetitive movements. This hypothesis can also account for PD akinesia where a raised threshold increases the difficulty to initiate movement.

Traditionally, the BG is thought to be responsible for interval timing in the seconds range while the cerebellum controls the sub seconds range outside of cognitive control[233]. It is unclear whether PD patients have disrupted time perception in the subseconds range, with one study reporting normal sub seconds timing in PD patients[234]. Functional imaging studies[235, 236] identified activation of the PFC, insula, premotor (lateral and SMA) parietal cortices, and cerebellum as well as inactivation of the BG in sub seconds duration judgement tasks, while others found putamen activation in sub seconds duration discrimination tasks[237, 238].

The role of the cerebellum in motor timing is well documented. Damage to the cerebellum results in disruption of duration discrimination in both sub and supra seconds ranges[239-242], and movement coordination[243, 244]. Specifically, patients show increased variability in intermittent temporal production (repetitive movements separated by a pause between each cycle, for example pausing between drawing each circle) and no impairment in continuous periodic

movements (continuous circle drawing) [245]. In fact, the cerebellum's involvement seems to depend on the presence of an event structure (seen in discrete movement production task and not continuous task). Repetitive transcranial magnetic stimulation (rTMS) inhibition of the cerebellum disrupts audio-cued finger tapping at 500ms intervals but not at 2000ms intervals while inhibition of the prefrontal and premotor cortices and not the SMA disrupts 2000ms-interval finger-tapping[246]. Duration discrimination tasks further evidence cerebellum's involvement in sub seconds and not supra-seconds interval perception[247].

Cognitive time processing depends on right hemispheric cortical network[236, 248, 249]. Lesion in the right but not left hemisphere disrupted timing in the milliseconds range and damage to the right inferior parietal lobe, dorsal lateral pre-frontal cortex (DLPFC), and frontal eye field were associated with abnormal timing[249]. Laterality seems to also play a role in time perception where lesions of the right and left hemispheres differentially affect temporal processing in patients[250]. Some suggest that the two hemispheres integrate information at different speeds[251-253].

1.6.4 Remote study design in measuring time perception

Studies on time perception and gait have been measured in a strictly controlled laboratory setting until recently. With technological advancement, many gait studies have been conducted in patients' homes where day-to-day function, uncontaminated by the white-coat effect, fatigue, and the stress of travelling to the lab or hospital, can be captured. No such studies have been done for time perception. In this thesis, for the first time, we will examine the ability of online tests to capture disruption in time perception in PD patients. The hope is

to use results from this study to better understand disrupted rhythms in gait, and future study will combine information from both datasets to achieve this goal.

1.7 Objective and Aim

This thesis uses IMUs to quantify Parkinsonian gait and examine how it is affected by three conditions: disease progression, dopaminergic medication, and DBS. The aim of these examinations is to determine a list of PD-sensitive and PD-specific measures indicative of underlying neural system integrity but not masked by symptomatic treatments, that can provide an earlier read-out of efficacy and guide an earlier go/no-go decision in clinical trials. The three conditions of gait examination are: progression over two years with three-month intervals, on- and off-PD medication, and on- and off-DBS. During the investigation process, gait irregularity, which may result from disturbances in internal rhythms, was identified as a major indicator of PD gait. Chapter 5 explores whether PD alters time perception to further understand the underlying mechanism for this disruption.

Chapter 2 Effect of Parkinson's Disease on Gait and Posture

2.1 Introduction

2.1.1 Gait Abnormalities in PD—what we know so far

Parkinsonian patients experience a range of symptoms including balance, posture, and gait problems. Poor balance and abnormal gait are among the most important motor impairments influencing PD patients' quality of life. Gait disturbances in PD can be divided into continuous disturbances such as shuffling, postural instability, reduced foot lifting[22], reduced stride length[23, 24], reduced arm swing, bradykinesia, stooped posture, and episodic disturbances[254] such as difficulty initiating movement due to muscle hypertonicity, akinesia, FOG[255, 256] and falls[257-260]. Continuous disturbances can be further classified into gait speed and amplitude abnormalities due to bradykinesia and rigidity, and gait rhythm disturbances. As part of the amplitude abnormalities, Parkinson's patients also exhibit the heel-to-toe characteristic, where the entire foot touches the ground at the same time as opposed to the heel touching the ground first as in normal walking[35, 261]. PD patients also exhibit reduced impact at heel strike, which is related to PD severity, and adopt a forefoot control strategy shifting the load of the body from the back of the foot towards medial and forefoot regions[261]. Gait symptoms can increase the tendency for patients to fall[255, 258-260, 262, 263], leading to injuries, and attract unwanted attention that frustrates and demoralizes patients[81]. There is a clear association of gait irregularity with falls risk[263 263, 264], and a reduction in gait irregularity may therefore have a direct effect in preventing falls and consequent injuries.

Gait disturbances due to PD worsen with disease progression and can sometimes be similar to gait disturbances caused by general aging. In the early PD stages[167] patients exhibit shorter step length[47, 48, 52], slower speed, lower cadence, and longer stride and stance duration. These changes are also typically seen in the aging process and are less specific to PD[47, 48, 52]. More specific gait symptoms are reduced arm swing amplitude (a potential prodromal PD marker)[265], increased interlimb asymmetry, impaired gait timing, reduced range of motion (ROM) of the hip, knee, and ankle[52], and less automatic ambulation[48, 180]. As PD progresses into the mild-to-moderate stage, symptoms that began on one side of the body progress to affect both sides, leading to decreased asymmetry compared to the early stage[188, 266]. Patients at this stage are more bradykinetic, with shuffling steps, long time spent on double-limb support during walking, increased cadence, further reduced arm and leg swing magnitude[267], reduced axial rotation[265], stooped posture, further impaired motor automaticity, and the presence of festination and FOG. In advanced PD, FOG occurrence becomes more frequent, and patients also experience further gait asymmetry[268], reduced balance and postural control leading to increased risk of falling.

2.1.2 Promising metrics for PD-specific gait biomarkers

Adapted from Horak and Mancini's review[41], potential PD-specific gait and balance metrics can be grouped into three categories based on neural control systems: postural sway, gait, and postural transition. Reduced arm swing, reduced trunk motion during gait, abnormal postural sway, reduced APA during postural transitions, and gait variabilities have been listed as the most promising measures[41]. Increased arm swing asymmetry and variability is associated with non-manifesting participants with leucine rich repeat kinase 2 (LRRK2) mutation and diagnosed PD patients, making it a promising prodromal motor marker of PD[265]. Postural sway and APA do not closely correlate with gait and turning measures, which are intercorrelated[269].

Factor analysis on gait mat data has been used to categorize independent domains of gait in several studies[270-272], the domains including pace, rhythm, variability, asymmetry, and postural sway. While traditional gait tracking focused on lower body movement from pressure sensors, gait tracking with IMUs enabled the inclusion of upper body acceleration features, namely arm and trunk acceleration and asymmetry, into gait analysis[269]. Upper body variables have been suggested to be moderately better at classifying PD gait than the traditional spatiotemporal characteristics[273]. In this study, postural transition is also included on top of gait and sway to give a more comprehensive examination of Parkinsonian gait.

Gait abnormality in walking starts before the first step is taken. PD patients have hypometric APA[86-88] that associates with delayed step onset, smaller step length, slower walking speed[274-276], and increased step time variability[276]. In early disease stage, there is a reduction in coronal displacement of the COP in PD patients compared to healthy controls[86, 90]; this reduced amplitude spreads to include the sagittal plane in later PD stages, accompanied with prolonged APA duration[277, 278]. During self-paced walking, the most visible clinical appearance is reduced arm swing, which is an early sign of gait impairment in denovo patients[279] (those who are diagnosed but haven not yet begun PD treatment), and is reflective of gait speed[280]. Patients have slower gait, less foot clearance, smaller steps[53], increased double support time, and stride time variability[24, 50]. Lower body gait features can be segregated into three groups[186]: spatial, temporal, and variability. Spatial parameters are amplitude-based, such as gait velocity and stride length. Temporal parameters are mostly based on the gait cycle, for example, cadence, stride time, double and single support time, and swing and stance times. Variability features, as the name suggest is the variability of spatial and temporal parameters, usually expressed in terms of standard deviation or coefficient of variation. Upper body parameters

highlight different aspects of motion from spatiotemporal features mentioned above and can contribute to PD classification[273, 281-284] and distinguish fallers from non-fallers[276]. In this thesis, both upper body variables and spatiotemporal variables will be examined.

Postural sway is a measure of postural instability[285] as complex sensorimotor control loops are responsible for keeping the body in an upright position[286]. Traditionally, sway has been measured with force plates under the feet sensing changes in the body's COP, a close correlate to the COM[62]. With advancements in technology and the use of IMUs, sway can be measured with an IMU attached to the pelvis, that records changes in body's COM directly[287]. Measures of postural sway can be characterised into four categories[55, 288]: sway area, velocity, frequency, and jerk, where jerk, RMS of amplitude and mean velocity, and centroidal frequency from IMU sensors have been found to be the most sensitive in delineating PD from controls[289]. Sway area has been related to the stability achieved by the postural control system while sway velocity to the amount of regulatory activity associated with this level of stability[290, 291]. The amount of regulatory activity, such as most frequent corrections of sway in PD, can be measured by taking the empirical measure of the smoothness of sway—jerk[292]. A study from positron emission tomography (PET) scans has shown correlation between DA denervation and postural sway[293]. Bradykinesia makes PD patients slower to respond to changes in postural perturbations[294] and alters sway. In particular, sway frequency is higher in PD patients[295-297] compared to healthy controls whose physiological sway frequency is typically below 1 Hz[298]. In prodromal PD states, risk for PD is associated with higher sway dispersion and decreased sway jerk[299]. In the denovo stage, PD patients show higher sway velocity[287], larger sway amplitude [70] and sway dispersion, increased sway area[300], especially in the medial-lateral direction, as well as more variable[64] sway jerk. Increased sway by PD patients might

reflect noisy signal integration from proprioceptive, sensory-vestibular, and mechanoreceptor information[301, 302] resulting in inaccurate body position and abnormal internal maps of stability limits[71, 303]. Sway jerk has been found to discriminate denovo patients from controls[65]. Larger sway size implies postural instability[58] and increased sway in the AP direction is associated with falls causing injuries[304]. Sway dispersion and velocity are likely to change with PD progression[65], and respond to medical and surgical PD treatments differently[297]. Although sway is often described as being abnormal in PD, an agreement on a set list of sway features that characterizes PD is yet to be made[71].

Postural transition is an interesting marker as bradykinetic PD patients are found to be much slower in adapting to changes in postural perturbations[294]. Postural transition includes turning and transition between sitting and standing positions. The use of inertial sensors has been validated against the traditional motion analysis through cameras to measure turning[305] and the pressure sensor walkway to measure walking[186]. Turning in PD is slower and may be interrupted, with smaller steps and more steps required to complete a turn[92, 305]. The TUG task has been used widely as a clinical measure of balance control during postural transitions for both the older adults[99-101] and patients with neurological disorders[102-104, 306, 307] because it consists of a sequence of sit-to-stand, walking, turning, and stand-to-sit tasks[90]. Traditionally, the TUG test has been assessed with a stopwatch where only a unidimensional measurement can be made. With new technology[51, 84] that allows gait recording with portable devices, we are now able to examine and reveal specific aspects of gait and balance affected by aging and disorders. Studies using the TUG test Time can separate fallers from non-fallers with PD or age matched elderly controls[308-310], and discriminate denovo PD patients from controls through trunk acceleration and vertical and ML jerk during turning[311].

As discussed in the previous chapter (1.6.1), because of the number of features' output from IMUs, we first need to find a list of metrics to measure PD-sensitive and PD-specific balance and gait behaviours, especially those that reflect functional integrity of underlying neural control systems, among the redundant features. After that, we need to establish a clear understanding of how these features change as PD progress. *Table 2.1* shows a list of the main gait parameters calculated by APDM® Mobility Lab (Mobility Lab, APDM Inc., Portland, OR) and their definitions[182]:

Table 2.1. A list of definitions for gait parameters examined in this chapter.

Category	Measured Parameters	Unit of measure	Definition
Gait—Pace	Cadence	Steps/min	The number of steps per minute, counting steps made by both feet
	Gait Cycle Duration	s	The duration of the gait cycle (one left plus right step duration)
	Gait speed	m/s	The forward distance (2 step lengths) travelled during the gait cycle divided by the gait cycle duration
	Stride length	M	The forward distance travelled by a foot during a gait cycle
	Step duration	s	The duration of a step
Gait—dynamic stability	Swing	% GCT	The percentage of the gait cycle in which the foot is not on the ground
	Double support	% GCT	The percentage of the gait cycle in which both feet are on the ground
	Stance	% GCT	The percentage of the gait cycle in which the foot is on the ground
Gait—Foot movement	Elevation at mid swing	M	The height of the sensor on the foot, relative to its start position during standing and measured at mid-swing
	Lateral step variability	cm	In three consecutive steps, the perpendicular deviation of the middle foot placement from the line connecting the first and the third step, another measure of step width
	Circumduction	cm	The amount that the foot travels perpendicular to forward movement while swinging forward during an individual stride
	Foot strike angle	deg	The dorsiflexion of the foot at initial contact
	Toe off angle	deg	The plantar flexion of the foot just as it leaves the floor at push off
	Toe out angle	deg	The lateral angle of the foot during the stance phase, relative to the forward motion of the gait cycle
Gait—arm and trunk movement	Arm swing velocity	deg/s	The maximum rotational velocity of the arm swing
	Arm ROM	deg	The angular range of the arm swing
	Lumbar ROM	deg	The angular range of the lumbar spine in the coronal/sagittal/transverse planes
	Trunk ROM	deg	The angular range of the thoracic spine in the coronal/sagittal/transverse planes
Turn and transition	Lean angle	deg	The angular range of motion of the trunk during the sit-to-stand or stand-to-sit transition
	Turn duration	s	The duration of the turn
	Turn velocity	deg/s	The peak angular velocity of the turn
Sway	95% Ellipse Axis	m/s^2	The confidence 95 ellipse, the smallest ellipse that will cover 95% of the points of the COM diagram
	Sway area	m^2/s^5	The area which encloses the data points of the trajectory, computed as the area spanned from the COM acceleration (ACC) per unit of time
	Centroidal frequency	Hz	The frequency at which the spectral mass is concentrated, or variability of the acceleration races power ranging from 0 to 1.
	Frequency dispersion	unitless	A unitless measure of variability of the frequency context of the power spectral density. 0 for pure sinusoid and increases with spectral bandwidth to 1.
	Mean velocity	m/s	Integration of the coronal and sagittal components of acceleration (pathlength/trial duration)
	Path length	m/s^2	Sway path, total length of COP acceleration trajectory
	Jerk	unitless	Indicates smoothness of sway calculated as a function of the time derivative of the acceleration excursion and duration[312].
	RMS Sway	m/s^2	Root mean square of acceleration time series in both the coronal and sagittal planes.
	Range	m/s^2	Range of COM displacement(acceleration)

Table 2.2. A list of common gait metrics and how each is affected by Parkinson's disease along with the type of gait measuring tool used. Gait lab include studies using video tracking, force plate, gait mat or pressure insoles. Red upward arrow indicates an increase in amplitude of the metric, blue downward arrow indicates decrease, and yellow circle indicates no significant difference was found.

Category	Parameter/metrics	PD	
		Wearable inertial sensors	Gait lab
Gait	Cadence	↓ 49, 90	↓ 47, 48, 52, 53
	Gait cycle duration	↑ 51	↑ 47, 48, 52, 53
	Stride length	↓ 49, 51, 66	↓ 24, 47, 48, 52, 53, 274-276, 313
	Elevation at mid-swing	↓ 49	↓ 22
	Trunk rotation (peak velocity)	↓ 90	
	Arm ROM	↓ 168	
	Stance	↑ 49, 51	↑ 47, 52 ○ 48
	Swing	↓ 49	↓ 48 ○ 47
	Double support time	↑ 51	↑ 24, 50
	Stride time variability / Step width		↑ 24, 47, 50, 52, 276
	Arm swing velocity	↓ 90	
	Gait velocity	↓ 49, 51	↓ 48, 52, 274-276
	Step width		↓ 48 ○ 47
	Toe Off Angle	↓ 49	
	Foot Strike Angle	↓ 49	
	APA acceleration		↓ 86-88
Postural Sway	Sway area	↑ 66	↑ 67-69
	Frequency dispersion		↑ 64
	95% Ellipse		↓ 64
	Path length	↑ 66	
	Jerk (derivative of trunk acceleration)	↑ 64-66, 289	
	Sway dispersion (RMS of trunk acceleration)	↑ 64, 65, 71, 287	↑ 64
	Sway velocity	↑ 64-66, 70, 287	↑ 69
Postural Transition	Turn duration	↑ 66, 305 ○ 90	
	Turn velocity (average)	↓ 66, 90, 98, 183	
	Turn angle	↓ 305	
	Steps required to make a turn	↑ 66, 98, 183, 305	

2.1.3 PD progression

Because of the heterogeneity of PD progression and the lack of a consensus on protocols and devices used to quantify gait and balance progression in PD, the ability to compare study results is limited[314]. One study examined patients within 18 months of PD diagnosis and identified step length and swing time to be affected by PD. Other studies examining patients later in the disease course, up to six years after diagnosis, also found step width, step width variability, swing and stance time variability and swing asymmetry as PD-related gait factors[315-317]. Variables including swing and stance time variability, swing asymmetry and step width variability are affected later in the disease course[173]. In this current study, our main aim was to see if wearable sensors can capture gait progression over a period of two years, measured at three-month intervals to capture early progression changes. Distinct gait domains deteriorate during different stages of PD based on disease duration, and PD in general causes a faster progression of aging effects compared to healthy controls[317]. Age-related changes in gait also contributes to PD gait progression where shared features of progression have been found for both aging and PD progression[173]. Features found to progress in PD include acceleration of lumbar motion in the early stages and stride time variability and stride regularity in the moderate stage PD[317]. Sway measures, especially in the medial-lateral direction, have been found to deteriorate over a year despite minimal changes in the MDS-UPDRS-III motor scores and is a promising feature to track PD progression[65]. Although dopaminergic medication usually has a beneficial clinical effect on patient's walking, the level of levodopa equivalent dosage does not correlate with gait abnormalities[47, 173].

This chapter will focus on gait, the control of locomotion, or coordination of the limbs, and dynamic equilibrium of the body's COM during walking. Characterising PD gait biomarkers

will potentially be useful in determining the clinical efficacy of new treatments, stratifying heterogeneous PD phenotypes, and diagnosing PD in its early stages.

2.1.4 Objective and aim

The aim of this chapter is to identify gait features that show significant progression within a two-year period. To achieve this goal, PD-specific gait features that distinguish Parkinson's patients from healthy controls at the first visit will be chosen. Then selected PD-specific features that progress significantly during two years of the study duration will be identified. We hypothesize that at a cross-sectional level, PD patients will have a reduction in gait amplitude features, increased variability in gait temporal features, larger and faster sway, and slower postural transition features. We expect to find temporal gait features, specifically variability features, to show progression over the nine visits.

2.2 Methods

2.2.1 Participants

All participants were recruited through the OxQUIP (Oxford Quantification in Parkinsonism) study which was conducted at the John Radcliffe Hospital in Oxford and was approved by the ethics committee (REC reference 16/SW/0262). The OxQUIP study is a large prospective cohort study of neurophysiological biomarkers in parkinsonian patients[136, 153, 318-322]. Written informed consent was obtained from all participants after the procedures were explained to them. PD participants had a diagnosis of idiopathic PD according to the UK PD brain bank criteria [323]. PD patients under the age of 50 were excluded because early-onset PD may have a different progression pattern than late-onset PD[324, 325]. Age matched healthy controls (HC) were often but not always the spouse of a patient.

Participants were excluded if they were unwilling or unable to give informed consent or had severe mental impairment due to dementia or psychosis. Participants with significant neurological co-morbidity, such as major stroke, that may obfuscate interpretation of neurophysiological or cognitive test results or medical or psychiatric illness that would interfere with completing initial or any of the follow up assessments were also excluded.
Healthy controls had no history of neurological disorders and were not taking any medication at the time of the examination. The above criterion is used for data discussed in Chapters 2,3, and 4.

2.2.2 Testing Protocol

Participants came every three months for a total of nine visits, and completed the same test battery consisting of:

1. *An MDS-UPDRS-III motor assessment*
2. *Gait assessment using a body area network of IMUs (APDM)*
3. *Neuropsychological test battery* including the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE).

Gait data was collected using the MobilityLab System including a network of six synchronized, body-worn IMUs (triaxial accelerometers, gyroscopes, and magnetometers). Sensors were positioned on both wrists and feet, on the trunk, and in the lumbar area. Patients performed three tasks wearing all sensors:

Walk test:

- Participants were asked to stand up straight with their arms placed by their sides. They were told upon hearing a tone to starting walking at a comfortable pace, up and down a quiet, uncarpeted 15m corridor, making turns when necessary. The participant was asked to stop walking on hearing a second tone after 2 minutes.

Sway:

- Participants were asked to stand straight up with their feet place on each side of a standardised block template. The template was removed, and the participant was asked to close their eyes for 30 seconds and remain standing upright. The 30-second duration of sway test is common practice in the field[65, 287].

TUG:

- The patient started the trials by sitting comfortably in a chair with their arms on their legs, and back against the seat. Participants were prompted by a starting tone at each trial to rise from the chair without using their arms and walk to a predestined object three meters from the chair, turn 180 degrees and walk back to the chair, and turn 180 degrees again to sit down. The trial was terminated when the participant's back rested against the back of the chair.

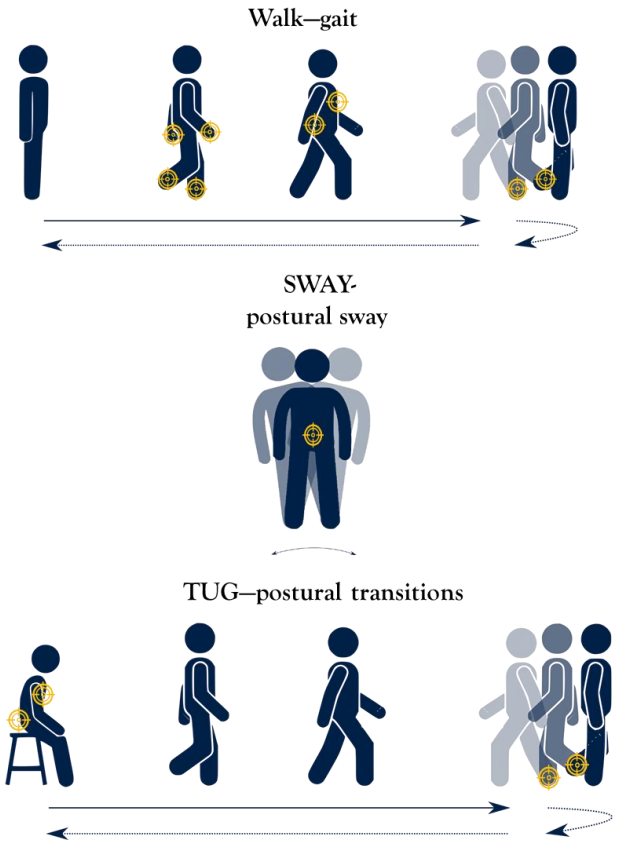


Figure 2.1. Experimental protocol for APDM gait assessment consisting of Walk, SWAY, and TUG tests. Walk: participant walked up and down a quiet corridor for a duration of two minutes. SWAY: Participant stood with their eyes closed for 30 seconds with feet apart. TUG: instrumented Timed Up and Go test, participant rose to stand, walked three meters, and then returned to the seated position. The yellow targets represent the sensors used to collect gait metrics from each gait tasks.

For all gait analysis in this thesis, data was first pre-processed. Instead of left and right side, parameters were listed as ipsilateral and contralateral to the side of onset for PD patients. Healthy controls were randomly assigned 0 or 1 and those assigned 1 had their left side marked as ipsilateral and right side contralateral and those assigned 0 had their left side assigned contralateral and right side ipsilateral. Stride length was normalised by height to account for the difference in height. Absolute values of all asymmetry measures were taken to normalise the side of asymmetry. Bilateral asymmetry index was used to accurately quantify asymmetry, as verified in a previous study[326]:

Equation 2.1. Asymmetry equation for bilateral asymmetry index

$$Asymmetry = abs(average(\frac{R-L}{R+L} \times 100\%))$$

Where R represents the amplitude on the right side and L represents the amplitude on the left side.

2.2.3 Cross-sectional analysis for parameters different at the first visit

A full list of parameters measured by APDM can be found in the appendix to this chapter. A total of 98 walking parameters, 25 sway parameters, and 11 transition parameters were analysed. Unpaired t-tests or Mann-Whitney U tests were used to identify parameters that were significantly different in the PD and control groups. The Benjamini-Hochberg process was used to correct for multiple comparisons.

2.2.4 Longitudinal analysis for PD progression parameters

Single missed visits were imputed with last observation carried forward and two or more consecutive missed visits resulted in exclusion. Missing data consisted of 0.44% of the entire data, with most of the missing data occurring in the APA features. APA features were difficult to capture partially due to the impulsivity of patients making the first steps. All parameters (without multiple comparisons correction) that were identified in the cross-sectional analysis as differing between PD and control groups were selected for longitudinal analysis. The cross-sectional results are being used here purely for feature reduction, to limit in a logical way, the number of comparisons performed on the longitudinal data. Asymmetry features for progression analysis were also left out because the progression on the contralateral and ipsilateral sides are different for each individual patient, which would add too much noise to the data. Repeated measures analysis of variance (ANOVA) was used to find any visit effect

amongst the parameters, and in cases where an effect of visit was found, pairwise comparisons were then used to compare each individual visit to baseline. Data collection for some of the first visits took place in a different lab space with different chair height and walk aisle dimensions. To limit the effect of external environment on TUG performance, the second visit was used as baseline in multiple comparisons for TUG duration.

2.3 Results

2.3.1 Demographics

64 PD patients and 50 controls were included in the study. Demographic (*Table 2.3*) and clinical information on the groups across visits (*Table 2.4*) are shown. Note that there was a male predominance in the PD group and female predominance in the control group, since many controls were spouses of PD patients. There was no significant difference in age between PD and control subjects (p=0.35). All patients were on dopaminergic medication throughout the duration of the visits.

Table 2.3. Demographics table of all included participants in this chapter. HC, Healthy Controls; PD, Parkinson's patients.

	HC (N=50)	PD (N=64)
Age		
Mean (SD)	65.3 (7.61)	64.0 (7.86)
Median [Min, Max]	65.9 [49.4, 81.9]	63.9 [46.0, 79.3]
Gender		
Male	22 (44.0%)	37 (57.8%)
Female	26 (52.0%)	26 (40.6%)
Handedness		
Left	7 (14.0%)	5 (7.8%)
Right	40 (80.0%)	58 (90.6%)
Ambidextrous	1 (2.0%)	1 (1.6%)
Ethnicity		
White	45 (90.0%)	62 (96.9%)
Mixed	2 (4.0%)	1 (1.6%)
Other	1 (2.0%)	1 (1.6%)
PD Side of Onset		
Left	0 (0%)	37 (57.8%)
Right	0 (0%)	25 (39.1%)
N/A	50 (100%)	0 (0%)
PD Duration		
Mean (SD)	NA (NA)	2.75 (1.75)
Median [Min, Max]	NA [NA, NA]	2.42 [0.167, 7.33]

Table 2.4. Clinical characteristics of controls and patients across the nine visits.

	Visit1		Visit2		Visit3		Visit4		Visit5		Visit6		Visit7		Visit8		Visit9	
	HC (N=50)	PD (N=64)	HC (N=44)	PD (N=64)	HC (N=45)	PD (N=60)	HC (N=43)	PD (N=58)	HC (N=43)	PD (N=56)	HC (N=40)	PD (N=55)	HC (N=37)	PD (N=52)	HC (N=35)	PD (N=48)	HC (N=27)	PD (N=44)
EQ5D																		
Mean (SD)	6.00 (1.74)	7.88 (2.48)	5.80 (1.44)	7.91 (2.45)	6.02 (1.41)	8.18 (3.06)	5.93 (1.35)	8.33 (3.10)	5.86 (1.25)	8.23 (2.80)	5.98 (1.59)	8.07 (2.69)	6.03 (1.52)	8.23 (3.17)	6.52 (1.72)	8.26 (2.99)	6.30 (1.49)	8.43 (3.14)
Median [Min, Max]	5.00 [5.00, 15.0]	7.00 [5.00, 15.0]	5.00 [5.00, 13.0]	7.50 [5.00, 15.0]	5.00 [5.00, 10.0]	8.00 [5.00, 20.0]	5.00 [5.00, 9.00]	8.00 [5.00, 19.0]	5.00 [5.00, 9.00]	8.00 [5.00, 17.0]	5.00 [5.00, 11.0]	8.00 [5.00, 16.0]	5.00 [5.00, 11.0]	7.00 [5.00, 19.0]	6.00 [5.00, 11.0]	8.00 [5.00, 18.0]	6.00 [5.00, 9.00]	8.00 [5.00, 19.0]
PDQ39																		
Mean (SD)	39.0 (0)	62.1 (19.3)	39.0 (0)	61.1 (18.2)	39.0 (0)	61.1 (21.6)	39.0 (0)	62.6 (21.1)	39.0 (0)	59.4 (15.3)	39.0 (0)	60.2 (17.9)	39.0 (0)	61.4 (19.1)	39.0 (0)	60.7 (18.9)	39.0 (0)	61.8 (17.6)
Median [Min, Max]	39.0 [39.0, 39.0]	57.0 [41.0, 129]	39.0 [39.0, 39.0]	57.0 [41.0, 119]	39.0 [39.0, 39.0]	55.0 [39.0, 144]	39.0 [39.0, 39.0]	56.0 [39.0, 144]	39.0 [39.0, 39.0]	58.0 [39.0, 100]	39.0 [39.0, 39.0]	55.0 [39.0, 116]	39.0 [39.0, 39.0]	54.0 [39.0, 131]	39.0 [39.0, 39.0]	58.0 [39.0, 124]	39.0 [39.0, 39.0]	57.0 [40.0, 123]
Health State																		
Mean (SD)	86.8 (12.2)	76.5 (13.6)	89.4 (11.2)	77.3 (13.8)	88.4 (11.2)	78.3 (15.0)	87.4 (12.0)	76.6 (17.1)	88.2 (12.7)	78.2 (15.3)	87.0 (13.1)	77.1 (16.4)	88.2 (12.0)	77.9 (20.8)	86.5 (14.5)	79.2 (17.0)	85.5 (13.2)	76.0 (18.5)
Median [Min, Max]	90.0 [50.0, 100]	80.0 [30.0, 100]	94.5 [50.0, 100]	80.0 [30.0, 96.0]	90.0 [50.0, 100]	80.0 [30.0, 100]	90.0 [50.0, 100]	80.0 [20.0, 100]	90.0 [45.0, 100]	80.0 [20.0, 100]	90.0 [45.0, 100]	81.0 [20.0, 97.0]	90.0 [50.0, 100]	85.0 [5.00, 98.0]	90.0 [40.0, 100]	85.0 [20.0, 100]	90.0 [45.0, 100]	83.5 [10.0, 95.0]
UPDRS-I																		
Mean (SD)	3.76 (3.10)	8.14 (5.13)	3.05 (2.89)	8.08 (5.78)	3.53 (3.20)	7.95 (5.62)	3.37 (3.29)	8.26 (5.93)	2.72 (3.18)	7.75 (5.98)	3.20 (3.82)	8.58 (6.16)	3.43 (3.67)	7.80 (5.61)	3.60 (3.26)	8.15 (6.02)	3.89 (3.76)	8.14 (5.52)
Median [Min, Max]	3.00 [0, 11.0]	7.00 [1.00, 23.0]	2.00 [0, 10.0]	6.00 [1.00, 24.0]	3.00 [0, 12.0]	7.00 [0, 22.0]	3.00 [0, 14.0]	6.50 [0, 27.0]	2.00 [0, 12.0]	6.00 [0, 28.0]	2.00 [0, 18.0]	7.00 [0, 29.0]	3.00 [0, 15.0]	7.00 [0, 28.0]	3.00 [0, 12.0]	8.00 [0, 32.0]	3.00 [0, 13.0]	7.00 [0, 21.0]
UPDRS-II																		
Mean (SD)	0.408 (1.27)	9.38 (7.11)	0.500 (1.64)	8.67 (6.69)	0.844 (1.83)	8.80 (7.68)	0.558 (1.31)	9.28 (7.62)	0.535 (1.72)	9.05 (6.39)	0.850 (2.03)	9.31 (6.79)	0.730 (1.81)	9.81 (7.14)	0.829 (1.65)	8.81 (6.83)	1.07 (2.06)	9.86 (7.42)
Median [Min, Max]	0 [0, 7.00]	7.00 [0, 31.0]	0 [0, 9.00]	7.00 [0, 35.0]	0 [0, 9.00]	6.00 [0, 39.0]	0 [0, 5.00]	7.00 [0, 35.0]	0 [0, 10.0]	8.00 [0, 27.0]	0 [0, 10.0]	7.00 [0, 24.0]	0 [0, 8.00]	8.50 [0, 34.0]	0 [0, 8.00]	7.00 [0, 30.0]	0 [0, 9.00]	8.00 [0, 29.0]
UPDRS-III																		
Mean (SD)	4.60 (5.94)	22.8 (12.8)	4.55 (4.54)	19.4 (11.9)	3.53 (3.43)	22.6 (13.3)	4.28 (5.03)	27.2 (16.1)	5.35 (6.48)	24.1 (13.8)	6.00 (8.20)	23.2 (15.7)	5.03 (6.69)	25.0 (17.6)	5.14 (6.13)	25.4 (14.6)	6.46 (9.54)	27.5 (16.2)
Median [Min, Max]	2.00 [0, 25.0]	23.5 [2.00, 72.0]	4.00 [0, 25.0]	18.0 [0, 49.0]	2.00 [0, 12.0]	20.5 [2.00, 52.0]	3.00 [0, 24.0]	24.0 [1.00, 75.0]	3.00 [0, 26.0]	23.0 [2.00, 57.0]	3.00 [0, 33.0]	21.0 [3.00, 85.0]	3.00 [0, 27.0]	21.5 [2.00, 83.0]	3.00 [0, 23.0]	26.5 [2.00, 61.0]	4.00 [0, 48.0]	24.0 [4.00, 62.0]
HY																		
Mean (SD)	0 (0)	1.52 (0.591)	0 (0)	1.68 (0.563)	0 (0)	1.90 (0.511)	0.0465 (0.305)	1.93 (0.491)	0.0698 (0.338)	2.02 (0.447)	0.150 (0.533)	2.05 (0.524)	0 (0)	2.14 (0.633)	0 (0)	2.10 (0.472)	0 (0)	2.16 (0.479)
Median [Min, Max]	0 [0, 0]	1.00 [1.00, 3.00]	0 [0, 0]	2.00 [1.00, 3.00]	0 [0, 0]	2.00 [1.00, 3.00]	0 [0, 2.00]	2.00 [1.00, 3.00]	0 [0, 2.00]	2.00 [1.00, 4.00]	0 [0, 2.00]	2.00 [1.00, 4.00]	0 [0, 0]	2.00 [1.00, 5.00]	0 [0, 0]	2.00 [1.00, 4.00]	0 [0, 0]	2.00 [1.00, 4.00]
Dyskinesia																		
Does not affect scoring	50 (100%)	64 (100%)	44 (100%)	63 (98.4%)	45 (100%)	58 (96.7%)	43 (100%)	58 (100%)	43 (100%)	56 (100%)	40 (100%)	55 (100%)	37 (100%)	49 (94.2%)	35 (100%)	46 (95.8%)	26 (96.3%)	42 (95.5%)
Affects scoring	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3.8%)	0 (0%)	2 (4.2%)	0 (0%)	2 (4.5%)
MoCA																		
Mean (SD)	26.8 (2.60)	26.6 (2.83)	27.5 (2.32)	27.2 (2.61)	27.4 (2.40)	27.7 (2.37)	27.8 (2.24)	27.0 (3.27)	27.7 (2.77)	27.5 (2.84)	28.2 (2.37)	27.6 (3.36)	28.6 (1.91)	28.0 (3.39)	28.7 (2.20)	28.0 (2.27)	28.5 (2.10)	28.4 (1.85)
Median [Min, Max]	27.0 [20.0, 30.0]	27.0 [16.0, 30.0]	28.0 [21.0, 30.0]	28.0 [19.0, 30.0]	28.0 [21.0, 30.0]	29.0 [20.0, 30.0]	29.0 [22.0, 30.0]	28.0 [15.0, 30.0]	29.0 [18.0, 30.0]	28.0 [15.0, 30.0]	29.0 [21.0, 30.0]	28.0 [9.00, 30.0]	29.0 [23.0, 30.0]	29.0 [11.0, 30.0]	29.0 [19.0, 30.0]	29.0 [19.0, 30.0]	29.0 [21.0, 30.0]	29.0 [24.0, 30.0]
MMSE																		
Mean (SD)	28.7 (1.65)	28.2 (1.86)	28.6 (1.35)	28.7 (1.62)	28.6 (1.47)	28.6 (1.76)	28.7 (1.52)	28.3 (2.25)	28.8 (1.25)	28.5 (1.93)	29.2 (1.57)	28.5 (2.84)	29.3 (1.30)	28.8 (1.79)	29.2 (0.942)	28.9 (1.28)	29.2 (1.05)	29.0 (1.53)
Median [Min, Max]	29.0 [21.0, 30.0]	28.0 [21.0, 30.0]	29.0 [24.0, 30.0]	29.0 [22.0, 30.0]	29.0 [24.0, 30.0]	29.0 [21.0, 30.0]	29.0 [25.0, 30.0]	29.0 [20.0, 30.0]	29.0 [25.0, 30.0]	29.0 [21.0, 30.0]	30.0 [22.0, 30.0]	29.0 [12.0, 30.0]	30.0 [25.0, 30.0]	29.0 [20.0, 30.0]	29.0 [26.0, 30.0]	29.0 [25.0, 30.0]	30.0 [27.0, 30.0]	30.0 [24.0, 30.0]
PhonemicFluency																		
Mean (SD)	43.6 (12.8)	42.8 (11.2)	45.1 (13.1)	44.8 (13.1)	48.3 (14.1)	47.6 (14.4)	48.7 (15.1)	48.4 (14.6)	49.3 (12.6)	49.1 (12.9)	51.0 (14.3)	49.1 (13.6)	53.0 (12.7)	50.2 (14.7)	54.5 (13.0)	53.3 (13.4)	53.2 (14.8)	52.6 (14.5)
Median [Min, Max]	41.5 [20.0, 78.0]	42.5 [15.0, 75.0]	46.0 [19.0, 75.0]	45.0 [14.0, 69.0]	50.0 [23.0, 98.0]	46.0 [14.0, 77.0]	49.0 [18.0, 95.0]	47.0 [19.0, 84.0]	50.0 [23.0, 78.0]	51.0 [13.0, 71.0]	53.0 [21.0, 82.0]	48.0 [21.0, 80.0]	54.0 [24.0, 74.0]	49.0 [20.0, 82.0]	56.0 [28.0, 89.0]	51.5 [17.0, 76.0]	53.0 [28.0, 90.0]	50.5 [20.0, 101]
SemanticFluency																		
Mean (SD)	41.5 (9.20)	40.6 (11.3)	41.5 (10.3)	40.9 (11.1)	42.2 (10.9)	43.0 (12.7)	43.7 (10.7)	42.9 (13.2)	44.5 (11.0)	44.4 (12.5)	44.6 (11.7)	44.1 (13.6)	46.5 (11.7)	44.9 (14.1)	46.5 (10.9)	46.6 (12.7)	44.6 (13.0)	46.8 (12.3)
Median [Min, Max]	40.5 [15.0, 71.0]	40.5 [16.0, 65.0]	40.5 [23.0, 67.0]	39.0 [20.0, 73.0]	41.0 [19.0, 76.0]	43.0 [21.0, 73.0]	44.0 [24.0, 77.0]	41.0 [14.0, 77.0]	43.0 [19.0, 73.0]	43.0 [21.0, 80.0]	43.5 [17.0, 77.0]	45.0 [12.0, 77.0]	47.0 [12.0, 76.0]	44.0 [13.0, 73.0]	47.0 [21.0, 75.0]	45.0 [20.0, 76.0]	45.0 [16.0, 79.0]	46.0 [21.0, 74.0]
Height (cm)																		
Mean (SD)	170 (10.3)	172 (8.83)	171 (10.1)	170 (15.5)	172 (10.0)	172 (8.95)	168 (28.0)	172 (8.67)	171 (10.2)	172 (8.79)	171 (9.87)	172 (8.90)	171 (9.76)	172 (9.20)	171 (9.37)	168 (26.3)	171 (10.1)	172 (8.44)
Median [Min, Max]	171 [154, 187]	172 [155, 193]	172 [154, 189]	171 [68.0, 193]	173 [155, 189]	172 [149, 193]	172 [0, 188]	172 [154, 194]	172 [155, 189]	172 [150, 192]	171 [154, 189]	171 [153, 193]	170 [156, 188]	173 [155, 190]	172 [155, 188]	173 [0, 190]	169 [154, 188]	173 [157, 191]
Weight (kg)																		
Mean (SD)	74.8 (14.0)	76.1 (14.4)	74.1 (18.3)	78.3 (18.1)	75.7 (14.2)	76.1 (14.7)	73.2 (18.1)	77.4 (14.7)	75.1 (14.3)	79.0 (18.7)	74.2 (13.3)	76.4 (13.8)	72.8 (13.3)	76.6 (14.7)	73.0 (13.4)	72.0 (16.3)	72.1 (13.1)	75.3 (14.0)
Median [Min, Max]	73.0 [51.0, 104]	76.0 [46.0, 120]	76.0 [0, 104]	76.0 [46.0, 162]	76.0 [50.0, 103]	74.0 [44.0, 120]	74.0 [0, 103]	76.0 [44.0, 122]	73.0 [50.0, 100]	77.0 [44.0, 166]	73.0 [49.0, 103]	76.0 [43.0, 123]	72.0 [49.0, 96.0]	76.0 [44.0, 124]	71.0 [49.0, 96.0]	71.0 [0, 104]	70.0 [50.0, 96.0]	73.0 [44.0, 122]

2.3.2 Cross-sectional analysis at visit one

Seven gait amplitude features, one sway feature, seven transition features, five variability features, and three asymmetry features differed significantly between the PD and HC groups. Ten features survived correction for multiple comparisons.

Table 2.5. Features with significant association with the PD disease state from unpaired t-test and Mann-Whitney U test along with their unadjusted p-value and critical value of the Benjamini-Hochberg correction. Parameters that remain significant after the correction are marked in bold. APA: anticipatory postural adjustment; I: ipsilateral; C contralateral; ROM: range of motion; %Diff; percentage difference between left and right sides; TUG: Timed-Up and Go task; CV: coefficient of variation; MDS-UPDRS-III: Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III (motor score).

	Parameter	**p-value**	**critical value**
Gait	**Lateral APA Peak (m/s^2)**	**0.0023**	**0.0029**
	Foot Strike Angle I (deg)	0.0044	0.0032
	Foot Strike Angle C (deg)	0.016	0.0044
	Trunk Coronal ROM (deg)	**0.00092**	**0.002**
	Arm Swing Velocity I (deg)	**0.0022**	**0.0023**
	Arm Swing Velocity C (deg)	0.013	0.0041
	Arm ROM I (deg)	**1.2E-09**	**0.00058**
Sway	Mean Velocity Sagittal (m/s)	0.04	0.0067
Transition	TUG Duration (s)	0.038	0.0058
	Sit to Stand Duration (s)	**0.000082**	**0.00088**
	Stand to Sit Duration (s)	0.038	0.0061
	Walk Turn Duration (s)	0.028	0.0056
	Walk Turn Velocity (deg/s)	**0.00012**	**0.0015**
	TUG Turn Duration (s)	**0.00014**	**0.0018**
	TUG Turn Velocity (deg/s)	**0.000093**	**0.0012**
Variability	Stance C (%GCT) CV	0.019	0.0047
	Swing C (%GCT) CV	0.039	0.0064
	Terminal Double Support I (%GCT) CV	0.048	0.007
	Arm ROM I (deg) CV	**0.0022**	**0.0023**
	Lateral Step Variability C (cm)	0.0098	0.0038
Asymmetry	Circumduction Asymmetry (%Diff)	0.0082	0.0035
	Arm Swing Velocity Asymmetry (%Diff)	0.028	0.0053
	Arm Range of Motion Asymmetry (%Diff)	0.019	0.005
Clinical score	**MDS-UPDRS-III**	**6.5E-15**	**0.00029**

During gait initiation, PD patients had a significantly slower lateral APA peak velocity (*Fig.2.2A*, p=.0023). In terms of amplitude during walking, PD patients had smaller ROM of the ipsilateral arm (*Fig.2.2E*, p<.001) and of the trunk in the coronal plane (*Fig.2.2D*, p<.001), and reduced arm swing velocity on the ipsilateral side (*Fig.2.2F*, p=.0022). It also showed increased variability in arm ROM (*Fig.2.4E*, p<.001). During postural transitions, patients required a longer time to stand up from a seated position (*Fig.2.3G*, p<.001), had a slower turn velocity in both the 2-minute walk (*Fig.2.3C*, p<.001) and TUG task (*Fig.2.3E*, p<.001), and had a longer turn duration in the TUG task (*Fig.2.3D*, p<.001). No significant difference was found for the sway features after multiple corrections.

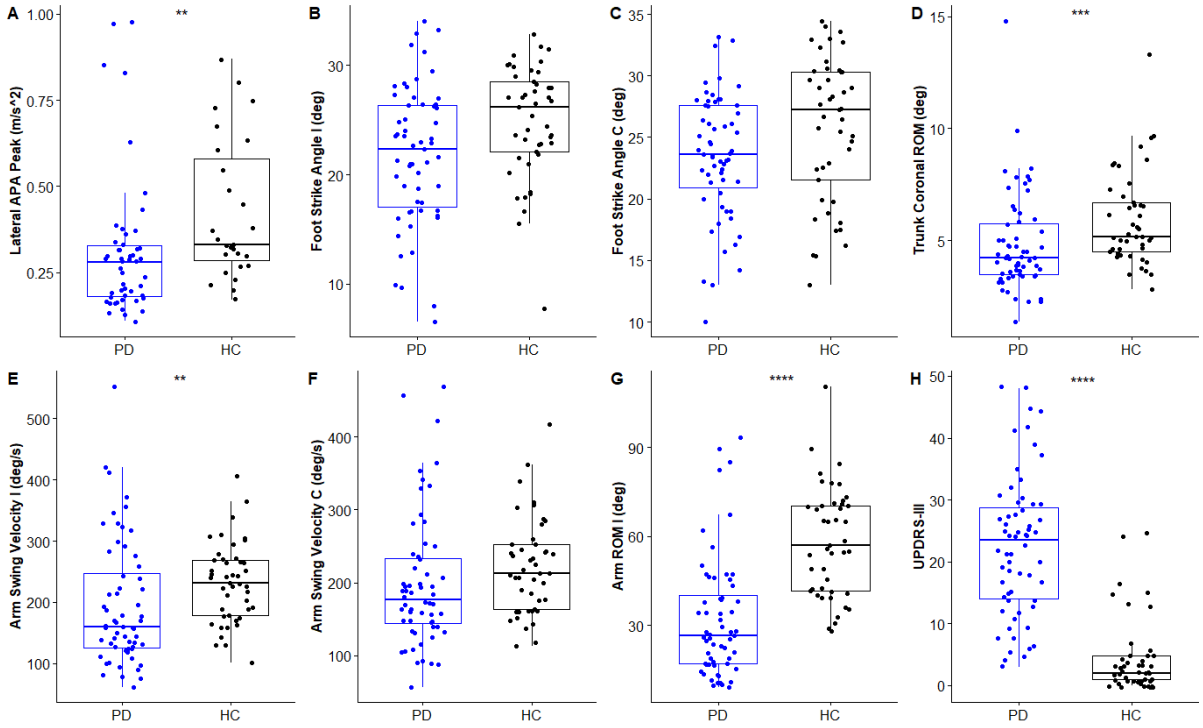


*Figure 2.2. Boxplots of walking features that differ between PD and HC groups. Features that remain significant after Benjamini-Hochberg correct are indicated by significance levels. * p<.05; ** p<.01; *** p<.001; **** p<.0001; all significance levels indicate original p-values. APA: anticipatory postural adjustment; ROM: range of motion; I: ipsilateral side; C: contralateral side; MDS-UPDRS-III: Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III (motor score).*

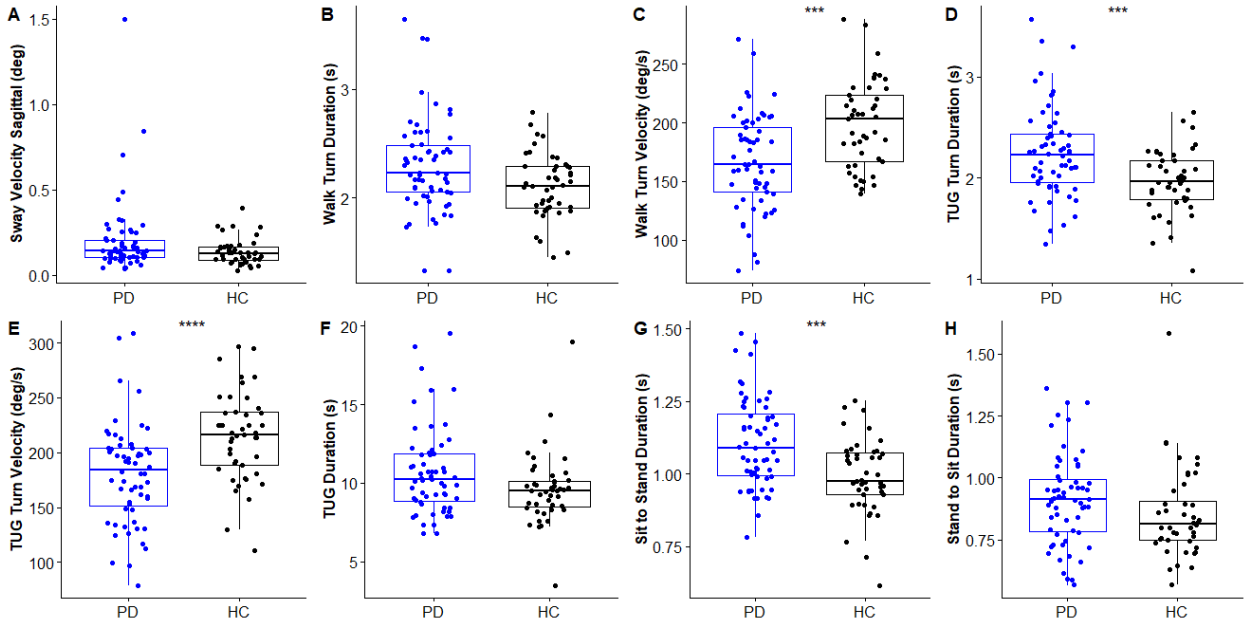


*Figure 2.3. Boxplots of sway and transition features that differ between PD and HC groups. Features that remain significant after Benjamini-Hochberg correct are indicated by significance levels. * p<.05; *** p<.001; **** p<.0001; all significance levels indicate original p-values. TUG: Timed-Up and Go task.*

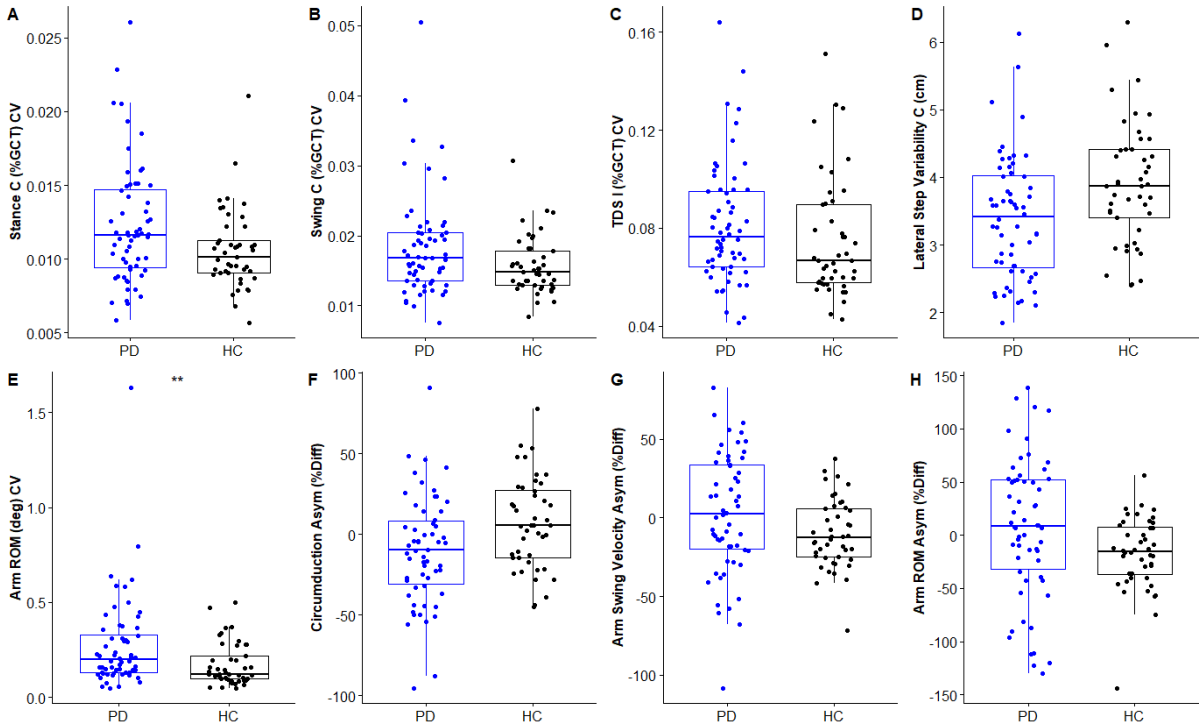


*Figure 2.4. Boxplots of variability and asymmetry features that differ between PD and HC groups. Features that remain significant after Benjamini-Hochberg correct are indicated by significance levels. ** p<.01; **** p<.0001; all significance levels indicate original p-values. I: ipsilateral side; C: contralateral side; TDS: terminal double support; ROM: range of motion; CV: coefficient of variation; Asym: asymmetry.*

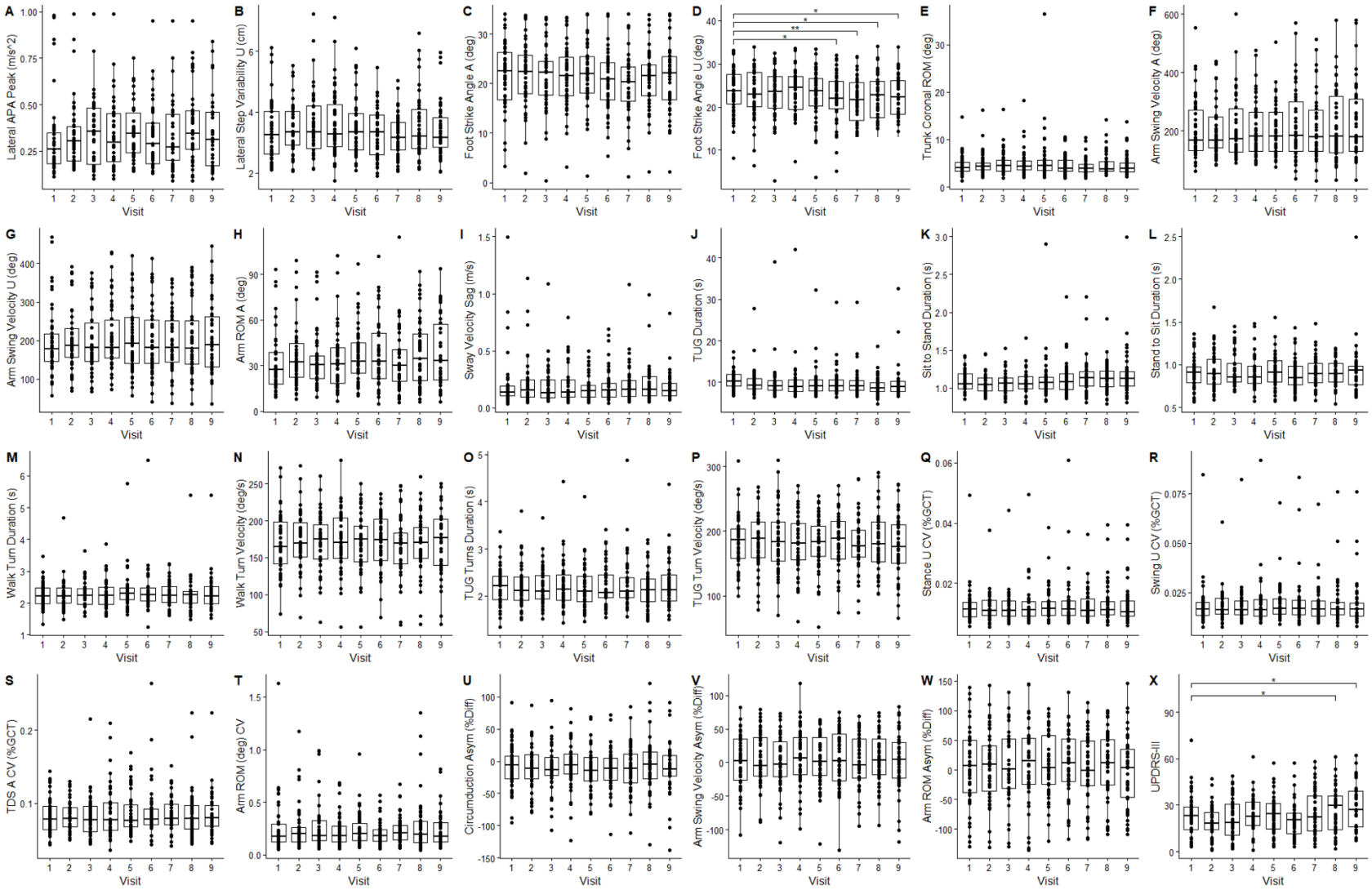
2.3.3 Progression of PD parameters across visits

Out of the 64 patients, 46 had nine visits after correction with last-observation-carried-forward method. There was a statistically significant effect of visit on foot strike angle on the contralateral side ($F=4.277$, $p<.001$), sit to stand duration ($F=3.628$, $p=0.003$) and MDS-UPDRS-III ($F=6.434$, $p<0.001$). Pairwise comparisons found significant decrease in foot strike angle from baseline by the sixth visit (*Fig.2.5D*) and significant increase in MDS-UPDRS-III scores by visit eight (*Fig.2.5X*). No other feature showed significant difference between visits in the post hoc pairwise comparisons.

Table 2.6. Progression of PD-specific features identified from the cross-sectional analysis in healthy controls and PD patients. The p-value from repeated measures ANOVA for each control and patient groups are listed. HC: healthy control; PD: Parkinson's disease patients; TD: Tremor Dominant; PIGD: Postural Instability and Gait Difficulty; APA: anticipatory postural adjustment; I: ipsilateral side; C: contralateral side; ROM: Range of Motion; TUG: Timed-Up and Go task; CV: coefficient of variation; MDS-UPDRS-III: Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III (motor score).

	Parameter	**HC**	**PD**
Gait	Lateral APA Peak (m/s^2)	0.7	0.35
	Foot Strike Angle I (deg)	0.26	0.048
	Foot Strike Angle C (deg)	0.051	**0.00045**
	Trunk Coronal ROM (deg)	0.19	0.19
	Arm Swing Velocity I (deg)	0.53	0.39
	Arm Swing Velocity C (deg)	0.47	0.71
	Arm ROM I (deg)	0.44	0.16
Sway	Mean Velocity Sagittal (m/s)	0.86	0.75
Transition	TUG Duration (s)	0.025	0.33
	Sit to Stand Duration (s)	0.13	**0.003**
	Stand to Sit Duration (s)	0.84	0.83
	Walk Turn Duration (s)	0.6	0.22
	Walk Turn Velocity (deg/s)	0.5	0.68
	TUG Turn Duration (s)	0.47	0.58
	TUG Turn Velocity (deg/s)	0.56	0.28
Variability	Stance C (%GCT) CV	0.67	0.65
	Swing C (%GCT) CV	0.64	0.7
	Terminal Double Support I (%GCT) CV	0.29	0.6
	Lateral Step Variability C (cm)	0.42	0.053
	Arm ROM I (deg) CV	0.42	0.45
Asymmetry	Circumduction Asymmetry (%Diff)	0.56	0.43
	Arm Swing Velocity Asymmetry (%Diff)	0.43	0.83
	Arm Range of Motion Asymmetry (%Diff)	0.4	0.16
Clinical Score	MDS-UPDRS-III	0.77	**1.3E-07**

*Figure 2.5. Pair-wise comparison of selected gait progression features over nine visits in PD patients. A: affected side; ROM: range of motion; TUG: Timed-Up and Go task; CV: coefficient of variation; MDS-UPDRS-III: Movement Disorder Society Unified Parkinson's Disease Rating Scale part III (motor score). *p<.05 (paired-T test of each visit against visit one, corrected by the Benjamini-Hochberg Process.)*



2.4 Discussion

2.4.1 Characteristic features of PD gait

At an average disease duration of 2.75 years, five walking features and four transition features were indicative of the PD disease state. Both spatial and temporal aspects of walking were affected by PD, in agreement with previous literature.

In the spatial aspect, the most prominent features were the reduced arm ROM and arm swing velocity on the ipsilateral side. This well-known clinical finding is reproduced here using inertial sensors. In the lower limbs, there is no statistically significant difference in the stride length, cadence, gait cycle duration, or double support time features, in contrast to previous literature[29]. One possible reason for the discrepancy would be that the cohort measured in this study was at a much earlier disease stage (average disease duration was 2.75 years) compared to that of the contrasting literature (average disease duration was 8.8 years). In a previous validation study, measures of double support time and single support time from APDM had moderate to poor agreement with measures from a pressure walkway[186]. This may be the reason for the absence of significant difference and suggest caution should be taken when interpreting results of these features from APDM sensors. PD patients exhibit a smaller foot strike angle that reflects the heel-to-toe characteristic where patients demonstrate reduced forces at the heel and forefoot and increased load under the midfoot[261, 327] This strategy is likely from patients compensating for the loss of postural control. Patients also showed a decreased trunk coronal ROM, reflective of the rigidity caused by PD. Looking at gait variability in the temporal aspect, variability in arm ROM is again the most prominent feature that distinguishes PD from controls.

Contrary to previous studies[64, 65, 287, 299], sway was not significantly different in the early PD cohort and no parameters were indicative of disease state. These studies examined PD patients in their prodromal or denovo states before levodopa medication was taken. It should be noted that whether sway is altered in denovo PD patients is debatable as another study has shown sway to be normal in denovo patients before becoming abnormal in advanced stages[58]. The discrepancy in results is likely caused by the effect of medication as medication is known to alter sway behaviour in patients[71, 328, 329]. Sway is also a poor predictor of MDS-UPDRS-III scores[29], which is also significantly altered by medication. The role of levodopa medication will be the topic of investigation in the following chapter. Sway velocity is strongly correlated with body weight[330], but no participant in this study was considered obese according to the body mass index. Age, sex, and physical fitness[331] are other potential confounders that should also be taken into account in future analysis of postural sway.

During gait initiation, PD patients exhibited a slower lateral APA acceleration at the first visit, this is the peak lateral lumbar acceleration during the APA where the COP is shifted to the swing leg. This difference was large enough to be identifiable even when patients are ON-medication in addition to being OFF-medication in a previous study[87].

During sit and stand transitions, PD patients took significantly longer to stand up from a seated position, possibly reflective of a combination of slower movement initiation, weakened muscles, and requiring a longer time to balance the change in positions. Sit-to-stand transitions in patients with neurological disorders are associated with fear of falling[332].

Turning was the most significantly impacted type of transition where patients turn slower with a longer duration. This difference was seen in both the two-minute walk and the TUG task,

where only one turn is made per trial. This result confirms previous finding that measures of turning are most indicative of patient status and most highly related to MDS-UPDRS-III ratings[29].

A previous study using the same measuring system has identified turning peak velocity, gait speed, and stride length to be most indicative of PD status, with turning measures correlating most strongly with MDS-UPDRS-III[29]. Results from this study confirm that turning velocity is indicative of early PD disease state but gait speed and stride length were not significantly different in the patient and control groups. This is likely because the cohort in the other study had an average disease duration of 8.8 years and were measured in the off-medication state. Compared to straight walking, turning is more demanding of dynamic postural stability and seems to be more vulnerable to neurological impairments as its impairment is present in earlier disease stages, and not masked by the effects of PD medication.

Descriptive analysis of the data shows a large distribution of data points in each feature in the patient group reflective of the heterogeneous nature of PD. Previous studies that identified these features had a smaller sample size compared to this one, with patients at a later disease stage. It could be that these stride length and cadence features were affected in a subgroup of patients at an early disease stage, but this difference is masked by the presence of a large number of other patients in whom these features are affected later on. Overall, foot and arm amplitude, variability in arm movement, and gait transition features (initiation, turns, sit to stand) are more prominent characteristics of PD and future work should closely examine these features in denovo patients as prodromal markers.

2.4.2 Progression features of PD gait

Foot strike angle on the contralateral side showed a consistent reduction from visit six (*Fig.2.5D*), six months earlier than progression was detected by the current clinical score MDS-UPDRS-III (*Fig.2.5X*). This is the most striking and impactful finding of this study as all patients assessed were on medication which is known to mask apparent progression in many other biomarkers like gait speed and stride length. Reduced foot strike angle implies reduced impact on foot strike and adaptation of a forefoot control strategy during walking possibly through adaptive mechanisms to avoid unsteadiness in PD gait. The level of foot strike angle reduction has also been associated with PD severity[261]. Here for the first time, we see that this change is measurable within 15 months using wearable IMUs.

Although sit-to-stand duration showed a significant group effect, no significant difference was seen between visits. There could be three explanations for this: that sit-to-stand duration deteriorates slowly during the two-year duration of the study, that the way PD affects walking is heterogeneous in nature, or that progression was masked by medication that improves symptoms. Another study using accelerometer sensors found a significant difference in ML sway over a course of one year in untreated PD patients[65]. Considering all patients were on medication and showed no statistically significant progression in sway over the duration of the study, medication seems to play an important role in normalising sway parameters in early PD patients. Exactly which gait and balance features are affected or masked by medication will be the topic of investigation in the next chapter. No other selected PD-specific feature showed a consistent progression throughout the nine visits. One possible conjecture for this can be the heterogeneity of PD, that patients with different motor phenotypes[333, 334] with different pathophysiology[335, 336] and progress at different rates[337, 338] may be adding noise to the

data, obscuring any trace of progression. However, after separating the patients into the two most well-studied motor phenotypes[333, 339], repeated measures ANOVA for PD-specific features did not show any statistically significant progression in further analysis. Considering the MDS-UPDRS-III is a composite score that considers various aspects of PD motor symptoms, breaking down walking and standing to its biomechanical components may not work sufficiently for tracking the PD progression. To track progression, it is evident that composite scores with factorization and modelling techniques should be applied in the future.

2.4.3 Limitations and Future Directions

All patients completed the protocol in a medicated state. Prescribed levodopa equivalent dosage varies amongst patients and sometimes between visits. PD medication's main effect is improving gait functions, which may mask underlying PD gait characteristics. Features that were identified in this state were impacted by PD and not completely treated by PD medications. It is also common for the type and dosage of PD medication prescribed to patients to change throughout a two-year period. Prescriptions are adjusted to give the best motor benefits to patients, and we assume that the medication level at each visit is optimal for each participant at that given time. This is often not the case with long waiting times before patients can see their neurologist and introduces noise to the data. The medication effect may be the reason for the absence of significant progression in many gait features. On the other hand, levodopa medication also introduces side effects such as dyskinesia, most often in later disease stages when patients are taking a much higher dose. Since patients in this cohort were in their early stages (less than eight years) of PD, we assume that levodopa side effects do not have a significant impact on the results.

Another limitation to this study was that the control group is either the spouses of PD patients or those that have sufficient interest or concern in neurological disorders and movement disorder to join the study. Taking care of patients with a movement disorder is both physically and mentally demanding and PD contributes to poorer mental health in spouses[340]. It is possible that spouses have a larger mental burden and experience some level of interpersonal synchronization[341] of PD gait during everyday life that may change the way they walk. Spouses of PD patients are also found to have larger sway velocity, and sway range in both sagittal and coronal planes compared to age-matched controls[342]. Participants who have prodromal symptoms of movement disorders are also more incentivized and likely to participate in gait research.

Due to the design of this study, some patients coming in for the second visits do a levodopa challenge by consent. The levodopa challenge requires the participant to refrain from any dopaminergic medication for at least 12 hours before their visit. At visit two, the participant will come in on an OFF-medication state, complete the protocol, take their usual dose of medication, and repeat the motor protocol in an ON-medication state. We assumed that a one-hour wait post medication is sufficient to return patients into the on-state. This may negatively impact gait performance at visit two in this chapter, as participants are likely to be more tired physically and mentally after the levodopa challenge. Since progression on individual gait features were not significant by the ninth visit, the negative impact from the challenge is unlikely to be large enough to show a significant visit effect, and this limitation should not alter results from the progression analysis.

2.4.4 Conclusion

In this chapter we set out to identify gait features of PD disease and PD progression in early PD patients. A total of nine features were significantly different in the patient group, including four gait, four transition, and one variability features. Most features that were PD-specific did not show a statistically significant progression. Progression in individual biomechanical components over two years may not be large enough or may be masked by symptomatic treatment effects, and future work should focus on factorizing and combining multiple components in building a model that can track PD progression in shorter time frames. Nevertheless, foot strike angle on the contralateral side was identified as a progression marker that showed measurable decrease at 15 months from the first visit, sooner than MDS-UPDRS-III which only showed significant difference by 21-months. Furthermore, this progression was observed in patients receiving medical treatment aimed at improving motor symptoms, making foot strike angle a more robust and sensitive biomarker than the current clinical rating scale in tracking PD progression.

Chapter 3 Effects of Medication on PD Gait and Posture

3.1 Introduction

3.1.1 Endogenous dopaminergic pathway

PD is caused by reduced DA levels in the brain due to degeneration of the SN of the BG. The direct precursor to DA is levodopa, which is normally converted from the amino acid tyrosine, produced in the liver, by tyrosine hydroxylase (*Figure 3.1*). Levodopa is then decarboxylated into the neurotransmitter DA to be released by dopaminergic neurons of the SN into the synaptic cleft to bind DA receptors on postsynaptic striatal neurons for downstream signalling. DA concentration at the synaptic cleft and its binding to DA receptors are responsible for the integrity of BG's functional ability to control and initiate movement. Synaptic DA concentration is regulated by processes of release, reuptake, and elimination[343]. DA in the synaptic cleft can either bind to DA receptors of the post synaptic striatal neuron, removed by astrocytes, or recaptured by DA transporters (DAT) on the presynaptic neurons (*Figure 3.2*).

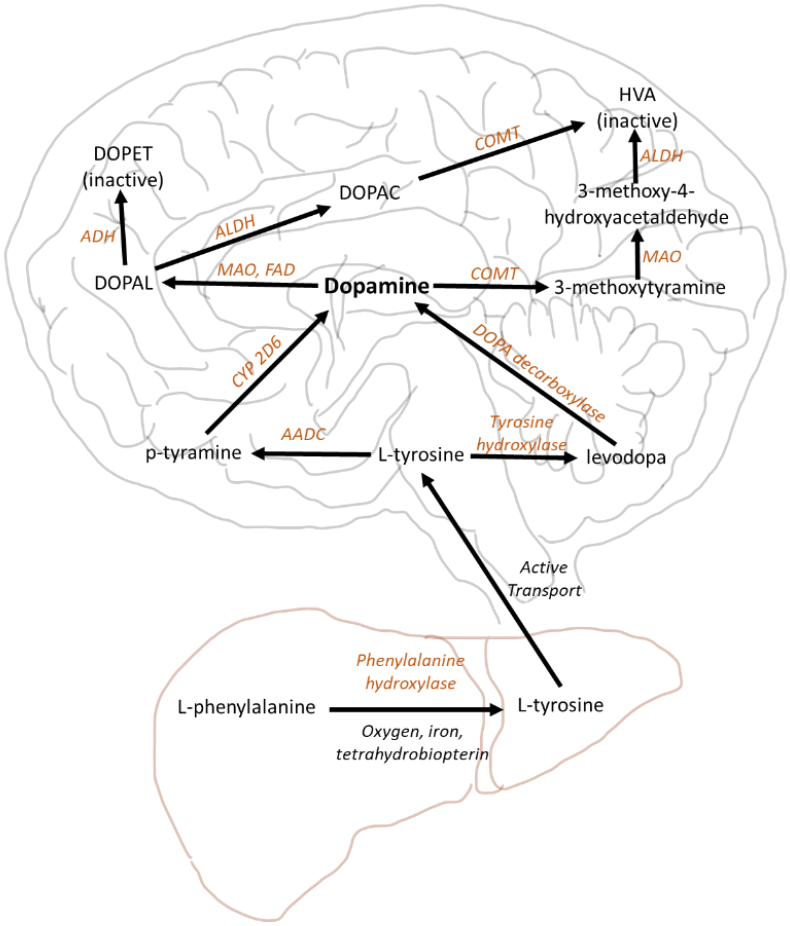


Figure 3.1. Schematic drawing of DA metabolism inside the brain. Enzymes are in orange. Levodopa, the direct precursor to dopamine, is synthesized either directly from tyrosine or indirectly from L-phenylalanine produced in the liver. It is converted to L-tyrosine which is then actively transported to the brain where it is hydroxylated into levodopa. Inside the presynaptic terminal, levodopa is decarboxylated by L-3,4-dihydroxyphenylalanine decarboxylase (DOPA decarboxylase) into DA that is secreted into the synaptic cleft. Under specific conditions, L-tyrosine can be directly decarboxylated by into p-tyramine which undergoes hydroxylation into DA[344, 345]. After DA reuptake into dopaminergic neurons or glial cells, it undergoes oxidative deamination into 3,4-dihydroxyphenylacetaldehyde (DOPAL). DOPAL, a reactive aldehyde can be inactivated into 3,4-dihydroxyphenylethanol (DOPET) or into 3,4-dihydroxyphenylacetic acid (DOPAC) then into inactive homovanillic acid (HVA) that is secreted through urine[346]. DA can also convert into to HVA by aldehyde dehydrogenase (ALDH) to be secreted. MAO: monoamine oxidase; COMT: catechol-O-methyltransferase; FAD: flavin adenine dinucleotide; ALDH: aldehyde dehydrogenase; AADC: aromatic L-amino acid decarboxylase.

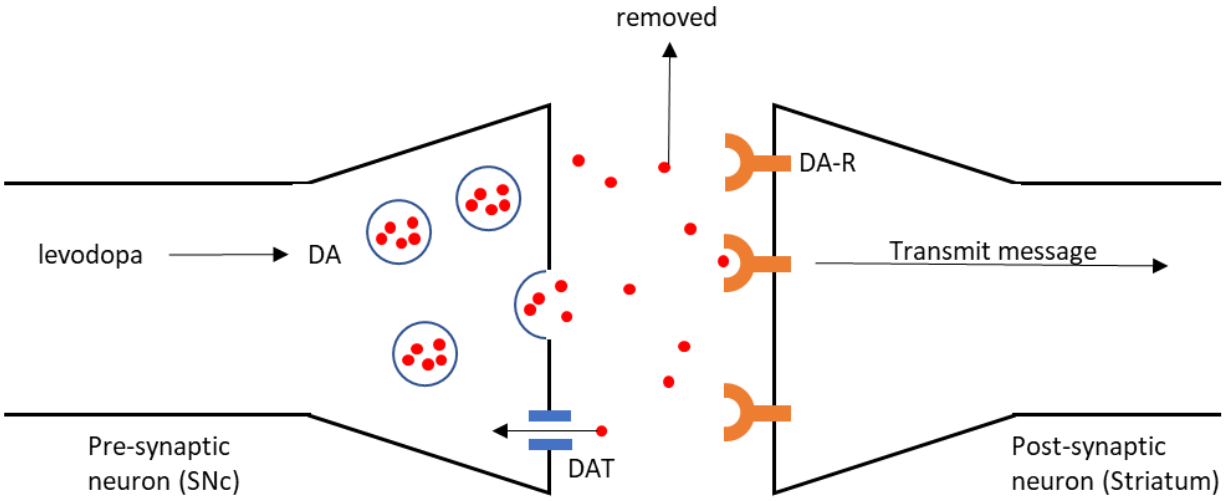


Figure 3.2. Schematic drawing of dopamine release, reuptake, and elimination processes. Red dots represent dopamine molecules. DA: dopamine; DAT: dopamine transporter; DA-R: dopamine receptor; SNc: substantia nigra pars compacta.

3.1.2 Levodopa treatment for PD—exogenous dopamine

The mainstay of treatment for depleted DA levels in PD is DA replacement therapy with levodopa[109, 110]. Levodopa was first used to treat motor symptoms of PD in humans in 1967[347], and the use of peripheral dopa decarboxylase inhibitors to prevent side effects[348]of peripheral metabolism of levodopa was introduced in the mid-1970s[349]. The most commonly prescribed drugs are co-careldopa (a combination of carbidopa and levodopa) and co-benaldopa (a combination of benserazide with levodopa) to minimize peripheral levodopa metabolism. L-3,4-dihydroxyphenylalanine (DOPA) decarboxylase inhibitors (benserazide and carbidopa) are polar and cannot cross the blood-brain barrier (BBB), thus they act to prevent conversion of levodopa into DA in the periphery but not in the brain[350, 351]. The reason for using levodopa instead of DA itself is because the DA molecule taken orally is too polar to cross the BBB, so it must be converted inside the central nervous system (CNS) from levodopa. Levodopa is usually administered orally and absorbed in the duodenum with a relatively short half-life of around 90 minutes[349]. Once inside the central nervous system, levodopa is taken up by the nigral dopaminergic neurons and converted to DA by the naturally occurring enzyme DOPA

decarboxylase. Converted DA is stored in pre-synaptic nigral neurons and released into the synaptic cleft to act on postsynaptic DA receptors as a neurotransmitter.

Levodopa reduce PD symptoms effectively in patients in earlier stages where SN function is relatively preserved. The therapeutic effect can be sustained well past the 90-min half-life even during occasional missed doses. Plasma level of levodopa is smooth in early patients. The continual loss of SN during progression shortens the therapeutic effect of each dose (or drug-effective window) and patients may experience worsened symptoms right before the next scheduled dose, called the "wearing off" effect. This is usually improved by increasing the frequency of doses. However, as disease further progress into later stages, continual dopaminergic cell loss narrows the therapeutic window and motor complication becomes more unpredictable[349].

Motor complications are a result of both disease severity[352-354] and levodopa use. Narrowed therapeutic window in more advanced patients often subject them to switching between an immobile state, during exceedingly low levodopa level, and dyskinetic state, where plasma levodopa level is too high. Dyskinesia is the involuntary and abnormal twisting hyperkinetic movements of the trunk, limbs, neck and face that generally occur at peak dose[355 356, 357]. Such levodopa-induced-dyskinesia (LID) often appears with prolonged usage of levodopa and may worsen to a point where it disrupts normal daily activities[358]. It is a result of fluctuations in pre- and post-synaptic DA levels in the nigrostriatal pathway caused by variable drug absorption and transit across the BBB[359, 360]. Dyskinesia can be broadly classified as chorea, a hyperkinetic and purposeless dance-like movement, and dystonia, sustained and abnormal muscle contractions. The occurrence and severity of dyskinesia varies, being absent in some patients

while being more disabling than bradykinesia and rigidity in others. It is present in 30-40% of patients during the first five years of levodopa administration and by 10 years it affects nearly 60% of patients[361, 362]. Motor fluctuations and dyskinesia are often the reason for patients to undergo surgical operation. DBS at either the STN or the GPi has been found to improve dyskinesia, albeit through different mechanisms: stimulation at the GPi directly improves dyskinesia while stimulation at the STN indirectly improves dyskinesia through reducing medication dose[363-368].

Other medications can be used in combination with levodopa to counteract the narrowing therapeutic window and motor complications. DA agonists with a longer half-life are used to reduce motor fluctuations and dyskinesia[369]. They bind the postsynaptic DA receptors at the striatum to activate downstream neurons[370]. Monoamine Oxidase B (MAO-B) inhibitors and Catechol-O-methyl transferase (COMT) inhibitors are used with levodopa to prevent DA degradation and prolong its half-life in the brain. Amantadine, a non-competitive antagonist of N-methyl D-aspartate (NMDA) glutamate receptor, triggers DA release and prevents reuptake. It can treat rigidity, resting tremor and fatigue and limit the severity of LID[371]. Intestinal levodopa gel infusion, where medication is continuously released into the upper gastrointestinal tract, can be used to decrease motor fluctuation with constant levels of plasma levodopa[372]; this can significantly reduce motor complications like dyskinesia[373-375], but is not commonly used due to its very expensive and invasive nature[376].

3.1.3 Medication Effect on Gait and Posture

In PD, DA deficiency disrupts the cortico-BG-thalamo-cortical loops that are important in motor, oculomotor, and higher cognitive function. In the motor circuit the putamen receives

input from the SMA, motor cortex and somatosensory cortex, passing it on to the GPi and SNr, then the ventral lateral and anterior nucleus of the thalamus before closing the loop to the cortex[377]. Levodopa medication indirectly raises brain DA levels and is effective in treating early PD symptoms including bradykinesia, rigidity, and tremor. Automatic postural control such as postural sway during stance and voluntary postural control such as gait initiation have been suggested to involve distinct BG circuits[378], and levodopa is known to be more effective improving voluntary, rather than automatic movements[379, 380]. Most studies[168, 170, 171, 174, 180] on the effect of dopaminergic treatment on gait have evaluated short-term differences between the on- and off-medication states, with patients first measured in the off-medication state, then given dopaminergic treatment, and measured again in the on-medication state within the same day, usually around an hour after they have taken their medication.

Gait metrics related to amplitude and speed benefit from dopaminergic medication. These include increased ROM of the trunk and arms, larger step length, increased gait speed and cadence, and greater arm swing velocity[168, 170, 174, 180, 381] (see *Table 3.*1). The effect of medication on cadence and double support time, however, is not as consistent[168, 170]. Published work is also suggestive of decreased gait variability with medication[170, 263] and increased symmetry of arm swing movements[180]. Through improving hypometria, levodopa has been found to increase APA amplitude[87, 168, 382] and increase length of the first steps[382]. However, results are inconsistent, with other studies not finding an increase in first steps sizes[168]. This is likely a result of the different disease stage at which measurement took place, dyskinesia not being controlled for, different task conditions such as starting width of the first step and measurement devices used.

Poor postural stability is a major problem in PD patients that is associated with risk of falling, compromised autonomy, and decreased quality of life. Postural sway can be measured either during movement initiation (dynamic balance) or during quiet stance (static balance)[383]. This chapter focuses on static balance, the ability to keep in position the COM. The MDS-UPDRS-III has one item on instability—the pull test, which is known to be poorly correlated with patients' ability to recover from external disturbances[384]. Reports on the effect of medication on postural instability are inconsistent, with some showing it improves and others suggesting it worsens[168, 385]. Discrepancies in medication effect on sway have been attributed to differences in research design, such as disease severity, inclusion/exclusion criteria, and type of measuring device used[71]. In addition, there is a lack of consensus on the interpretation of sway amplitude. Although an increased sway area is commonly viewed as "worsened" sway, it is also an important indicator of motor exploration, beneficial during childhood development[386, 387] and aging[388-390].

The effect of levodopa on sway is mostly seen in the coronal plane rather than the sagittal plane[71, 391]. Increased sway in the coronal plane has been associated with increased falling risk in older adults[392, 393]. The dopaminergic system has been suggested to be involved in regulating muscle tone during stance, where depleted dopaminergic transmission increases muscle tone and lower limb tremor, which may contribute to posture and stability changes[79]. Clinically, examinations of sway before and after medication show no significant improvement in balance [125, 334]. Other studies have shown levodopa to make sway more abnormal through decreasing stiffness while not improving postural control[380] or improve proprioceptive and kinaesthetic deficits[76].

Dopaminergic treatment does not significantly improve turning in place[394, 395], but some studies have found levodopa to increase turning speed and decrease the number steps required to make a turn during walking[168, 394]. The effect of levodopa on gait parameters is summarized in *Table 3.1*.

Table 3.1. A list of common gait metrics and how each is affected by Parkinson's disease and levodopa medication along with the type of gait measuring tool used. Red upward arrow indicates an increase in amplitude of the metric, blue downward arrow indicates decrease, and yellow circle indicates no significant difference was found. Gait labs include all traditional measurement of gait including video tracking, force plate, gait mat, and pressure insoles.

Category	Parameter/metrics	PD	Medication	
			Wearable inertial sensors	Gait lab
Gait	Cadence	↓ 47-49, 52, 53, 90	↑ 168	↑ 178 ○ 169, 171
	Gait cycle duration	↑ 47, 48, 51-53	↓ 168	○ 169, 171, 174
	Stride length	↓ 23, 24, 47-49, 51-53, 66, 274-276, 313	↑ 168	↑ 169-172, 174, 175
	Elevation at mid-swing	↓ 22, 49		
	Trunk ROM	↓ 90	↑ 168	
	Arm ROM	↓ 90, 168	↑ 168	
	Stance	↑ 47, 49, 51, 52 ○ 48		
	Swing	↓ 48, 49 ○ 47		
	Double support time	↑ 24, 50, 51	○ 168	↓ 171, 172, 178
	Stride time variability	↑ 24, 47, 50, 52, 276		↓ 170, 178 ○ 169
	Arm swing velocity	↓ 90, 279	↑ 168, 180	
	Gait velocity	↓ 48, 49, 51, 52, 274-276	↑ 168	↑ 169-172, 174, 396
	Step width	↓ 48 ○ 47		
	Toe Off Angle	↓ 49		
	Foot Strike Angle	↓ 49		
	APA acceleration	↓ 86-88	↑ 168	↑ 87, 382
Postural Sway	Sway area	↑ 66-69	↑ 168	↑ 71, 397 ↓ 398
	Frequency dispersion	↑ 64		↑ 71, 385
	Centroidal Frequency coronal		↓ 168	
	95% Ellipse	↓ 64, 71		↑ 397
	Path length	↑ 66		
	Jerk (derivative of trunk acceleration)	↑ 64-66, 289	↓ 168	
	Sway dispersion (RMS of trunk acceleration)	↑ 64, 65, 71, 287	↑ 168	↑ 71, 385
	Sway velocity	↑ 64-66, 69-71, 287	↑ 168	↑ 385 ↓ 398
Postural Transition	Turn duration	↓ 66, 305 ○ 90	↓ 168	
	Turn velocity	↓ 66, 90, 98, 183	↑ 168	
	Steps required to make a turn	↑ 66, 98, 183, 305	↓ 168	

3.1.4 Objective and aim

The aim of this chapter is to identify postural and gait features affected by medication. Particularly, exploration of features that are affected by both PD and medication. For this reason, ON- and OFF-medication groups were compared to health controls and then to each other. We hypothesize that medication will improve PD specific abnormalities in a range of postural and gait features including cadence, gait speed, stride length, trunk and arm ROM, in addition to sway jerk and turn velocity, and other PD-specific sway and transition parameters will have a significant response to levodopa medication.

3.2 Methods

3.2.1 Participants

Participants were recruited based on the same protocol described in Chapter 2 (*2.2.1 Participants*) with the additional requirement that patients are willing and able to refrain from taking any dopaminergic medication for at least 12 hours before the visit. The OFF-medication state is defined as at least 12 hours without antiparkinsonian medication, and the medication on state is one-hour post dose. Participants were tested in the OFF-medication state first and then allowed to take their usual dose of dopaminergic medication. After an hour the patients were retested with the same tasks in their ON-medication state. Age-matched healthy controls were tested only once.

3.2.2 Testing Protocol

The testing protocol and pre-processing of the data were the same as previously described (*2.2.2 Testing Protocol*) with the exception that gait analysis and MDS-UPDRS-III (motor assessment) were repeated in the ON-medication state.

Lateral step variability was calculated as follows: for every three consecutive steps on the same side, the perpendicular displacement of the middle foot placement from the line connecting the first and third steps were recorded. The reported lateral step variability is the standard deviation of these displacements (*Figure 3.4*).

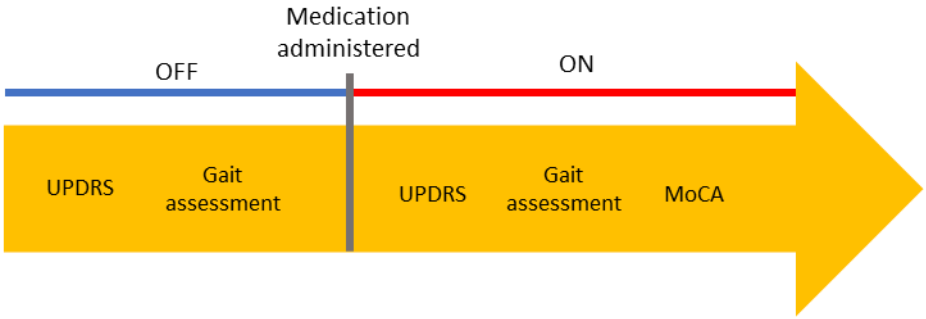


Figure 3.3. Experimental protocol for quantifying levodopa effect on gait. OFF: off-medication state, ON: on-medication state; UPDRS: Unified Parkinson's Disease Rating Scale, MoCA: Montreal Cognitive Assessment.

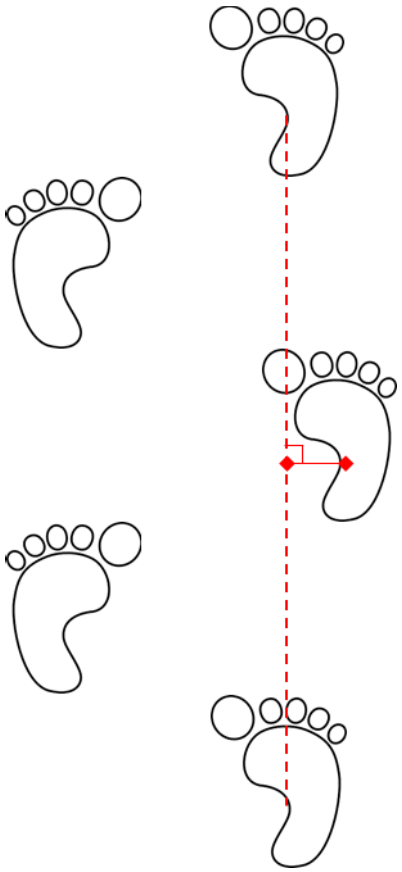


Figure 3.4. Schematic demonstration of lateral step variability. The dashed line represents the vertical line connecting the first and the third step, the diamond-mound line represents the perpendicular displacement from the dashed line. Reported lateral step variability is the standard deviation of this quantity across the total number of steps.

3.2.3 Analysis for determining features affected by levodopa medication

Missing data consisted of 1.0% of the entire dataset. The motor features examined were described in (*2.1.2 Promising metrics for PD-specific gait biomarkers*) and *Table 2.1*. Since we are interested in PD-specific features that are affected by medication, unpaired t-tests were first used to select features that had a significant difference ($p<0.05$) between the control and off-medication groups. Paired t-tests or Wilcoxon signed rank tests (WSRT) were then used to find selected PD-specific features that had a significant response to medication. The Benjamini-Hochberg method was used to correct for multiple comparisons. Only parameters with p-values less than the critical value of the Benjamini-Hochberg process were considered significant. Pair-wise analysis was then conducted on the selected features for ON- and OFF-states against the control group, where Dunn test was used for non-parametric features and multiple pair-wise t-test for parametric features.

3.3 Results

3.3.1 Demographics

48 PD patients completed the levodopa challenge and were included for analysis along with 43 age-matched controls. Demographic details are reported in *Table 3.2*.

Table 3.2. Demographics table of participants in this chapter. HC, Healthy Controls; PD, Parkinson's patients.

	HC (N=43)	PD (N=48)
Age		
Mean (SD)	65.7 (7.58)	62.6 (12.6)
Median [Min, Max]	66.3 [49.7, 82.2]	63.7 [0.250, 79.5]
Gender		
Male	20 (46.5%)	27 (56.3%)
Female	23 (53.5%)	21 (43.8%)
Handedness		
Left	5 (11.6%)	3 (6.3%)
Right	37 (86.0%)	45 (93.8%)
Ambidextrous	1 (2.3%)	0 (0%)
Ethnicity		
White	41 (95.3%)	47 (97.9%)
Mixed	1 (2.3%)	1 (2.1%)
Other	0 (0%)	0 (0%)
UPDRS-III OFF		
Mean (SD)	4.49 (6.25)	25.5 (12.8)
Median [Min, Max]	2.00 [0, 25.0]	26.0 [5.00, 54.0]
UPDRS-III ON		
Mean (SD)	NA (NA)	18.5 (11.4)
Median [Min, Max]	NA [NA, NA]	16.5 [0, 49.0]
PD Side of Onset		
Left	0 (0%)	29 (60.4%)
Right	0 (0%)	19 (39.6%)
N/A	0 (0%)	0 (0%)
PD Duration (months)		
Mean (SD)	NA (NA)	37.0 (20.1)
Median [Min, Max]	NA [NA, NA]	34.0 [5.00, 87.0]
Onset age		
Mean (SD)	NA (NA)	61.7 (8.71)
Median [Min, Max]	NA [NA, NA]	60.3 [46.7, 79.8]
LEDD		
Mean (SD)	NA (NA)	481 (224)
Median [Min, Max]	NA [NA, NA]	410 [180, 1200]

3.3.2 Gait features and their response to medication

42 features including MDS-UPDRS-III were significantly different between the off-medication and control groups. Within these features, 14 had a significant medication effect (*Table 3.2*).

These include nine gait means features, four gait variability features, and the MDS-UPDRS-III, which were selected for pairwise comparison.

Table 3.3. Features with significant association with PD disease state and medication state from paired and unpaired t-test and Wilcoxon tests along with their unadjusted p-value and critical value of the Benjamini-Hochberg correction. Parameters that remain significant after the correction are marked in bold. Median was used instead of mean value for nonparametric parameters. c.v.: critical value; I: ipsilateral; C: contralateral; ROM: range of motion; TUG: Timed-up-and-Go test; TDS: terminal double support; %Diff; percentage difference between left and right sides; CV: coefficient of variation; %GCT: percentage of gait cycle time; MDS-UPDRS-III: Movement Disorder Society—Unified Parkinson's Disease Rating Scale (motor score).

	Parameter	Control mean ± std	OFF mean ± std	ON mean ± std	OFF vs Ctrl p-value	OFF vs ON p-value	c.v.
Gait	**Stride Length I (m/h)**	0.76 ± 0.069	0.72 ± 0.11	0.73 ± 0.097	0.034	<0.001	0.007
	Stride Length C (m/h)	0.78 ± 0.072	0.74 ± 0.11	0.74 ± 0.097	0.007	<0.001	0.0058
	Gait Speed I (m/hs)	0.73 ± 0.095	0.7 ± 0.12	0.7 ± 0.11	0.037	<0.001	0.01
	Gait Speed C (m/hs)	0.75 ± 0.096	0.71 ± 0.12	0.72 ± 0.11	0.013	<0.001	0.0093
	Foot Strike Angle I (deg)	26 ± 5.1	21 ± 7	22 ± 6.5	0.0016	<0.001	0.0023
	Foot Strike Angle C (deg)	27 ± 5.9	23 ± 6.3	23 ± 5.6	0.0061	0.0094	0.014
	Lumbar Sagittal ROM (deg)	5.3 ± 2	6.6 ± 2.8	6.4 ± 2.5	0.011	0.28	0.035
	Trunk Coronal ROM (deg)	5.2 ± 2.1	4.1 ± 2.4	4.5 ± 2.7	0.019	<0.001	0.0047
	Trunk Transverse ROM (deg)	8.4 ± 2.3	7.4 ± 2.2	7.8 ± 2.4	0.039	0.012	0.016
	Arm Swing Velocity I (deg/s)	230 ± 64	160 ± 79	170 ± 88	<0.001	0.023	0.019
	Arm ROM I (deg)	57 ± 18	27 ± 18	34 ± 22	<0.001	<0.001	0.0035
Sway	Mean Velocity (m/s)	0.13 ± 0.072	0.15 ± 0.11	0.18 ± 0.099	0.037	0.72	0.045
	Mean Velocity Sagittal (m/s)	0.12 ± 0.076	0.15 ± 0.11	0.17 ± 0.098	0.04	0.8	0.048
	Path Length Coronal (m/s^2)	3.3 ± 1.5	4.1 ± 3.5	3.8 ± 1.3	0.04	0.11	0.028
Transition	Walk Turn Duration (s)	2.1 ± 0.29	2.3 ± 0.33	2.3 ± 0.35	0.0043	0.31	0.036
	Walk Turn Velocity (deg/s)	200 ± 37	170 ± 42	170 ± 40	<0.001	0.38	0.041
	TUG Turn Duration (s)	2 ± 0.31	2.3 ± 0.46	2.2 ± 0.44	<0.001	0.15	0.03
	TUG Turn Velocity (deg/s)	210 ± 40	180 ± 43	190 ± 44	<0.001	0.042	0.021
	Sit to Stand Duration (s)	0.98 ± 0.13	1.1 ± 0.22	1 ± 0.17	0.0086	0.26	0.034
	Stand to Sit Duration	0.81 ± 0.18	0.88 ± 0.21	0.9 ± 0.19	0.016	0.67	0.044
Variability	Double Support I (%GCT) CV	0.055 ± 0.018	0.065 ± 0.032	0.066 ± 0.02	0.021	0.19	0.033
	Double Support C (%GCT) CV	0.052 ± 0.017	0.061 ± 0.024	0.061 ± 0.02	0.014	0.53	0.043
	Gait Speed I (m/s) CV	0.038 ± 0.017	0.047 ± 0.024	0.045 ± 0.022	0.0094	0.063	0.022
	Gait Speed C (m/s) CV	0.04 ± 0.015	0.047 ± 0.027	0.046 ± 0.027	0.02	0.31	0.038
	Circumduction I (cm) CV	0.36 ± 0.14	0.31 ± 0.096	0.31 ± 0.11	0.021	0.029	0.02
	Circumduction C (cm) CV	0.33 ± 0.1	0.3 ± 0.096	0.32 ± 0.1	0.027	0.01	0.015
	Foot Strike Angle I (deg) CV	0.065 ± 0.049	0.094 ± 0.076	0.079 ± 0.045	0.0026	<0.001	0.0081
	Foot Strike Angle C (deg) CV	0.063 ± 0.037	0.085 ± 0.13	0.082 ± 0.059	0.026	0.064	0.023
	Single Limb support I (%GCT) CV	0.016 ± 0.0041	0.019 ± 0.0094	0.019 ± 0.0064	0.0041	0.09	0.027
	Single Limb support C (%GCT) CV	0.017 ± 0.0041	0.018 ± 0.0099	0.018 ± 0.0057	0.017	0.077	0.026
	Stance I (%GCT) CV	0.011 ± 0.0031	0.011 ± 0.0075	0.012 ± 0.0041	0.048	0.17	0.031
	Stance C (%GCT) CV	0.01 ± 0.0027	0.012 ± 0.0033	0.012 ± 0.0033	0.0063	0.43	0.042
	Step Duration I (s) CV	0.02 ± 0.0079	0.02 ± 0.013	0.021 ± 0.013	0.045	0.84	0.049
	Stride Length I (m) CV	0.03 ± 0.012	0.036 ± 0.021	0.033 ± 0.017	0.0034	0.019	0.017
	Stride Length C (m) CV	0.029 ± 0.009	0.035 ± 0.023	0.033 ± 0.02	0.0045	0.072	0.024
	Swing C (%GCT) CV	0.015 ± 0.0041	0.017 ± 0.0094	0.018 ± 0.0069	0.0075	0.14	0.029
	TDS I (%GCT) CV	0.067 ± 0.025	0.081 ± 0.021	0.08 ± 0.022	0.013	0.31	0.037
	TDS C (%GCT) CV	0.073 ± 0.021	0.082 ± 0.039	0.083 ± 0.025	0.018	0.34	0.04
	Lateral Step Variability I (cm)	3.6 ± 0.99	3.3 ± 0.81	3.7 ± 0.85	0.016	0.0011	0.012
	Lateral Step Variability C (cm)	3.9 ± 0.9	3.2 ± 0.87	3.6 ± 0.95	<0.001	0.0016	0.013
	Arm ROM I (deg) CV	0.12 ± 0.11	0.22 ± 0.14	0.21 ± 0.19	0.0044	0.75	0.047
Clinical Score	**MDS-UPDRS-III**	2 ± 6.1	26 ± 13	17 ± 11	<0.001	<0.001	0.0012

Medication significantly increased stride length, gait speed, lateral step variability, and foot strike angle on both sides, bringing them back to the normative range (*Fig.3.5A-H, A'-H'*). Variability of circumduction on the contralateral side was increased by medication (*Fig3.5I, I'*), although the difference between the OFF and control group became insignificant after correction. PD patients had increased variability in the foot strike angle on the ipsilateral side which was reduced by medication to the normative range (*Fig3.5J, J'*).

On the upper body, medication increased trunk ROM in both coronal and transverse planes (*Fig3.6A-B, A'-B'*). A significant increase in ipsilateral arm ROM was also observed however the medication effect was not enough to fully improve the reduced ROM (*Fig3.6C, C'*). Similarly, the MDS-UPDRS-III score for the On-medication state still differed from controls despite a significant medication effect (*Fig3.6D, D'*).

PD increased sway velocity and path length in addition to slowing transitions. However, among the selected PD-specific parameters, none had a significant response to medication (*Table 3.2*).

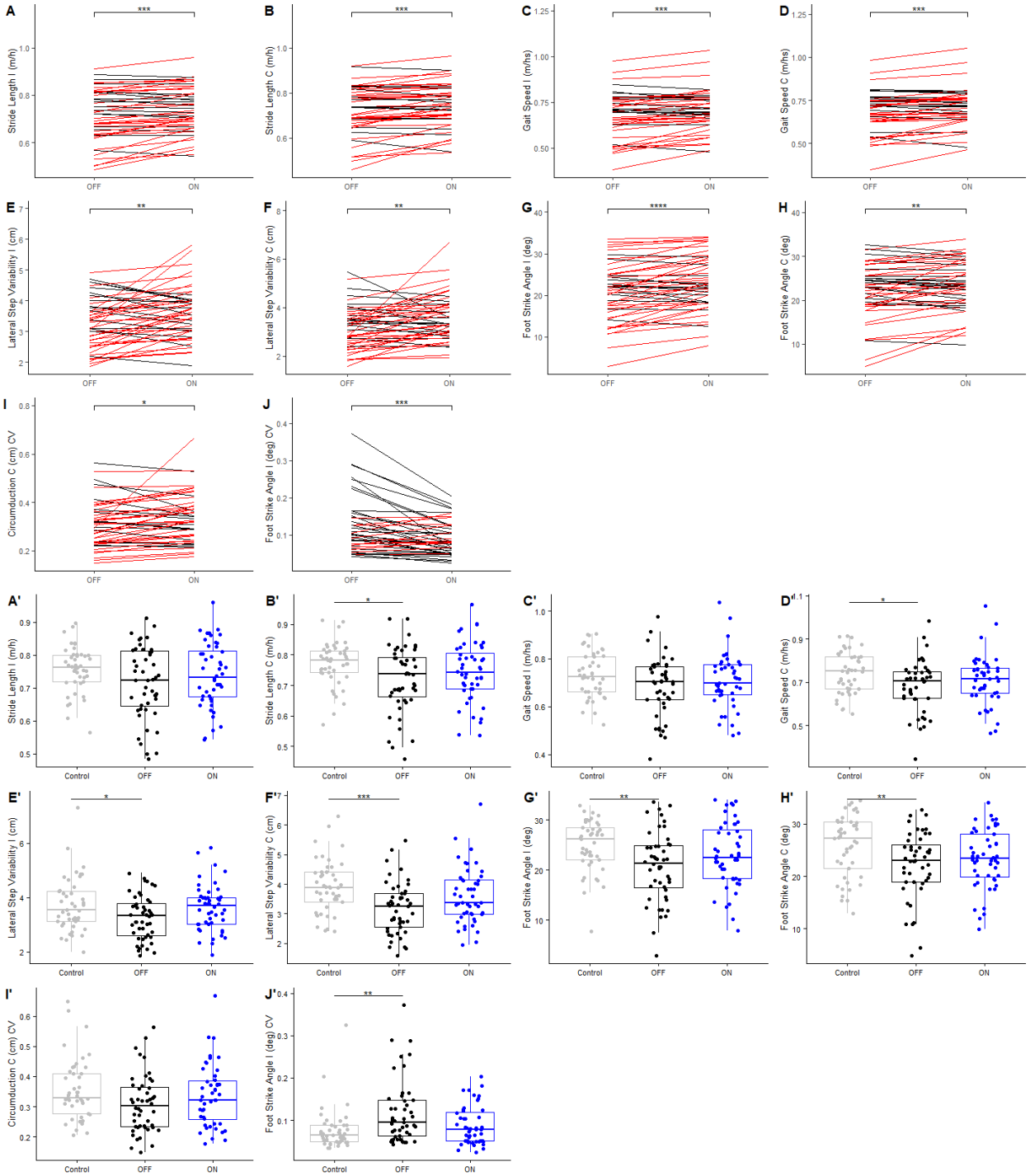


*Figure 3.5. Paired-t tests and pairwise comparisons of selected lower limb gait features between OFF- and ON-medication states and compared to the controls. Stride length and gait speed were height corrected. I: ipsilateral side; C: contralateral side; CV: coefficient of variation;). *p<.05, **p<.01, ***p<.001, ****p<.0001 (unpaired-pairwise T test of each medication group healthy control group, corrected by the Benjamini-Hochberg Process). In the top half, participants with increasing values by medication is indicated in red and decreasing in black.*

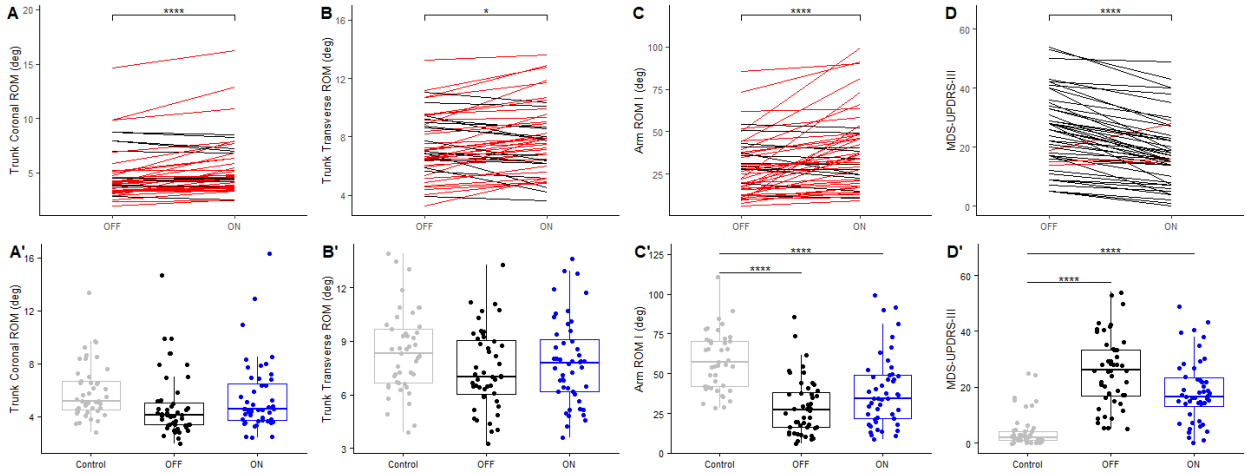


*Figure 3.6. Paired-t tests and pairwise comparisons of selected upper limb features and clinical score between OFF- and ON-medication states and compared to the controls. I: ipsilateral; C: contralateral; MDS-UPDRS-III: Movement Disorder Society—Unified Parkinson's Disease Rating Scale part III (motor score*p<.05, ****p<.0001, (unpaired-pairwise T test of each medication group healthy control group, corrected by the Benjamini-Hochberg Process.) In the top half, increasing values by medication is indicated in red and decreasing in black.*

3.4 Discussion

3.4.1 Levodopa improves gait speed and amplitude

In this chapter we used a robust analysis method to first select features that were affected by PD with the help of a control group. This method prevented the inclusion of features affected by levodopa but not necessarily PD-specific. We identified three lower limb amplitude features (both sides), three upper body ROM features, and four variability features to have a significant response to levodopa. PD patients have slower movement (bradykinesia) over a reduced ROM (hypometria). Rigidity and limited range of motion in PD were improved by levodopa, where it increased trunk coronal and transverse ROM, and arm ROM. Although medication increases arm ROM significantly, it remains hypometric in the on-medication state.

Hypometric spatial gait features in PD were corrected by levodopa. In the lower body, levodopa medication increased walking speed and stride length, in agreement with another study using the same device[168]. At the same time, it also had significant effect on less studied features: lateral step variability and foot strike angle. Lateral step variability was decreased by PD and brought to a level similar to that of controls by medication (*Fig3.5E', F', Fig.3.6A'*). Increase in lateral step variability may reflect reduced degrees of freedom in the ML plane possibly from stiffness. This can likely cause reduced adaptability to make adjustments during walking. HCs can more easily overcome an obstacle by shifting the foot in the ML plane while patients face difficulties in adjusting their steps. Lateral balance during walking is crucial as humans are more unstable laterally[399]. Similar patterns of change were observed in both lateral step variability and trunk coronal ROM. Both features were decreased by PD in the off-medication state and increased to a level similar to that of controls by medication. Ad hoc analysis showed these two features in fact correlated with each other when all groups, control,

off-medication, and on-medication, were combined (*Figure 3.7*, P<0.001). This shows a link between lateral foot placement and upper body ROM during gait, and that PD patients make smaller lateral corrections during walking compared to controls which is reversed by medication, likely resulting from stiffness and rigidity caused by PD. The variability of lateral step placement has also been a feature of interest for understanding changes in balance during aging[400]. However, since it may have already been affected by aging in the control group, coefficient of variation for lateral step variability was not selected as PD-specific for further examination of levodopa effect.

One contribution to increased gait speed was patients having a larger impact angle at each foot strike. PD patients are known to adopt a fore-foot technique in walking where the first ground contract of the foot during walking is significantly shifted from heel to forefoot[401]. This agrees with our finding that the foot strike angles in patients in the off-medication state were significantly reduced from age-matched controls. This difference was reduced by levodopa where the foot strike angle increased after taking medication. One previous study did not find levodopa to significantly improve the forefoot technique[401]. Reasons for this discrepancy include the small sample size (12 foot-strikes measured for each patient), different means of measurement used (electropodography), and the role of increased attention on a shorter task to increase toe clearance[402] in the previous study. Improved heel strike increases toe clearance, which reduces fall likelihood, and improves stride length[402], in agreement to results from this chapter. This is another supporting evidence for foot strike angle as a reliable marker for symptomatic PD severity, in addition to results from the last chapter indicating foot strike angle as a more sensitive marker for PD progression than the current clinical rating scale.

Variability of foot strike angle is also reduced by medication which we will discuss in the following section.

3.4.2 The effect of Levodopa on gait variability is limited

PD made walking more variable. All of the 19 PD-specific gait variability features selected had a higher variability in the PD group compared to the control group except for circumduction, which had a marginal difference. Although medication was effective in increasing spatial parameters during gait, variability of these features remained higher than controls (*Table 3.3*). Variability of gait cycle features, which represents balance control during gait, like single limb support CV, terminal double support CV, stance CV, and swing CV were also more variable in both ON- and OFF-medication states and did not show a significant improvement after medication was taken. This suggests that although patients walk faster on-medication, the rhythmicity of their walk is not necessarily improved. Although gait speed has been the most used outcome parameter for gait[403, 404], faster walking does not equate to higher quality of walking if someone walks fast with poor balance. Here we see levodopa medication having differential effects on the spatial and temporal aspects of walking, suggesting that at least partially different neural mechanisms are responsible for each aspect[269, 271]. This supports differentiating gait components during gait analysis and clinical assessments to better understand walking disabilities, and as different antiparkinsonian drugs act on different aspects of walking[405], it may lead to more personalised treatment.

One exception to levodopa's lack of effect on gait variability is foot strike angle on the ipsilateral side. PD caused ipsilateral foot strike angle to reduce and become more variable, and both amplitude and variability aspects were improved by levodopa medication to be

comparable to the control group. This makes foot strike angle a sensitive marker for both PD and levodopa effect. Interestingly, contralateral foot strike angle variability was not significantly altered by levodopa. In Chapter 2, progression in foot strike angle was also observed in the contralateral side alone. Further work should focus on characterising bilateral heel-to-toe characteristic of PD gait to distinguish progression and treatment responses.

3.4.3 Postural sway and transition features are not altered by levodopa

PD-specific sway amplitude features were not significantly changed by levodopa. This is in contrast to a previous study showing that levodopa increases postural sway abnormalities through increasing sway area and velocity[71]. This is likely due to the different disease stages examined in the two studies: Rocchi et al.[71] studied the effect of medication in PD patients with 8-21 years of disease duration (UPDRS-III in off-medication state : 21.5-85) while this study looked at patients earlier in the disease state (0.4-7.25 years of duration), with a lesser severity (UPDRS-III in off-medication state : 5-54). Future studies should take disease severity into account when addressing sway abnormalities in PD. Another study[385] using force plate found medication to increase RMS and velocity in the coronal plane in a group of 28 patients (average UPDRS-III was 35.6, disease duration not given).

Similarly, PD-specific transition features for turning and sit-stand were not improved in the medication-ON state. A previous study[168] has found medication to reduce turn duration only in the severe group (defined as Hoehn & Yahr stage 3), indicating that like sway, transition parameters' response to levodopa are different across different levels of disease severity. The same study also suggested medication to only improve turn velocity in patients with dyskinesia[168]. The absence of levodopa effect in these sway and transition features, which

include mean sway velocity, sagittal sway velocity, sway coronal path length, turn duration, turn velocity, sit to stand duration, and stand to sit duration, makes them possible markers of PD state or PD progression that is unmasked by medication effect in the early disease stages. Turn velocity and duration remained unaffected by medication in both the two-minute walk task and the TUG task. This suggests the possibility of implementing the TUG task in place of the 2-min walk for measuring transition features for quicker clinical assessments in the future.

3.4.4 Conclusion

In this chapter, we identified bilateral stride length, gait speed, lateral step variability and foot strike angle as well as ranges of motion of the trunk and the ipsilateral arm to be significantly improved by levodopa. Contrary to our hypothesis, gait rhythm variability, postural sway and transition features were not significantly altered by levodopa in patients in the early disease stages. This result means changes in these features may not be masked by the effect of levodopa, and they are thus promising biomarkers to measure underlying changes in disease state during levodopa treatment. Foot strike angle amplitude and variability were again identified as a promising feature to track disease stage and treatment response in addition to progression and should be further examined in future studies.

Chapter 4 Effect of DBS and Medication on PD Gait Variability

4.1 Introduction

4.1.1 Deep Brain Stimulation and PD gait variability

Disorders of gait are a common feature of PD. They can be classified into two types, which commonly coexist: gait speed and amplitude abnormalities due to bradykinesia and rigidity, and gait rhythm disturbances. Elevated gait variability is associated with an increased falls risk[406, 407].

Overall straight-line gait speed, and the amplitude of parameters including step length, trunk motion and arm swing, are improved by dopaminergic medication[170]. Other parameters such as cadence, turning in place, and aspects of gait initiation are less responsive[405]. Published work is suggestive of decreased gait variability with medication[170, 406], but the literature is sparse. DBS of the STN is an effective treatment for PD, improving rigidity, bradykinesia, and tremor, and reducing motor fluctuations[408, 409]. It usually results in a substantial reduction in levodopa requirements, which may in turn reduce levodopa-induced side effects. STN-DBS improves many of the same gait parameters as medication, producing greater overall speed and stride amplitude, and reduced double limb support time[410, 411]. The benefits are not universal, and a proportion of patients will have worse gait on stimulation[412-414]. A single previous study has suggested that STN-DBS may reduce parkinsonian gait variability[415]. In contrast to the other published studies[170, 406] no effect of medication on variability was found in this latter study.

4.1.2 Cholinergic involvement in gait rhythmicity

There is evidence that gait irregularity in PD may not be a primarily dopaminergic issue. As well as dopaminergic neuronal degeneration in the SNc, there is also degeneration of cholinergic neurons in the pedunculopontine nucleus (PPN)[416-418], an area which has a major role in coordination of gait and posture. Postural and gait disturbance can be produced in animals by purely cholinergic PPN lesions without any dopaminergic degeneration at all[419]. In humans the extent of freezing and falling correlates with the degree of cholinergic PPN neuron loss found at postmortem[419]. Although the evidence is at this point still fairly preliminary, there are indications that acetylcholinesterase inhibitors may make gait more regular and stable: rivastigmine reduces the standard deviation of step time[420], and donepezil reduced fall frequency in PD in one study[421]. There is evidence from LRKK2 mutation carriers that gait variability can already be abnormal as a very early prodromal feature[422]; this is compatible with a role for the PPN, which is believed to be affected as early in the pathological process (Braak stage 3) as the SN[423]. In addition, the cholinergic system is implicated in rapid eye movement sleep behaviour disorder, which may occur as a prodromal feature of PD.

There are reciprocal connections between the PPN and STN which are likely to be activated by STN-DBS. We therefore hypothesized that STN-DBS might improve gait variability by modulating PPN function. Because the proposed mechanism is cholinergic, this is something that dopaminergic medication should not do, and so we would expect measures of gait variability to be affected by DBS but not by medication.

In this study we use a wearable IMU array to accurately quantify multiple gait parameters in PD patients both on and off their treatment (levodopa or STN-DBS), to compare and contrast

the effects of dopaminergic medication and STN-DBS on gait variability. In addition to lower limb gait parameters, the analysis also includes some upper limb and trunk variables, to investigate whether the treatments have consistent effects body wide. Modern systems can measure dozens of gait features, and to restrict the analysis to a reasonable number, we selected those that are prominent in the literature. These included stride length[22, 41, 424, 425], toe out angle[426], foot strike angle[22, 427], single limb support time[425, 428], arm ROM[41, 180, 265, 424], and trunk ROM in sagittal, coronal, and transverse planes[22, 41, 70, 424].

Often in previous studies the variability present within each parameter has been expressed in terms of its standard deviation or coefficient of variation for multiple gait cycles in a testing session (for example the standard deviation of stride length during a 2-minute walk). However, these measures potentially conflate long term variability (e.g. gradual slowing, which is not necessarily pathological) with short term variability (true irregularity). Gradual slowing may reflect the progressive decrement in the amplitude and speed of movement over time that is a hallmark of PD, or it may simply reflect fatigue. We are primarily interested in the short-term variability and have used analysis methodology that aims to separate this out. The technique used, Poincaré analysis, is commonly employed in quantitative analysis of other physiological phenomena, in particular heart rate variability, and it has been used in the analysis of gait in healthy individuals[429].

4.1.3 Objective and aim

The aim of this chapter is to compare and contrast the effect of STN-DBS with medication on gait and posture features. ON- and OFF-medication and DBS groups will first be compared to healthy controls to see whether or not PD treatments can correct PD symptoms. Then, gait

and postural changes from each treatment will be compared to each other to elucidate whether both treatment act on the same aspects of gait and posture. Both dopaminergic medication and STN-DBS can improve the amplitude and speed of gait in PD, but relatively little is known about their comparative effects on gait variability. We hypothesize both treatments to improve speed and amplitude features, and have contrasting effect on variability features.

4.2 Methods

4.2.1 Participants

Participants were recruited through the OxQUIP study at the John Radcliffe Hospital in Oxford. OxQUIP is a large prospective cohort study of neurophysiological biomarkers in parkinsonian patients and is approved by the ethics committee (REC reference 16/SW/0262). Informed consent was obtained from all participants after explaining the procedures to them. The study included adult participants of either sex with normal or corrected-to-normal vision in both eyes. PD participants had a diagnosis of PD according to UK PD brain bank criteria[323] and MDS criteria[430]. Age-matched healthy controls had no history of neurological disease and were often but not always the spouse of a patient. Participants were screened with the MMSE and those with significant cognitive impairment were excluded. All included participants in this study had MMSE scores of at least 25.

Demographic data, clinical characteristics, and rating scores are shown in *Table 4.1*. For simplicity within this chapter, participants without DBS, who are tested ON- and OFF-medication, are referred to as the medication group, and those with DBS, who are tested on and off stimulation, are referred to as the DBS group. DBS patients were tested in the on-medication condition throughout; STN-DBS typically reduces medication requirements by 30-50% and in this case the DBS group had a mean dose in levodopa equivalent units (LEU) that was 42% less than the medication group.

Two groups of PD patients were recruited. A group with bilaterally implanted STN-DBS systems was tested first with stimulation on. The system was then switched off and after 30 minutes the patients were retested with the system remaining off for the duration of testing.

Another group of patients without DBS systems but at a similar disease stage were tested in the medication off and then medication on states. The medication off state is defined as at least 12 hours without dopaminergic medication, and the medication on state is one hour post dose. Age-matched healthy controls were tested once. Dyskinesias were not observed in the patients during testing, but we cannot exclude that subtle dyskinesias were present; this is considered further in the Discussion.

4.2.2 Experimental design and statistical analysis

Testing consisted of gait analysis and MDS-UPDRS-III. Gait data was collected using a body worn network of 6 IMUs (MobilityLab System, APDM) with synchronized sensors positioned on both wrists and both feet, the trunk, and the lumbar area. Each sensor comprised triaxial accelerometers, gyroscopes, and magnetometers. This system has already been used for gait assessment in PD in several studies[183-185]. Patients performed a two-minute walk in a quiet, uncarpeted 15m corridor making turns when necessary. Periods of straight-line walking and turns were segregated by the software and only straight-line walking variables were analysed for this study. Values for each subject are the mean of right and left sided values. There were no missing data within the selected set of features examined.

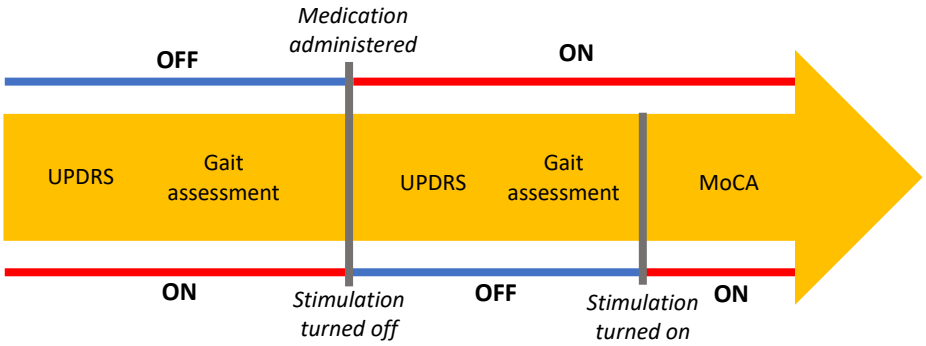


Figure 4.1. Experimental protocol for quantifying levodopa and STN-DBS stimulation effect on gait. OFF: off-medication state, ON: on-medication state; UPDRS: Unified Parkinson's Disease Rating Scale, MoCA: Montreal Cognitive Assessment.

4.2.3 Analysis

Step by step measures of gait parameters were exported from MobilityLab and processed using GraphPad Prism (GraphPad Software, www.graphpad.com). Poincaré analysis was used for quantification of variability during gait. A Poincaré plot, also known as a first return map, is a scatter plot in which each successive value of a given variable (for example stride length) is plotted against the one before, i.e. $x = f(i)$; $y = f(i+1)$. This is shown schematically at the top left of *Figure4.4*. Deviation of points from the line of identity ($y = x$) occurs due to step-to-step variability in the parameter concerned. This short-term variability is quantified using the standard deviation of the distance from the identity line, known as SD1, where:

$$SD1 = \sqrt{\frac{\sum((x-y) - \overline{(x-y)})^2}{2n}}$$

The spread of data points along the identity line represents long term variability, for example due to gradual slowing over the testing session. It is quantified by its standard deviation SD2, where:

$$SD2 = \sqrt{\frac{\sum((x+y) - \overline{(x+y)})^2}{2n}}$$

SD1 and SD2 were calculated for each parameter analysed for each participant in each condition.

Groups were compared using paired *t*-tests where data were normally distributed, and the Wilcoxon signed rank test otherwise. Correction was made for multiple comparisons using the Benjamini-Hochberg method with a false discovery rate of 5%.

4.3 Results

4.3.1 Demographics

Demographic data, clinical characteristics, and rating scores, for both PD patients and the healthy control group are shown in *Table 4.1*. The effects of medication and DBS on gait parameters are depicted in *Figure 4.2* which shows off and on values of each parameter for the two interventions; each pair of points linked by a line represents a single patient. Gait parameters from the healthy controls were used to generate age-matched normative ranges, defined as the central 95% of the range of control values. These are shown in the figures as grey bands; the horizontal dashed lines are control means. *Table 4.2* gives mean values per parameter, group, and condition, and details of the statistical comparison of off/on values.

Table 4.1. Demographics, clinical characteristics, and rating scale scores in both the PD patient and healthy control groups. ID, identification number; PD, Parkinson's disease; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr score; DBS, Deep Brain Stimulation; LEU, levodopa equivalent unit; M, male; F, female. Figures in parentheses are ranges. For the DBS participants, 'ON' and 'OFF' refer to the state of the patient's stimulator system, their medication state not being altered.

ID	Age (yrs)	Gender	PD Duration (yrs)	MDS-UPDRS PART 3 ON	MDS-UPDRS PART 3 OFF	H&Y ON	H&Y OFF	DBS duration (yrs)	LEU (mg)	Medication
DBS01	65	F	18	33	40	3	3	4	1235	Amantadine, Co-beneldopa, Co-careldopa CR, Entacapone/levodopa/carbidopa, Ropinirole
DBS02	65	F	15	29	36	2	2	2	410	Co-beneldopa, Rasagiline, Ropinirole
DBS03	56	M	10	34	93	0	3	1	700	Amantidine, Co-careldopa, Entacapone/levodopa/carbidopa
DBS04	51	M	7	26	38	1	1	3	400	Co-beneldopa
DBS05	54	M	12	36	50	2	3	2	250	Amantadine, Co-careldopa
DBS06	58	M	12	60	72	2	2	5	650	Co-beneldopa, Pramipexole PR
DBS07	56	M	10	37	58	2	2	3	350	Amantadine, Co-careldopa
DBS08	62	M	11	34	55	2	2	3	620	Co-careldopa, Rotigonin
DBS09	57	F	3	40	68	3	3	2	0	None
DBS10	60	F	11	28	38	2	2	2	200	Co-careldopa, Pramipexole PR
DBS11	64	M	9	17	48	2	2	1	435	Co-careldopa, Pramipexole PR, Rasagiline, Opicapone
Stimulation group	58.9±4.4 (51-65)	7M:4F	10.7±3.7 (3-18)	34.0±10.2 (17-60)	54.2±16.9 (36-93)	1.9±0.8 (0-3)	2.3±0.6 (1-3)	2.5±1.1 (1-5)	477±310 (0-1235)	
MED01	62	M	8	18	41	2	2		1564	Co-beneldopa, Co-careldopa, Entacapone, Rasagaline
MED02	69	M	3	17	29	2	2		680	Co-beneldopa, Ropinirole
MED03	63	M	6	27	49	2	2		500	Co-beneldopa, Rasagiline
MED04	63	M	12	26	49	2	2		2000	Co-careldopa, amantadine, rasagiline
MED05	59	M	3	14	39	2	2		948	Co-careldopa, entacapone
MED06	74	M	7	19	43	2	2		940	Cobeneldopa MR, Entacapone/levodopa/carbidopa
MED07	63	F	12	28	65	3	3		1200	Co-beneldopa, Entacapone/levodopa/carbidopa
MED08	70	M	20	39	38	2	2		300	Co-beneldopa
MED09	61	M	7	11	44	2	2		1140	Co-beneldopa, Co-beneldopa CR, Pramipexole, Safinamide
MED10	58	M	16	24	59	2	2		660	Apomorphine pen, Co-beneldopa, Opicapone, Rotigotine, Safinamide
MED11	74	M	8	32	41	2	2		610	Co-careldopa, Rasagiline, Ropinirole XL, Trihexyphenidyl
MED12	65	M	8	27	47	2	2		1340	Co-careldopa, Co-careldopa CR, Opicapone, Ropinirole
MED13	70	M	7	16	41		2		325	Entacapone/levodopa/carbidopa, Rasagiline
MED14	54	F	5	11	42	2	2		1278	Co-careldopa CR, Entacapone/levodopa/varbidopa, Rasagiline, Ropinerole XL
MED15	70	M	13	22	58	2	2		441	Co-beneldopa, Co-beneldopa CR, Entacapone, levodopa/carbidopa
Medication group	65±5.8 (54-74)	13M:2F	9.0±4.6 (3-20)	22±7.7 (11-39)	46±8.9 (29-65)	2.1±0.2 (2-3)	2.1±0.2 (2-3)		928±475 (300-2000)	
Control group	57.9±6.5 (51-80)	19M:23F		3.5±4.2 (0-16)						

4.3.2 Lower limb gait parameters

Both medication and DBS significantly improved stride length (*Fig.4.2A*, medication p = 0.0016, *t*-test; DBS p = 0.019, *t*-test) towards the control mean, while medication further significantly increased gait speed (*Fig.4.2B*, p = 0.0012, *t*-test). Medication and DBS also both had a normalising effect on lower limb angles, significantly increasing the foot strike angle (*Fig.4.2F*, medication p = 0.0062, *t*-test; DBS p = 0.0051, *t*-test) and toe-off angle (*Fig.4.2H*, medication p = 0.0012, *t*-test; DBS p = 0.019, WSRT). There was no significant treatment effect for absolute toe-out angle. The stride time (or gait cycle duration) was not significantly affected by treatment; however, medication did have a significant effect on the standard deviation of stride time (*Fig.4.2J*, p = 0.025, *t*-test).

4.3.3 Axial and upper limb gait parameters

Medication consistently and significantly increased all axial and upper limb ROM parameters, including the arm ROM (*Fig.4.2L*, p = 0.0005, *t*-test), lumbar ROM in the coronal, sagittal, and transverse planes (*Fig.4.2M*, p = 0.0005, *t*-test; p = 0.0002, *t*-test; p = 0.0067, *t*-test), and trunk ROM in the coronal, sagittal, and transverse planes (*Fig.4.2N*, p = 0.0034, WSRT; p = 0.025, WSRT; p = 0.030, *t*-test). No such effect was seen with stimulation except for an increase in lumbar coronal ROM of borderline significance (*Fig.4.2M*, p = 0.036, *t*-test).

Table 4.2. Effect of medication and DBS on gait parameters quantified as mean values per parameter, group, and condition, expressed in parentheses as range and percentage of healthy control mean values. HC, healthy control; DBS, Deep Brain Stimulation; superscript: t, Paired-T test; w, Wilcoxon signed rank test; GCT, gait cycle time; deg, degree; Std, standard deviation; CoV, co-variance; ROM, range of motion.

Parameter	**HC group**	**Medication group**			**DBS group**		
	Mean	**Mean value (Range; % of HC)**		**p-value**	**Mean value (Range; % of HC)**		**p-value**
		off	**on**		**off**	**on**	
Lower limb							
Stride length (m)	1.34	1.04 (0.51-1.5; 77)	1.29 (1.1-1.6; 95)	**0.0016^{t}**	0.964 (0.85-1.5; 72)	1.11 (0.57-1.3; 83)	**0.019^{t}**
Gait Speed (m/s)	1.27	0.964 (0.5-1.5; 76)	1.19 (0.97-1.5; 93)	**0.0012^{t}**	0.895 (0.76-1.4; 71)	1.04 (0.52-1.3; 82)	0.051^{t}
Cadence (steps/min)	116	113 (95-138; 97)	110 (101-115; 95)	0.45^{w}	111 (93-128; 96)	113 (102-124; 97)	0.69^{t}
Stride Time (s)	1.05	1.08 (0.88-1.3; 103)	1.09 (1.02-1.2; 104)	0.80^{w}	1.09 (0.95-1.3; 104)	1.07 (0.97-1.2; 103)	0.70^{w}
Single-Limb Support (%GCT)	40.5	39.1 (31-44; 97)	39.9 (36-43; 98)	0.17^{t}	39.9 (35-46; 98)	40.5 (39-45; 100)	0.20^{t}
Foot Strike Angle (deg)	26.5	13.6 (-0.88-32; 51)	21.5 (18-34; 81)	**0.0062^{t}**	7.72 (1.2-22; 29)	15.4 (1.3-32; 58)	**0.0051^{t}**
Toe-Out Angle (deg)	8.90	8.45 (-8.4-20; 95)	9.15 (-8.7-21; 103)	0.53^{t}	7.15 (-6.1-21; 80)	3.70 (-16-22; 42)	0.34^{t}
Toe-Off Angle (deg)	36.9	32.0 (23-43; 87)	36.7 (32-43; 99)	**0.0012^{t}**	32.5 (26-38; 88)	34.5 (28-39; 93)	**0.024^{t}**
Stride Length Std (m)	0.0400	0.0623 (0.03-0.11; 155)	0.0517 (0.02-0.08; 129)	0.18^{w}	0.0682 (0.02-0.13; 170)	0.0532 (0.035-0.13; 133)	0.19^{t}
Stride Time Std (s)	0.0210	0.035 (0.015-63; 170)	0.0259 (0.12-0.049; 123)	**0.025^{t}**	0.058 (0.017-0.11; 276)	0.0371 (0.014-0.12; 177)	0.083^{w}
Stride Time CoV (%)	1.99	3.56 (1.4-7.3; 179)	2.75 (1.2-6.4; 138)	0.19^{w}	5.33 (1.6-9.7; 267)	3.51 (1.4-10; 176)	0.10^{w}
Axial							
Lumbar coronal ROM	8.09	6.12 (2.7-10; 76)	8.13 (3.3-12; 100)	**0.0005^{t}**	8.10 (4.7-15; 100)	9.65 (3.5-14; 119)	**0.036^{t}**
Lumbar sagittal ROM	5.41	4.94 (2.7-8.6; 91)	6.66 (3.9-10; 123)	**0.0002^{t}**	6.65 (3.9-14; 123)	5.70 (4.0-14; 105)	0.10^{w}
Lumbar transverse ROM	9.40	7.70 (3.4-17; 82)	12.2 (4.9-20; 130)	**0.0067^{t}**	9.39 (3.2-17; 100)	9.65 (3.9-17; 103)	0.80^{t}
Trunk coronal ROM	5.27	4.03 (1.7-6.4; 76)	6.52 (3.9-13; 124)	**0.0034^{w}**	4.87 (2.7-7.5; 92)	5.60 (1.9-8.3; 106)	0.24^{t}
Trunk sagittal ROM	5.05	4.40 (1.9-11; 87)	5.61 (3.3-8.8; 111)	**0.025^{w}**	4.62 (2.5-8.5; 91)	4.75 (3.0-9.4; 94)	0.70^{w}
Trunk transverse ROM	4.38	7.57 (3.8-11; 173)	9.61 (4.9-13; 220)	**0.030^{t}**	8.86 (4.6-13; 202)	9.00 (5.0-14; 205)	0.78^{t}
Upper limb							
Arm ROM (deg)	56.6	23.3 (6.6-67; 41)	49.8 (23-89; 88)	**0.0005^{t}**	26.3 (11-94; 47)	39.8 (8.0-102; 70)	0.41^{w}

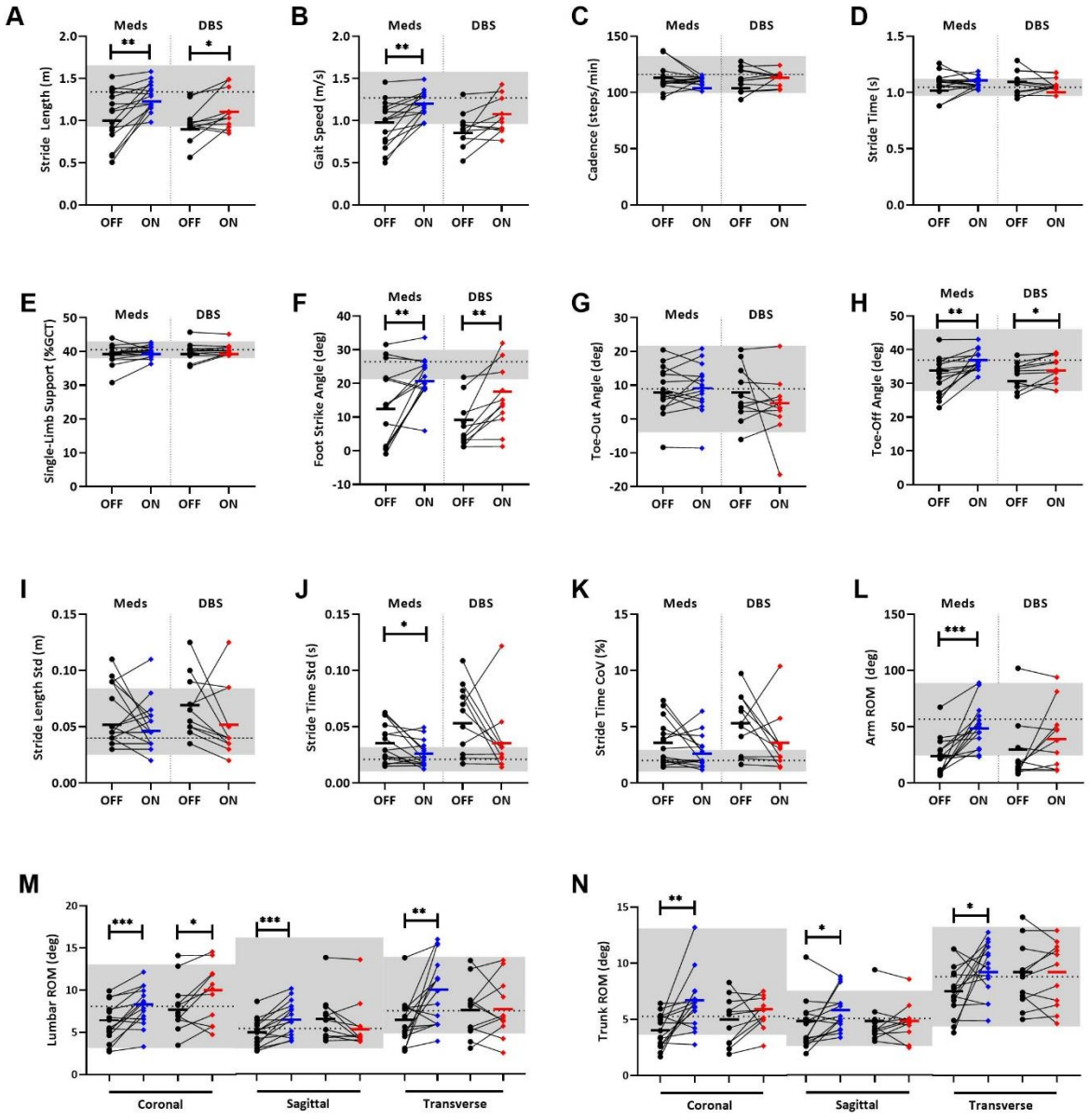


Figure 4.2. Step-by-step analysis of patient stride length under STN-DBS vs medication treatment (example individual participant data shown for 5 medication challenge and 5 DBS participants). Green, right leg; Orange, left leg, Grey, normative range, calculated as the 95% confidence interval of each parameter from the age-matched control group.

4.3.3 Variability in gait parameters

Figure 4.3 shows the step-by-step values of stride length on and off therapy for all participants in the medication and DBS groups. In these examples, some of the medication group patients can be seen to have increased variability on treatment (MED01, MED03, MED05, MED06, MED07, MED11), while DBS patients DBS02, DBS03, DBS05, DBS10, and DBS11 appear to have decreased variability on treatment.

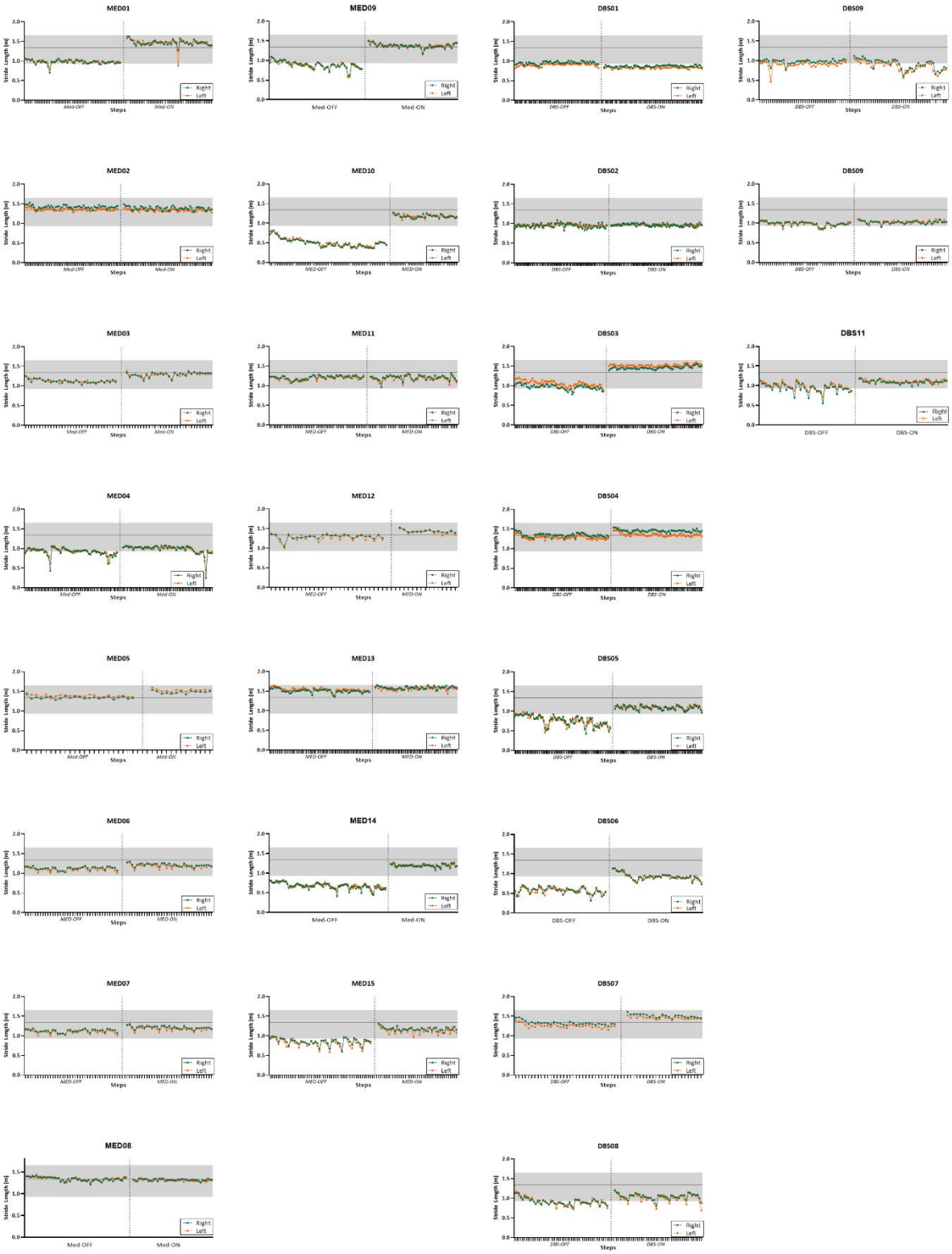


Figure 4.3. Step-by-step fluctuations of stride length under STN-DBS vs medication treatment. Green, right leg; Orange, left leg, Grey, normative range, calculated as the 95% confidence interval of each parameter from the age-matched control group.

To separate long term from short term variability, Poincaré analysis was carried out for each parameter, patient, and treatment condition. As an example, the analysis for toe out variability is shown in *Figure 4.4*. The larger plot at top left shows the principles of Poincaré analysis, with the standard deviation perpendicular to (SD1) and along (SD2) the identity line being calculated separately, and respectively representing short- and long- term variability. Data from a sample of healthy controls is shown in the top two rows. In rows 3-5 data from the medication group is shown; the scatter of points was in many cases greater in the ON-medication condition (blue points) than the OFF-medication condition (black points), signifying an increase in variability. The lower two rows are the DBS group; the points in the ON-DBS condition (red points) were in many cases clustered more tightly than in the OFF-DBS condition (black points), signifying decreased variability.

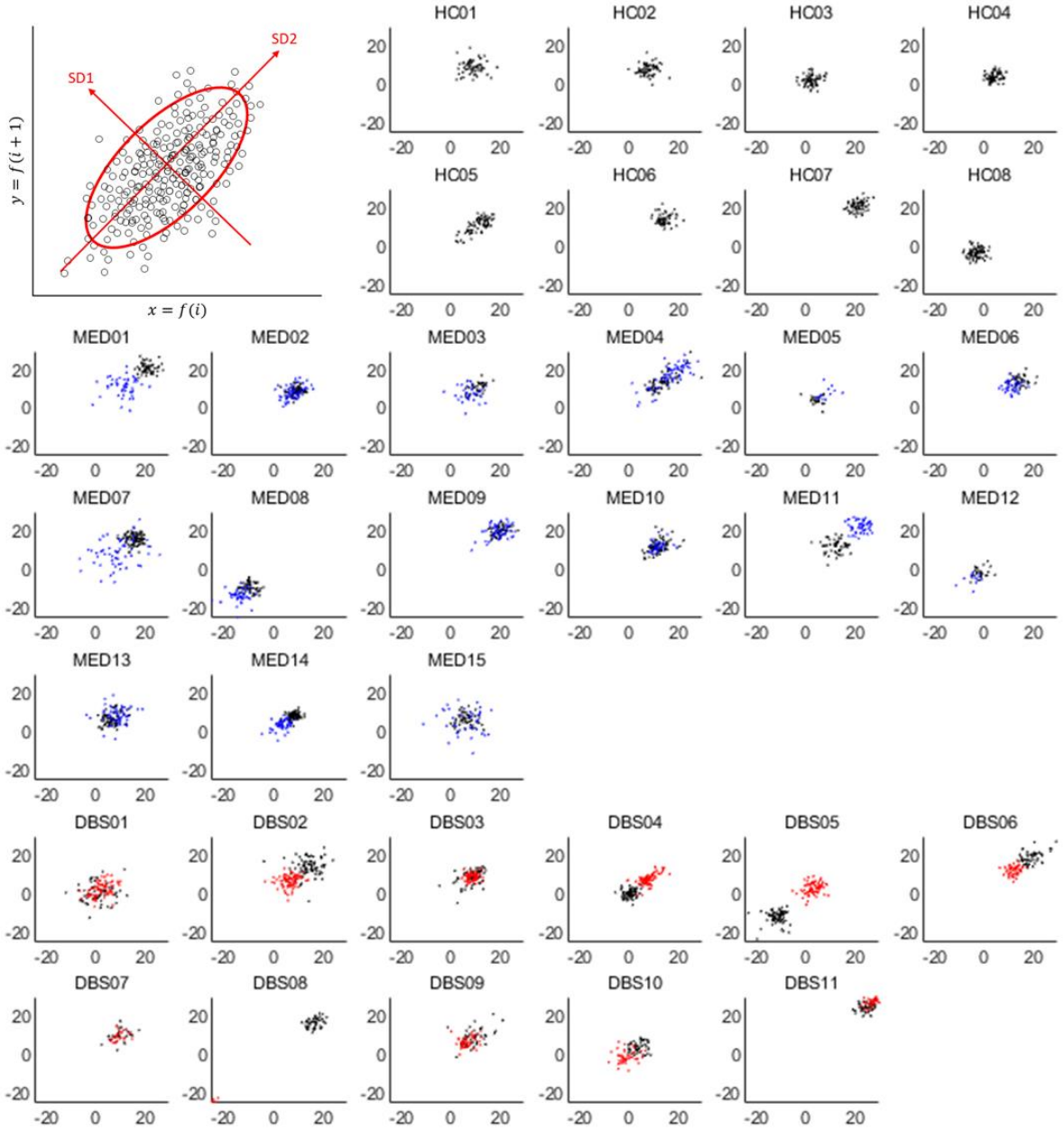


Figure 4.4. Poincaré plots of toe out angle on and off treatment in the STN-DBS and medication groups and the control group. Larger plot at top left shows the principles of Poincaré analysis, with the standard deviation perpendicular to (SD1) and along (SD2) the identity line being calculated separately, and respectively representing short- and long- term variability. The upper two rows of small graphs show data from a sample of the healthy controls. The third to fifth rows are the medication group and sixth and seventh rows are the DBS group. Black, off treatment; Blue, ON-medication; Red, ON-DBS. Axis scale unit in degrees.

Figure 4.5 shows the changes in SD1 (short-term variability) and SD2 (long-term variability) produced by medication or DBS. Each point on each plot represents the difference in on versus off treatment variability for an individual patient. In the lower limbs, medication significantly increased short- and long-term toe out angle variability (*Fig.4.5B*, $p = 0.0015$, WSRT; $p = 0.022$, WSRT), while leaving the other parameters unaffected. In contrast, STN-DBS decreased both short- and long-term toe out angle variability (*Fig.4.5B*, $p = 0.021$, *t*-test; $p = 0.0077$, *t*-test). DBS also decreased short-term variability in stride length (*Fig.4.5A*, $p = 0.049$, *t*-test), toe off angle (*Fig.4.5C*, $p = 0.029$, *t*-test), foot strike angle (*Fig.4.5D*, $p = 0.0029$, WSRT), and single-limb support (*Fig.4.5E*, $p = 0.0020$, WSRT) as well as long-term variability in single-limb support (*Fig.4.5E*, $p = 0.042$, WSRT).

Both SD1 and SD2 for trunk ROM increased significantly with medication in all planes: coronal (*Fig.4.5J*, $p = 0.0086$, WSRT; $p = 0.0004$, WSRT), sagittal (*Fig.4.5K*, $p = 0.0015$, WSRT; $p = 0.026$, WSRT), and transverse (*Fig.4.5L*, $p = 0.030$, *t*-test; $p = 0.026$, WSRT). DBS did not significantly change the variability in any of the measures of body ROM (*Fig.4.5G-L*).

Mean arm ROM variability was increased (in both SD1 and SD2) by medication in 10 out of 15 patients, although the change was not statistically significant. DBS produced no change in arm ROM variability.

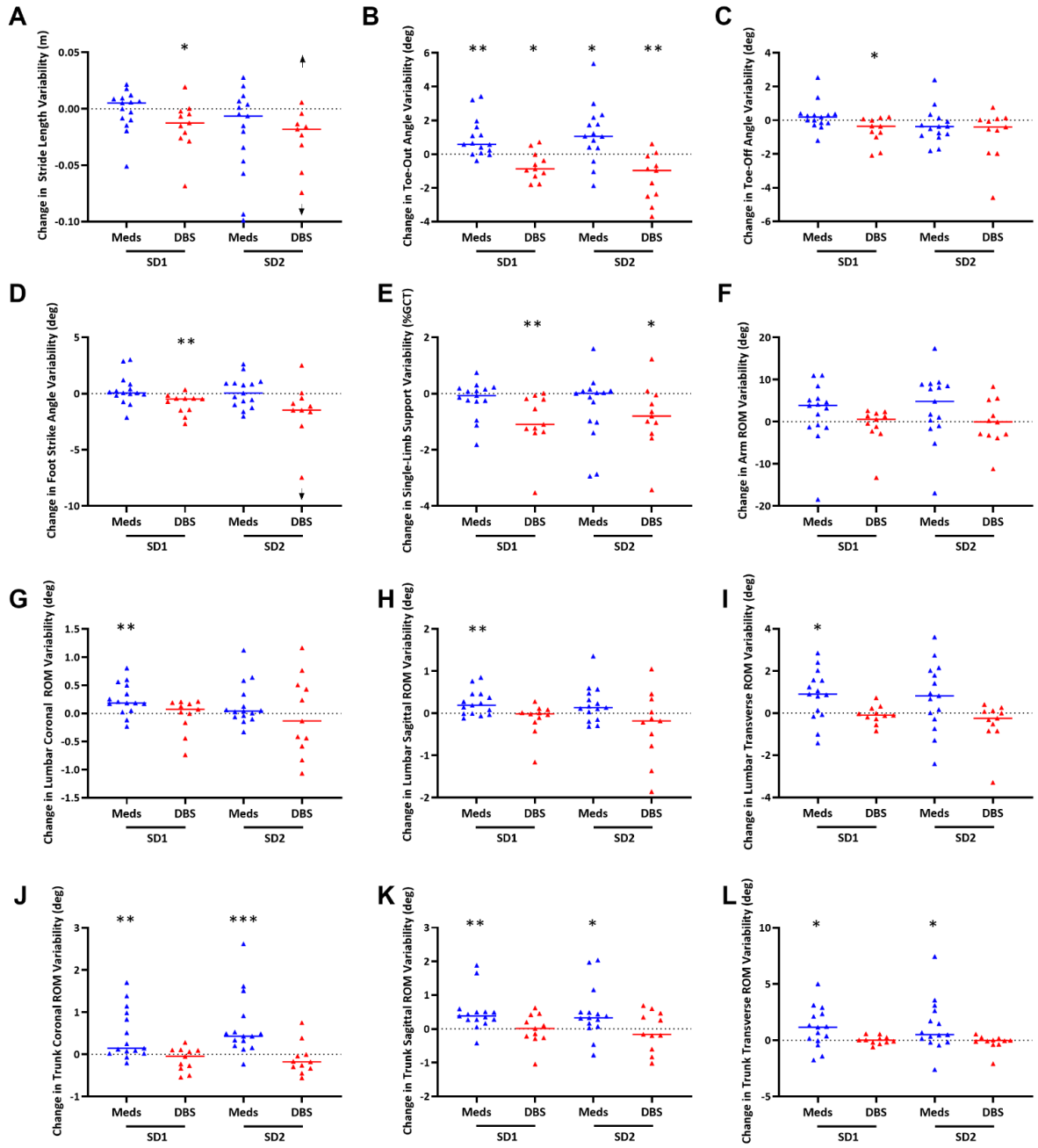


*Figure 4.5. Short-term (SD1) and long-term (SD2) variability changes from STN-DBS or medication effect. Abbreviations: * denotes $p < 0.05$, ** denotes $p < 0.01$, and *** denotes $p < 0.001$. Arrowhead denotes data point out of scale.*

4.4 Discussion

We found that STN-DBS reduced step to step variability in a range of lower limb gait parameters in PD, while dopaminergic medication had no significant effect. The lack of effect of medication is at odds with previous literature[170, 406], while the results of DBS back the conclusion of earlier work[415]. Our findings suggest that STN stimulation, but not dopaminergic medication, modulates circuits that control gait rhythm, and therefore that control of amplitude and rhythm may be separate. This idea is reinforced by the observation that in the DBS group there was a reduction in variability of some gait parameters (such as toe out angle and single limb support) in the absence of any significant systematic change in the amplitude of these parameters.

The disagreement with previous work about the effect of medication on variability may be accounted for by the way in which variability is being measured. Bryant et al[170] used the CV of four gait parameters across the whole walking assessment. Slowing due to bradykinesia/fatigue can contribute to variability on this measure. Medication or DBS would both lessen bradykinesia, therefore either would reduce the overall SD/CV even if the *short-term* variability was not altered at all. Participants DBS05, DBS03, and MED04 in *Figure 4.3* are examples with slowing when off treatment that disappears when on treatment. It is therefore possible that our SD1 is simply measuring a different thing to the CV measure. Interestingly our data for stride length do show a nonsignificant trend to reduced variability in SD2 (long term variability) which would fit with a reduction in bradykinesia.

One previous study looking specifically at single limb support (swing) time variability showed no change in variability with DBS[428]. We found it to be unaffected by medication but clearly

reduced by DBS. The explanation may lie in the specific task used by – stepping in place. This is likely to be qualitatively different in terms of neural control to normal gait with forward movement.

As described in the introduction, there is evidence to suggest that degeneration of cholinergic neurons in the PPN occurs in PD[416-418] and underlies gait rhythm disturbance[419], and this could explain the lack of response to levodopa. We believe that STN-DBS improves Parkinsonian gait regularity by modulating PPN activity. Evidence from PET imaging provides further support for this idea[431]. How might DBS do this? One obvious possibility is activation of glutamatergic neurons projecting from the STN to the PPN, which then excite cholinergic PPN neurons. However, STN to PPN projections are sparse, accounting for some 1% of STN neurons[432]. Alternatively, STN-DBS might activate glutamatergic STN efferents to the GPi and the SNpr, which both project to the PPN and could therefore modulate its activity. However, the GPi and SNpr to PPN connections are both inhibitory. STN stimulation could also directly activate the cholinergic neurons by retrograde stimulation of their PPN-STN projections[432-434], and we believe this is the more likely explanation for our findings.

Cholinergic PPN neurons project very widely, to targets including the SN[433, 435-440], STN[432-434], thalamus[433, 440], pallidum[433, 439-441], striatum[433], SC[439, 442], cerebral cortex[433], and spinal cord. Dual labelling and single neuron tracer studies show that individual cholinergic PPN neurons project to many of these targets through multiple axon collaterals[439, 443]. Antidromic activation of branches in the STN by DBS, will lead to orthodromic activation of all the collaterals, causing widespread activation of PPN targets as if the signals were coming from the PPN itself. Thus, STN-DBS could act to boost cholinergic PPN activity in a wide range of locations including

other parts of the BG, the midbrain locomotor region (MLR), which comprises the PPN itself and adjacent cuneiform nucleus), and spinal locomotor centres. This is illustrated in *Figure 4.6*.

This hypothesis leads to testable predictions. Firstly, we would expect STN-DBS to have cholinergic effects on other nuclei to which the PPN also projects. One such location is the SC[442], which receives projections from both the SNc and the PPN. The SC is a critical structure in the generation of saccadic eye movements, which have been studied extensively in PD patients[319, 444-446], including patients with DBS[8, 447, 448]. In the visually guided prosaccade task, the subject moves their eyes as quickly as possible towards a novel visual target. The prosaccadic latency (PSL), i.e. the time between stimulus presentation and the onset of the saccade, is mildly (7%) prolonged by levodopa[444]. In contrast, injection of the cholinergic agonist nicotine into monkey SC *reduced* PSL by 40%[449], while the strong central anticholinergic drug promethazine increased it[450]. STN-DBS shortens PSL[8, 447, 451, 452], in keeping with a cholinergic, but not a dopaminergic, effect. Furthermore, DBS of the GPi, which also receives cholinergic PPN afferents[441], also shortens PSL to a similar degree[8]. In the case of the STN, the DBS effect could be mediated by driving the excitatory projection to the SNpr, which itself sends an inhibitory projection to the SC. However, the route from the GPi is less obvious. Retrograde activation of the PPN arborisation from either location would provide a unifying explanation for the similar effect on saccades.

Secondly, activating the same cholinergic PPN arborisations from a different location should have a comparable effect on gait regularity. In keeping with this, DBS of the GPi, which is carried out for similar symptoms to STN-DBS, appears to have a similar beneficial effect on

gait[453]. To our knowledge there is no literature examining gait variability in GPi-DBS patients in depth, and we intend to investigate this in future work.

Direct stimulation of the PPN itself might be expected to have a more potent effect, and the PPN has been explored by several groups as a target for DBS[454-461], specifically in the setting of FoG, which could be viewed as an extreme form of rhythm disturbance. FoG is linked to severe PPN degeneration[419]. PPN DBS however will not treat dopaminergic deficits and the group of patients to whom it is theoretically best suited – those with freezing but little upper body parkinsonism – is small. This has led some to experiment with dual STN/PPN stimulation[455]. Importantly, it should be noted that according to our hypothesis STN stimulation is exciting a select group of PPN neurons in a specific way, and the effects of DBS directly to the PPN will be qualitatively as well as quantitatively different to the effects of retrograde activation from STN stimulation. Direct stimulation could activate all cell types in the PPN as well as PPN afferents; there would therefore be effects on multiple other upstream and downstream nuclei that would not be seen with activation from the STN.

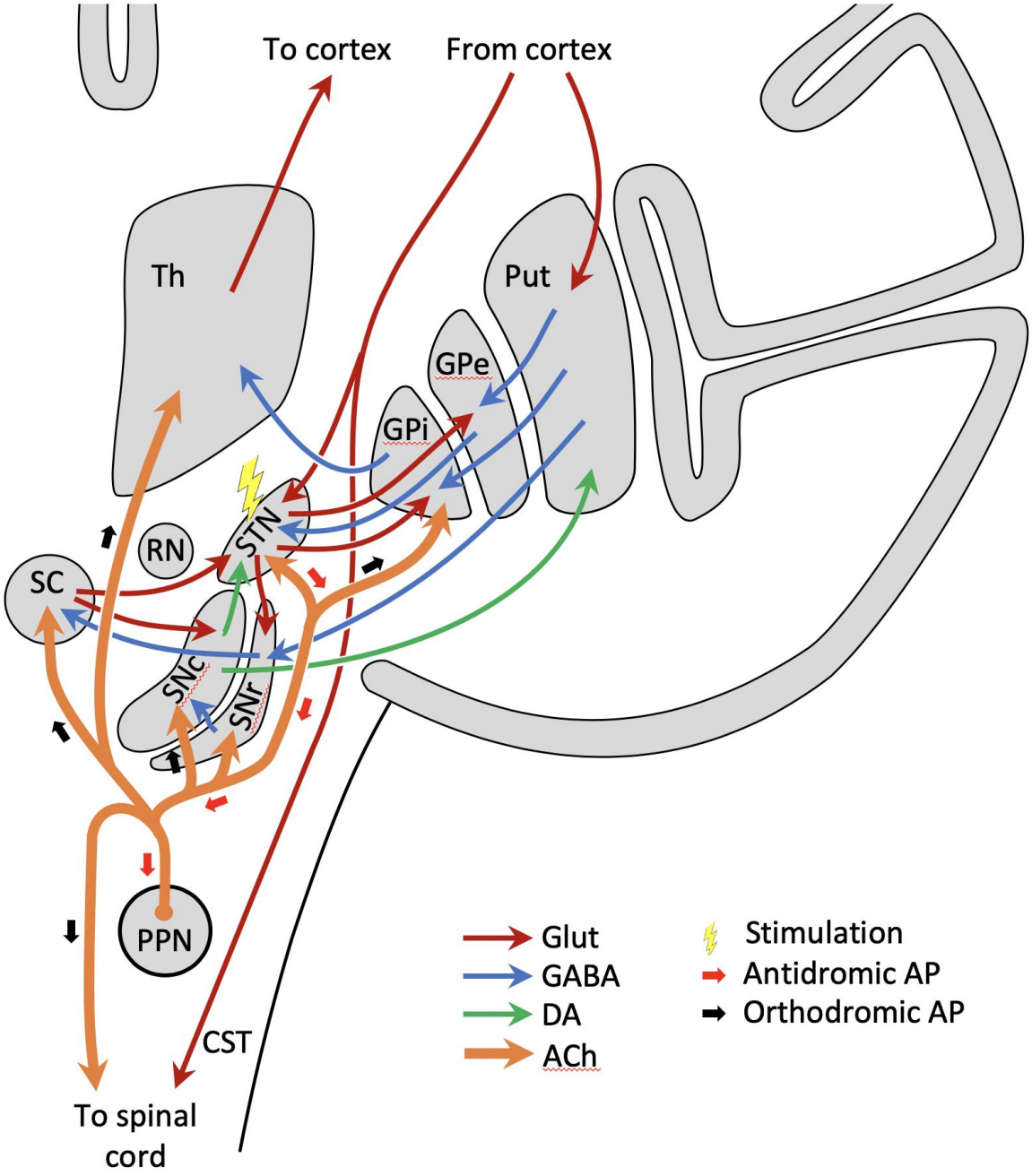


Figure 4.6. The proposed explanation for the effects shown in the study. Stimulation of the subthalamic nucleus (lightning bolt symbol) results in antidromic action potentials (APs) in afferent cholinergic fibres from the PPN (small red arrows). When these reach branch points, they generate orthodromic APs in all of the other collateral branches (small black arrows), activating multiple other PPN projection targets. Th, thalamus; Put, putamen; GPe, globus pallidus externus; GPi, globus pallidus internus; STN, subthalamic nucleus; RN, red nucleus; SNc, substantia nigra pars compacts; SNr, substantia nigra pars reticulata; SC, superior colliculus; PPN, pedunculopontine nucleus; CST, corticospinal tract; Glut, glutamate; GABA, gamma aminobutyric acid; DA, dopamine; ACh, acetyl choline.

4.4.1 Effects on the trunk and upper limbs

The effects of medication and DBS on the trunk and upper limbs were strikingly different: arm swing ROM was significantly increased by medication, while DBS produced a smaller and non-significant change. This may be accounted for by the fact that the DBS patients were in the on-medication state, so that much of the possible improvement in arm ROM had already been made by medication. Variability of trunk ROM were also unaffected by DBS but increased by medication. The same pattern was observed in the lower limbs where lower limb variability was unaffected by medication and reduced by DBS.

The extent to which arm swing is passive, with the arm viewed as a mass damper in the form of a pendulum driven by movement at the shoulder[462-464], or active, produced by muscle activity under control of a central pattern generator[465, 466], has long been debated. It is probably a combination of the two[467], with passive motion complemented by some added muscle activity, possibly to provide small movement corrections that keep arm swing coordinated with the rest of the body. In PD, arm swing is typically asymmetrically reduced, even in an early phase of the disease, and exhibits an altered phase relationship with lower limb movement. Lower limb bradykinesia in PD may lessen shoulder movement and thus pendulum drive, and increased damping due to parkinsonian rigidity will reduce arm swing amplitude and alter its phase relationship with lower limb movements. The changes in arm swing might also be viewed as evidence for dysfunction in a putative pattern generator for upper limb motion. The fact that medication produces a greater increase in arm ROM than DBS, despite DBS being highly effective in alleviating rigidity, might further suggest that, unlike lower limb gait rhythm, arm swing is under the control of a pattern generator that is DA dependent. There is an interesting parallel with swimming in PD, which is affected both by

bradykinesia and impaired interlimb coordination: levodopa appears to improve the former, but not the latter[468].

The trend to increased arm swing variability we observed with medication seems at odds with this as it would suggest that the function of such a pattern generator was more, rather than less, impaired with the addition of exogenous levodopa. A possible explanation for the increase in variability with medication would be the induction of dyskinesias. Overt dyskinesias were not observed in the patients during testing; nevertheless, we cannot be certain that subtle dyskinesias were not present, and if present these would likely appear in the sensor data as increased movement variability.

Another interpretation is also possible: that the increased range and variability of arm movements with medication is simply the result of a reduction in damping of arm movement together with higher amplitude and more irregular pendulum drive at the shoulder, due to higher levels of gait variability and consequently higher range and irregularity of trunk movements. This would produce the concomitant increases in amplitude and irregularity of arm swing. The absence of significant change in most of the measures of range and irregularity of arm and trunk movement resulting from DBS may then simply be a consequence of the reduction it produces in lower limb parameter variability.

Measuring gait variability has become much easier in recent years with the proliferation of wearable sensors[136] that are replacing motion detection camera systems, video recording analysis, and force sensitive mats in many gait laboratories. While studies conducted previously often analysed only a few measures, modern systems can potentially report on in

excess of 100 items. This presents significant issues with regard to multiple comparisons, particularly with small datasets as is typical of DBS studies. Which of these variables are the most clinically relevant is an important and unexplored question. Here we restricted our analysis to a small subset, selected on the basis of prevalence in the literature.

It is noteworthy that many of the MDS-UPDRS-III items include amplitude, speed, and variability in the same question. We believe that with gait, the segregation of amplitude and rhythm is clear; it is an open question as to whether that also applies to other movements, for example finger tapping. IMU systems should be able to separate these features out and answer this question.

4.4.2 Study limitations

DBS patients in this study were on their medication throughout. Some of the effects of DBS on absolute values of gait parameters may have been different in magnitude if testing had been in the off-medication state. For example, the relatively small increase in arm ROM with DBS may have been because much of the possible improvement had already been made by medication; the lack of significant increase in arm ROM with DBS may therefore be a false negative finding. In addition, because the on- and off-DBS conditions were tested sequentially, the effect of medication may also have been slightly different in the two states. The sequence of testing within each group was not randomized and on-medication was tested after off-medication, while off-DBS was tested after on-DBS, and it is therefore possible that effects such as fatigue may have played a role. Nevertheless, the changes in *variability* are clear and differ not just quantitatively but qualitatively between the groups. We therefore feel that it is unlikely that these are confounded by medication state.

Data from the two sides of the body were combined for analysis here, but PD is characteristically asymmetrical. While the principal qualitative conclusions of this study are unlikely to be affected by this, it would be of interest in future to compare quantitatively the effects of treatment on variability on the most affected and least affected sides.

The principal use of Poincare analysis in medical research has been in the analysis of heart rate variability. Significant heart rate variability is normal, and a lack of variability is pathological. In this study, we are making the opposite assumption, i.e. that a reduction in variability is a good thing. Increased gait variability is certainly associated with PD, and with falls. We must acknowledge however that we do not have direct evidence that the variability is causative of falls, and that reducing the variability will by itself reduce falls. Lengthy periods of passive monitoring will be needed to investigate this association, complemented by the use of tools such as the Activities-specific Balance Confidence (ABC)[469] or Falls Efficacy Scales (FES)[470]. Only then will we know if the difference in the effect of DBS and medication on gait variability is large enough to be clinically important. The type of system we have used here lends itself well to passive monitoring of falls and gait variability, and it is an issue that will be pursued in future work.

4.4.3 Conclusion

PD and DBS-specific parameters were identified in this chapter. Gait parameters sensitive to PD and DBS include stride length, foot strike angle, toe off angle, turn angle and velocity, path length, frequency dispersion, and jerk. Parameters sensitive to PD but not DBS include arm ROM, sway mean velocity, RMS sway, range, and the 95% ellipse axis radius. We also found

that medication increases upper body variability during gait, while DBS reduces step to step variability in the lower body and proposed the retrograde activation of the cholinergic system via the PPN to be the explanation for this finding.

Chapter 5 Time Perception in PD

5.1 Introduction

5.1.1 Time perception in PD

Cognitive deficits are common in PD and range from mild cognitive impairment to dementia, often dramatically reducing quality of life[471]. Neurodegenerative diseases such as PD are often diagnosed using subjective questionnaires[472] based on motor symptoms, as no diagnostic blood test or imaging finding precisely correlates with pathological presence. However, like motor symptoms, cognitive symptoms can be measured and used as metrics of comparison[205]. Consequently, accurate measurements of the non-motor, cognitive symptoms are essential when assessing the progression of disease, the benefits of current treatments and the efficacy of candidate treatments.

Physiological models suggest that attention and memory are predicated on the brain's ability to perceive the sense of time[473]. An impairment in this neural ability[474] can manifest as mild or severe cognitive impairment[475]. The perception of time can be defined as a neural process in the same manner as the perception of taste and smell. However, unlike taste and smell perception that uses specific chemoreceptors, neural process for time perception relies on complex neural pathways[476] in which the BG plays an important role[477].

The BG has been hypothesised to act as a temporal pacemaker[478] regulated by DA to allow us to perceive time[479]. A hallmark feature of PD[480] is the progressive degeneration of dopaminergic neurons in the SN pars compacta of the BG. A loss of DA manifests as characteristic motor symptoms such as tremors, fluctuations in gait, and rigidity. Studies focusing on patients with diseases that affect dopaminergic pathways such as PD[195], HD[223],

and schizophrenia[224] all show impaired time processing. In addition to affecting motor symptoms, DA deficiency in PD may also underlie non-motor symptoms. Altered time-keeping function may also contribute to disrupted gait rhythmicity, leading to problems such as increased fall risk and FOG which happen in the later stages of PD. DA alters subjective time perceived in the seconds to minutes range in both animals and humans[214], and dopamine-antagonists' receptor affinity is known to negatively correlate with perceived duration[216, 217]. Perception has been shown to be improved or worsened by activation or deactivation of dopaminergic neurons respectively[220]. These systems are connected through the frontal-striatal loop and play an interactive role in duration discrimination of time intervals. In addition to regulating the speed of the internal clock, DA also modulates attentional processing of temporal information[481]. The involvement of the frontal cortex, active in working memory and decision making, in the BG dopaminergic circuit makes it difficult to differentiate whether abnormalities in time perception result from a core timing or global cognitive impairment[482].

The circuitry involved in time perception relies on a host of neural networks[483] involving the BG, hippocampus, parietal and insular cortices, and cerebellum. Degenerative damage to these networks may give rise to specific time perception phenotypes. In fact, the symptomatic variability of PD phenotypes is also present in time perception where two groups with increased or normal variability was found within a group of PD patients[484].

5.1.2 Models for interval time perception

Theoretical models for the mechanisms behind interval timing, the perception and behavioural control with respect to time in the seconds to minutes range, have been proposed to involve neural oscillators[485], sustained neural activation[486-488], network dynamics[489] or switching among

behavioural states[490]. Of these, the internal clock model (or pacemaker-accumulator model) proposes that a linear metric of time is integrated by an accumulator counting action potentials from neurons oscillating at fixed rate[248]. However, this model does not take into the account that sub and supra second time perception depend on distinct mechanisms and systems. The state-dependent networks model proposes time-dependent changes in the state of neural networks, instead of an interval clock, to keep track of time. It is based on the neuronal property where synaptic strength can increase as function of the amount of time elapsed since the last action potential[491, 492]. Another model suggests change in firing rate of neuronal populations encode time in this time range[493] and underlie the ability of the cerebellum to generate precisely timed motor responses[494]. Stimulus triggers change in synaptic efficacy through short-term synaptic plasticity of both excitatory and inhibitory synapses to tune neurons to fire in response to specific intervals. This is called the striatal beat-frequency model[495], where striatal MSNs detect patterns of cortical oscillation that represent stimuli. The MSNs receive large projections from the cortex and thalamus, each with 10-30 thousand dendritic spines[496]. There are much more PFC projections to the BG than the other way around. They have a low discharge rate and high threshold. The MSN integrates tonic discharge signals from the frontal cortex and unloads at specific moments to trigger working memory update through disinhibiting the thalamus via GPi. Detection and integration of cortical information is modulated by dopaminergic afferents of the SNc that synapses onto MSN cell bodies. In 6-hydroxydopamine (OHDA)-lesioned rats MSN neurons shows higher firing probability[497] leading to increased cortex and STN coupling[498].

Beta-oscillatory signals in the striatal beat-frequency model reflect the integrity of time-keeping functions[499], which is impaired by PD and modulated by BG circuits through

dopamine[500-502]. Beta coupling within and between functionally interconnected nodes in the cortico-thalamic-BG circuit disrupts temporal coordination of dynamic motor output impairing motor function[503-506]. PD patients with dopamine-depleted circuitries are found to have pathologically enhanced cortical-BG oscillation in the beta range (13-30Hz)[507, 508]. The degree of increased beta oscillation in the STN correlates with drug response to DA medications but not with baseline motor deficits[509]. Exogenous STN stimulation at the beta range (10-20Hz) cause akinesia and bradykinesia[510-512] and stimulation inducing low-frequency oscillation generate tremor and pathological oscillation[513]. Amplified beta oscillation in PD is likely from a delayed consequence of chronic DA depletion rather than acute absence of DA receptor stimulation[509], since synchronised activity appears after the first manifestation of PD motor symptoms in 1-methyl-4-phenol-2,3,6-tetrahydropyridine (MPTP) monkeys[514] and 6-OHDA rats[508] under gradual PD induction protocols.

DA depletion also increases uncertainties in time estimation ability of the BG[515] and DA antagonists decelerate subjective clock speed in proportion to their receptor affinity[217, 516]. MPTP monkeys demonstrate enhanced synchrony in the neurons in the primary motor cortex[517]. Although it is evident that beta oscillation is associated with PD, beta oscillation on its own, is not sufficient to develop Parkinsonian rigidity and akinesia[518].

5.1.3 Distinct neural timing systems based on duration

It is thought that distinct groups of striatal neurons regulate motor response and temporal coding in the striatum[206] and detect coincidental activation of the thalamo-cortico-striatal circuits to code patterns for temporal coding. Timing can also be separated into the automatic system (temporal pattern generators motor sequence learning, etc) and the cognitively

controlled system (for memory and attention), each controlled by distinct neural pathways[229, 235]. Automatic timing system oversees discontinuous timing in the sub seconds range and involves the cerebellum interacting with the SMA, primary motor cortex and primary somatosensory cortex. Continuous events that require attention are controlled by the cognitively controlled timing system which involves the BG, DLPFC, intraparietal sulcus and premotor cortex. These events usually involve the striatum and SN projecting to the PFC and require a higher cognitive level where time intervals are kept in memory.

Time perception in the sub seconds, durations of less than one second, and supra seconds, durations of more than one second, range seem to involve different parts of the brain through distinct, but not mutually exclusive, neural networks. Its underlying mechanisms might not be completely independent of each other[519] and share common mechanisms[229, 235]. Based on the interval length, the automatic timing system and the cognitively controlled timing system are proposed to be dissociated and work in parallel[520]. Temporal processing of intervals longer than 500ms is cognitively mediated and could be influenced by concurrent cognitive processing while that of shorter intervals is more perceptual in nature and inaccessible to cognitive control[521, 522].

5.1.4 Time perception assessment

Accurate estimation of time is crucial in daily activities and the ability to process time includes a wide range of intervals from milliseconds to days and seasons[206]. Timing in the millisecond-to-minutes range is crucial to many forms of cognitive processing[523] and studies have hypothesized different interval spans to involve different processes: 100 ms to around 1.3 s[524-526], 3 s[527], 7 s[528], or longer. Discrimination of intervals longer than 1.3 s is known to be more

difficult[248, 529] and require more cognitive capacity[526]. For this reason, interval durations of both shorter and longer than 1.3 s were selected for this study.

Temporal processing can be investigated through either prospective or retrospective paradigms[530]. Participants evaluate time durations with advance knowledge of doing so in prospective paradigms, and do not have prior notice of time judgement requirement in the retrospective paradigm. These two paradigms involve distinct cognitive processes with the former encoding temporal information as an integral part of the experience of the time period and the latter encoding incidentally. Methods in the prospective paradigm include time production where a participant is asked to produce a specific interval duration (such as two seconds); verbal estimation task where the participant translates the subjective stimuli duration into clock units; time reproduction where participants are asked to reproduce the target duration of the stimuli interval previously presented; and duration comparison where participants are asked to compare two stimuli intervals. Many different tests have been used to examine time perception[525, 531-533], but this chapter will focus on duration discrimination under the prospective paradigm because we are more interested in rhythm perception (and production in walking) than interval timing.

In addition to the type of test and temporal interval tested, the type of stimuli is also important in designing a time perception experiment. It is known that time perception for the auditory modality is more precise compared to the visual modality[525, 534, 535], and this superiority has been postulated to be caused by the automaticity of temporal processing in audition[482]. The presentation of temporal intervals, whether the temporal intervals are "filled" with one continuous stimuli between onset and offset or "empty" with a silent duration without any

stimuli, can also affect temporal performance[482]. "Filled" intervals were chosen for this particular study because it provided a straightforward command that requires the least about of time (as opposed to repeated intervals for "empty" intervals). To avoid any "migration effect"[195, 536] that is frequently observed in PD where short intervals are over-produced and long intervals are under-produced when presented together[537], each participant was assigned the same interval (either subseconds or seconds) for the two stimuli modalities tested.

In interval comparison tests, the order that the intervals are successively presented includes a time-order error[538, 539]. When the standard interval is constantly presented first, better discrimination performance is observed compared to when the comparison duration is presented before the standard interval[519, 540-542]. The time-order error causes the second duration to appear longer than the first for short durations and the opposite for long durations (over 50 s)[543].The standard-comparison order is used throughout the task in this chapter for consistency.

5.1.5 Objective and aim

PD is known to affect parts of the brain that are thought to be involved in perceiving the passage of time, but the nature and degree of any actual time perception problems that result is not well understood. This chapter aims to measure differences in time perception, using both auditory and visual stimuli, between patients with PD and healthy controls. We first measure whether time perception sensitivity to auditory and visual stimuli is different in sub-second- and second-time intervals. Then, perceptive error under each condition will be quantified to elucidate any pathological over- or under-estimation in time duration. Additionally, response time in each trial will be used to find whether PD alters intra-individual

response variability. We hypothesize PD participants will have worse sensitivity in the seconds duration and not the subseconds duration, and larger error in all conditions.

Though initially designed as an in-person study, because of the outbreak of a global pandemic, the experiment was adapted into an online-only, virtual study. This adaptation provided a unique opportunity to enrol a larger number of international participants and use this study to evaluate the feasibility of future virtual studies focused on cognitive impairment. To our knowledge this is the only time perception study, focusing on PD, which measures the differences in perception using both auditory and visual stimuli. The cohort involved is the largest to date, comprising over 800 participants.

5.2 Methods

The protocol was approved by the University of Oxford Medical Sciences Division Research Ethics Committee (R64730/RE001).

5.2.1 Participants

Participants were recruited to PD and HC groups. Participants in the PD group had an established diagnosis of PD with an age at disease onset of over 50 years. Participants with any non-PD neurological conditions, conditions affecting hearing or vision, or those that received DBS surgery were excluded from the study. Participants who did not complete the entire study within a two-hour limit were also excluded from data analysis to ensure the consistency of testing environment and conditions.

We calculated the minimum sample size needed for the study using the G*Power software[544], selecting a medium effect size of 0.40 with 90% power at a significance level of $p < 0.05$, assuming normally distributed populations with equal variance. A total of 113 subjects for each group were determined to be necessary for analysis using a Wilcoxon-Mann Whitney test. As participants were randomised to complete tests with one of two different time intervals, a total of 226 participants were required for each of the PD and HC groups. PD patients were recruited through various Parkinson's associations worldwide and healthy controls above the age of 50 were recruited using Prolific (www.prolific.co). Participants were reimbursed in line with Prolific's recommended rates (£7.5/hr) and provided informed consent before being allowed to proceed to the study. Recruitment proved to be straightforward, and this minimum was easily exceeded.

5.2.2 Stimuli and procedure

We tested participants' time perception providing them with both visual and auditory stimuli. The visual stimulus was a clock figure displayed on a screen, of a design inspired by Benjamin Libet's seminal time perception experiment[545]. The design is included in supplementary material. The auditory stimulus consisted of sinusoidal tones at 440 Hz generated using MATLAB R2019a.

The tasks were completed online using participants' own devices, including smartphones, tablet computers, laptops, and desktops. The study was hosted on the Gorilla platform[546] (www.gorilla.sc) and all tasks were implemented in JavaScript. All participants first completed a questionnaire collecting information on age, gender, duration of PD, other medical conditions, and current medications.

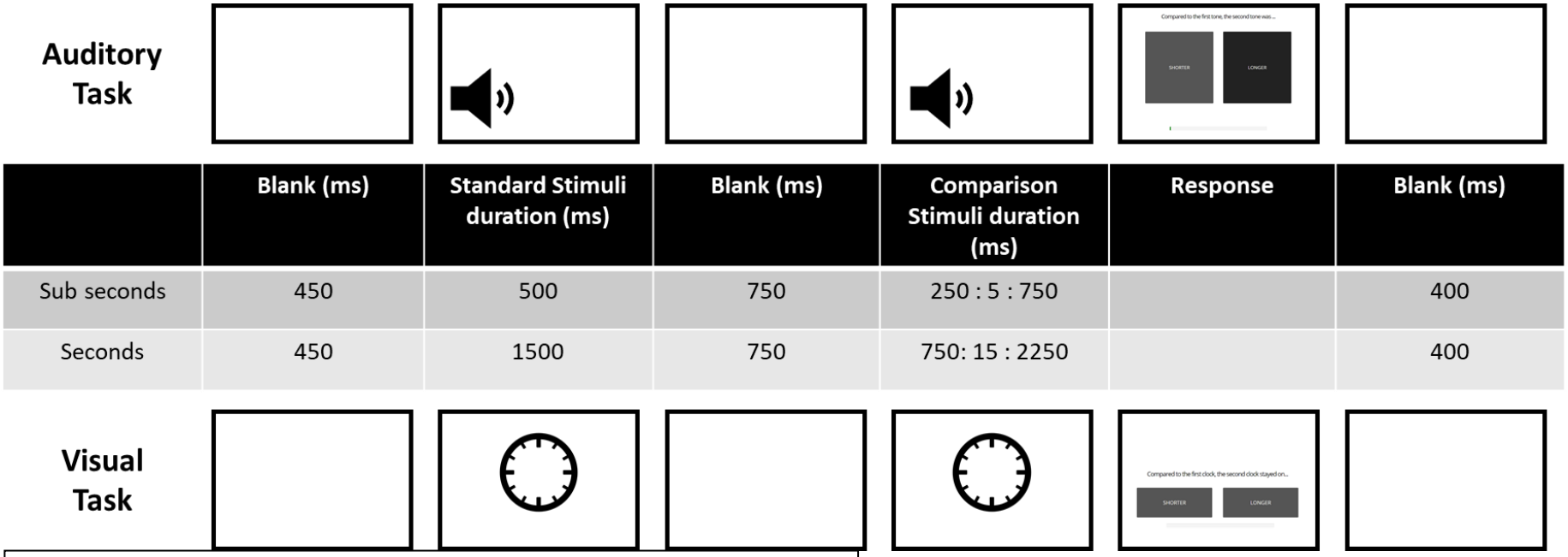
Within each group (PD or HC), participants were then randomly assigned to one of two subgroups. One subgroup, referred to as the 'subseconds' group, were tested using stimuli with a reference duration of 500 ms for both visual and audio tasks. The other subgroup, referred to as the 'seconds' group, were tested using stimuli with a reference duration of 1500 ms for both visual and audio tasks. For each participant, the order of the two tasks (visual then audio or vice versa) was randomised. The auditory task was preceded by a test audio clip and instruction to participants to adjust their devices' audio levels so that they could hear the audio clip clearly.

Both visual and audio tasks started with two practice trials to familiarise the participant with the task and their response method (keyboard or touch screen response), followed by up to

100 actual trials. Each trial began with a blank screen for 750 ms, followed by a standard stimulus (auditory: tone or visual: flashing clock) of fixed duration (500 ms for the subseconds group and 1500 ms for the seconds group), then another blank screen for 750ms, followed by a comparison stimulus of the same modality, with a duration that could be longer or shorter than the standard stimulus. Participants were asked to respond by indicating whether the second stimulus duration was longer or shorter than the standard stimulus duration.

There were 100 possible comparison stimulus durations ranging from 0.5 to 1.5 times the standard stimulus duration with increments of 1% of the standard stimulus duration, and the standard duration was not re-used (i.e., for the subseconds group the comparison stimulus durations ranged from 250ms to 750ms with 5ms increments excluding 500ms, and for the seconds group the comparison stimulus durations ranged from 750ms to 2250ms with 15ms increments excluding 1500ms). Comparison stimulus durations were sampled randomly without replacement from the pool of possible values. The number of trials (100) was decided by pilot data collected on both PD and HC to achieve lowest inter-individual variability while preventing fatigue.

The maximum length of each task was 100 trials but to secure against fatigue in participants, a routine was incorporated to terminate the task early if two requirements were met: a minimum of 55 trials had been conducted, and the rolling 10-point coefficient of variation of estimates of the logistic regression slope was less than 2% for 5 consecutive trials. Pseudocode for the early stopping algorithm can be found in the appendix (*Supplementary Figure 5.6*).



	Blank (ms)	Standard Stimuli duration (ms)	Blank (ms)	Comparison Stimuli duration (ms)	Response	Blank (ms)
Sub seconds	450	500	750	250 : 5 : 750		400
Seconds	450	1500	750	750: 15 : 2250		400

Figure 5.1. Experimental set up of the auditory and visual tasks.

5.2.3 Data Analysis

Due to the nature of the task, all trials that fulfilled the inclusion criteria (*5.2.*1) did not have missing data (the study will not move on to the next trial if a response was not recorded). For each trial, a response of "shorter" was assigned the value 0 and "longer" the value 1. The responses were then plotted against the duration of the comparison stimulus and fitted with a logistic regression curve. The slope of the curve at its 50% point (yellow cross in *Figure 5.2*) is a measure of the sensitivity of time perception (a higher value implying a sharper cut-off between 'shorter' and 'longer'). The left or right shift of its 50% point from the standard duration quantifies any systematic error of comparison of the duration of first (standard) and second (comparison) stimuli. It is calculated as the proportional shift away from the standard duration.

The Logistic Regression model equation was:

$$P = \frac{1}{1 + e^{-(\beta_0 + \beta_1 * X)}} \quad (1)$$

Where P is the probability of giving a response of "longer", X is the duration of the comparison stimulus, e is the base of the natural logarithm, β_0 varies with the shift of the curve, and β_1 dictates the slope of the curve (rate of probability change per unit X). From the two coefficients of the logistic regression model β_0 and β_1, sensitivity and error of time perception are calculated as:

$$Sensitivity = \ln \beta_1 \quad (2)$$

$$Error = \left(-\frac{\beta_0}{\beta_1} - standard\right) / standard \quad (3)$$

Where standard is the duration of the comparison stimuli in ms.

Because the distribution of logistic regression slopes was highly positively skewed in both PD and control groups, a logarithmic transformation was performed to permit parametric analysis. To ensure participants understood the task, and to only include trials where an active discrimination was made, tasks with negative slopes were excluded as well as participants with invalid or missing audio or visual task data. In line with established procedures in reaction time research[547], all trials with response times shorter than 250ms or longer than three standard deviations above the group mean were removed from analysis. Response time is defined as the time between the end of last stimulus to the detected response from the participant in milliseconds.

Participants were randomized to either the seconds or subseconds group and two logistic regression models were fitted for each participant, one for each of the audio and the visual task. Mann-Whitney U tests were used to compare the sensitivity and error between the PD and HC groups for each combination of reference duration (seconds vs subseconds) and stimulus modality (auditory vs visual).

Intraindividual variability (IIV) of reaction time has been speculated as a cognitive predictor of mild cognitive disorders[548, 549]. Intraindividual standard deviation is one of the simplest indices that can be computed to quantify IIV, however, this does not consider the systematic time-related effects or the different comparison durations on the response time. To factor out the effects associated with comparison duration, residual scores from linear regression of response time against comparison duration were taken and converted to T scores by trials

before the standard deviation of the *T* scores were taken as IIV uncontaminated by systematic effects and confounding factors. Bonferroni correction was used to correct for multiple comparisons.

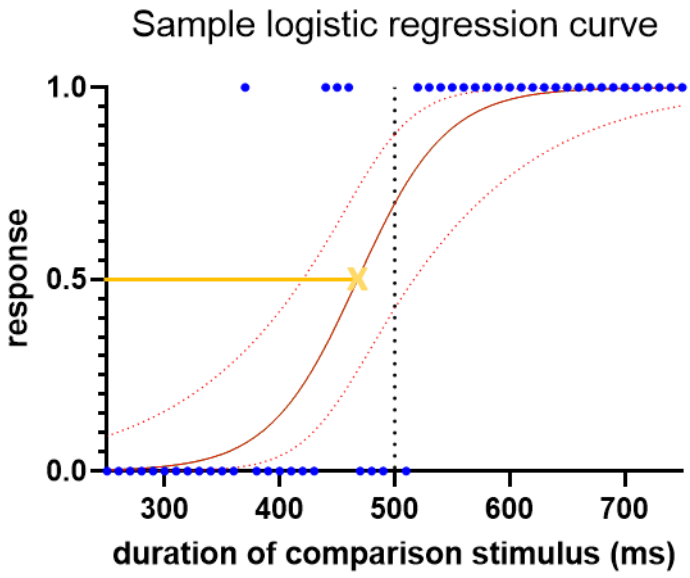


Figure 5.2. Sample logistic regression curve for the subseconds interval, demonstrating the spread of the responses, 0 indicates "shorter" and 1 indicates "longer". The slope of the curve, and the shift of its 50% point from the standard duration (500ms), are used to quantify the sensitivity and error of time perception respectively. The difference threshold is marked by the yellow cross where a difference in stimuli durations were distinguished 50% of the time.

5.3 Results

5.3.1 Demographics

320 patients with self-identified PD were recruited through a multitude of Parkinson's associations worldwide and 620 healthy controls above the age of 50 were recruited using Prolific (www.prolific.co). 15 patients and 51 controls were excluded from analysis due to not understanding the task, not completing both auditory and visual tasks, or health conditions. Of the 292 patients and 569 controls included for analysis, the mean age in the two groups was similar (66.5 years for PD vs 65.8 years for HC). The groups did not differ significantly in gender (54% female in the PD group vs 60% female in HC; $p = 0.10$, two sample proportion z-test). Within the PD group, the average disease duration was 6.5 years, with participants ranging from newly diagnosed to up to 28 years. Most PD patients were taking levodopa (86%) while some were taking alternative PD medications (10%) or no medication at all (3%). Self-reported time since last medication ranged from 0-24 hours with a median of 2.5 hours. The majority of participants were white (89% in PD group and 94% in HC) and used a computer as opposed to a phone or tablet to complete the task (77% in PD and 84% in HC). Windows was the most common operating system used in this cohort of participants (58%), followed by macOS (19%).

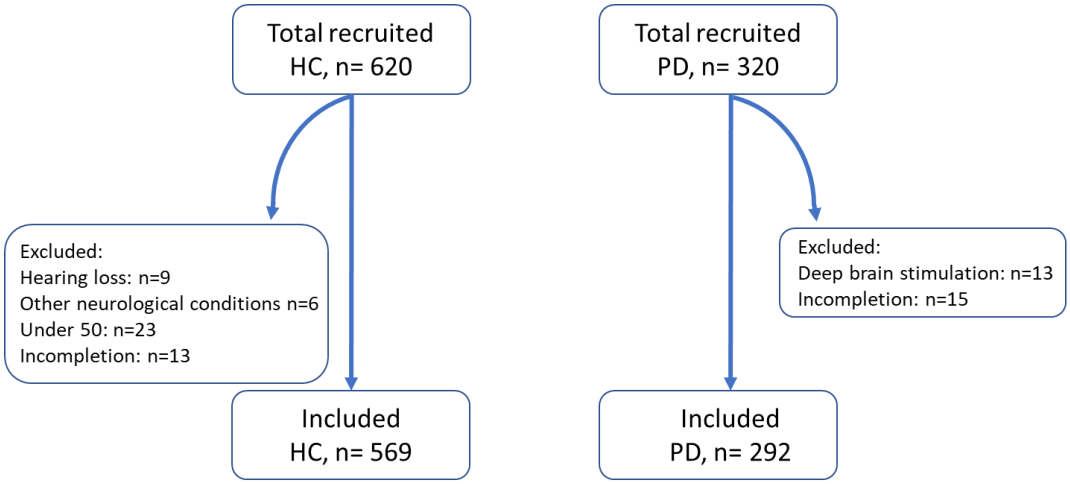


Figure 5.3. Number of control and patient participants recruited, excluded and included for analysis. HC: healthy control; PD: Parkinson's disease patients. Other neurological conditions included multiple sclerosis and epilepsy.

Table 5.1. Demographics table of Parkinson's disease (PD) group and Healthy Control (HC) group performing the seconds or subseconds task.

	Subseconds		Seconds		Overall	
	HC (N=269)	PD (N=129)	HC (N=300)	PD (N=163)	HC (N=569)	PD (N=292)
Age (years)						
Mean (SD)	65.6 (5.35)	66.5 (6.83)	66.1 (5.54)	66.5 (7.52)	65.8 (5.45)	66.5 (7.21)
Median [Min, Max]	65.0 [50.0, 87.0]	66.0 [50.0, 85.0]	65.5 [52.0, 86.0]	67.0 [50.0, 85.0]	65.0 [50.0, 87.0]	67.0 [50.0, 85.0]
Sex						
Male	100 (37.2%)	61 (47.3%)	127 (42.3%)	73 (44.8%)	227 (39.9%)	134 (45.9%)
Female	169 (62.8%)	68 (52.7%)	173 (57.7%)	90 (55.2%)	342 (60.1%)	158 (54.1%)
Handedness						
Left	35 (13.0%)	13 (10.1%)	29 (9.7%)	19 (11.7%)	64 (11.2%)	32 (11.0%)
Right	234 (87.0%)	111 (86.0%)	269 (89.7%)	140 (85.9%)	503 (88.4%)	251 (86.0%)
Ambidextrous	0 (0%)	5 (3.9%)	2 (0.7%)	4 (2.5%)	2 (0.4%)	9 (3.1%)
Ethnicity						
Asian	2 (0.7%)	1 (0.8%)	4 (1.3%)	1 (0.6%)	6 (1.1%)	2 (0.7%)
Hispanic or Latino	2 (0.7%)	0 (0%)	1 (0.3%)	2 (1.2%)	3 (0.5%)	2 (0.7%)
Other (please specify)	5 (1.9%)	1 (0.8%)	5 (1.7%)	1 (0.6%)	10 (1.8%)	2 (0.7%)
White	250 (92.9%)	102 (79.1%)	284 (94.7%)	157 (96.3%)	534 (93.8%)	259 (88.7%)
Black or African American	0 (0%)	0 (0%)	3 (1.0%)	0 (0%)	3 (0.5%)	0 (0%)
Jewish	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)	1 (0.2%)	0 (0%)
PD Duration (years)						
Mean (SD)	NA (NA)	6.35 (4.88)	NA (NA)	6.57 (4.65)	NA (NA)	6.47 (4.74)
Median [Min, Max]	NA [NA, NA]	5.00 [0.0137, 24.0]	NA [NA, NA]	5.00 [0.00800, 28.0]	NA [NA, NA]	5.00 [0.00800, 28.0]
PD Medication						
denovo	0 (0%)	4 (3.1%)	0 (0%)	6 (3.7%)	0 (0%)	10 (3.4%)
levodopa	0 (0%)	110 (85.3%)	0 (0%)	142 (87.1%)	0 (0%)	252 (86.3%)
others	0 (0%)	14 (10.9%)	0 (0%)	15 (9.2%)	0 (0%)	29 (9.9%)
TimeSinceLastMed (hours)						
Mean (SD)	NA (NA)	3.21 (3.49)	NA (NA)	3.33 (3.37)	NA (NA)	3.28 (3.41)
Median [Min, Max]	NA [NA, NA]	2.00 [0, 21.0]	NA [NA, NA]	3.00 [0, 24.0]	NA [NA, NA]	2.50 [0, 24.0]
Device						
computer	221 (82.2%)	102 (79.1%)	255 (85.0%)	122 (74.8%)	476 (83.7%)	224 (76.7%)
mobile	33 (12.3%)	12 (9.3%)	28 (9.3%)	15 (9.2%)	61 (10.7%)	27 (9.2%)
tablet	15 (5.6%)	15 (11.6%)	17 (5.7%)	26 (16.0%)	32 (5.6%)	41 (14.0%)
Operating System						
Android	28 (10.4%)	11 (8.5%)	27 (9.0%)	17 (10.4%)	55 (9.7%)	28 (9.6%)
Chromium	7 (2.6%)	1 (0.8%)	8 (2.7%)	1 (0.6%)	15 (2.6%)	2 (0.7%)
iOS	23 (8.6%)	16 (12.4%)	22 (7.3%)	24 (14.7%)	45 (7.9%)	40 (13.7%)
Linux	1 (0.4%)	1 (0.8%)	1 (0.3%)	1 (0.6%)	2 (0.4%)	2 (0.7%)
Mac	32 (11.9%)	37 (28.7%)	52 (17.3%)	41 (25.2%)	84 (14.8%)	78 (26.7%)
Ubuntu	5 (1.9%)	1 (0.8%)	1 (0.3%)	0 (0%)	6 (1.1%)	1 (0.3%)
Windows	173 (64.3%)	62 (48.1%)	189 (63.0%)	79 (48.5%)	362 (63.6%)	141 (48.3%)

5.3.2 Duration discrimination of PD vs healthy controls

Duration discrimination sensitivity was represented by log values of the slope of each logistic regression curve, where a larger value represents steeper slope and better sensitivity. After Bonferroni correction, statistical significance ($p_{unc} < 0.0125$) was observed in visual task in the seconds range and auditory task in the subseconds range. In the seconds interval, patients had a significantly worse visual sensitivity compared to that of controls (-4.89±0.46 HC vs -4.71±0.47 PD, p=0.036). In the sub seconds interval, patients had a significantly worse auditory sensitivity (-3.43 ±0.50 HC vs -3.60±0.48 PD, p=0.0078) compared to that of controls.

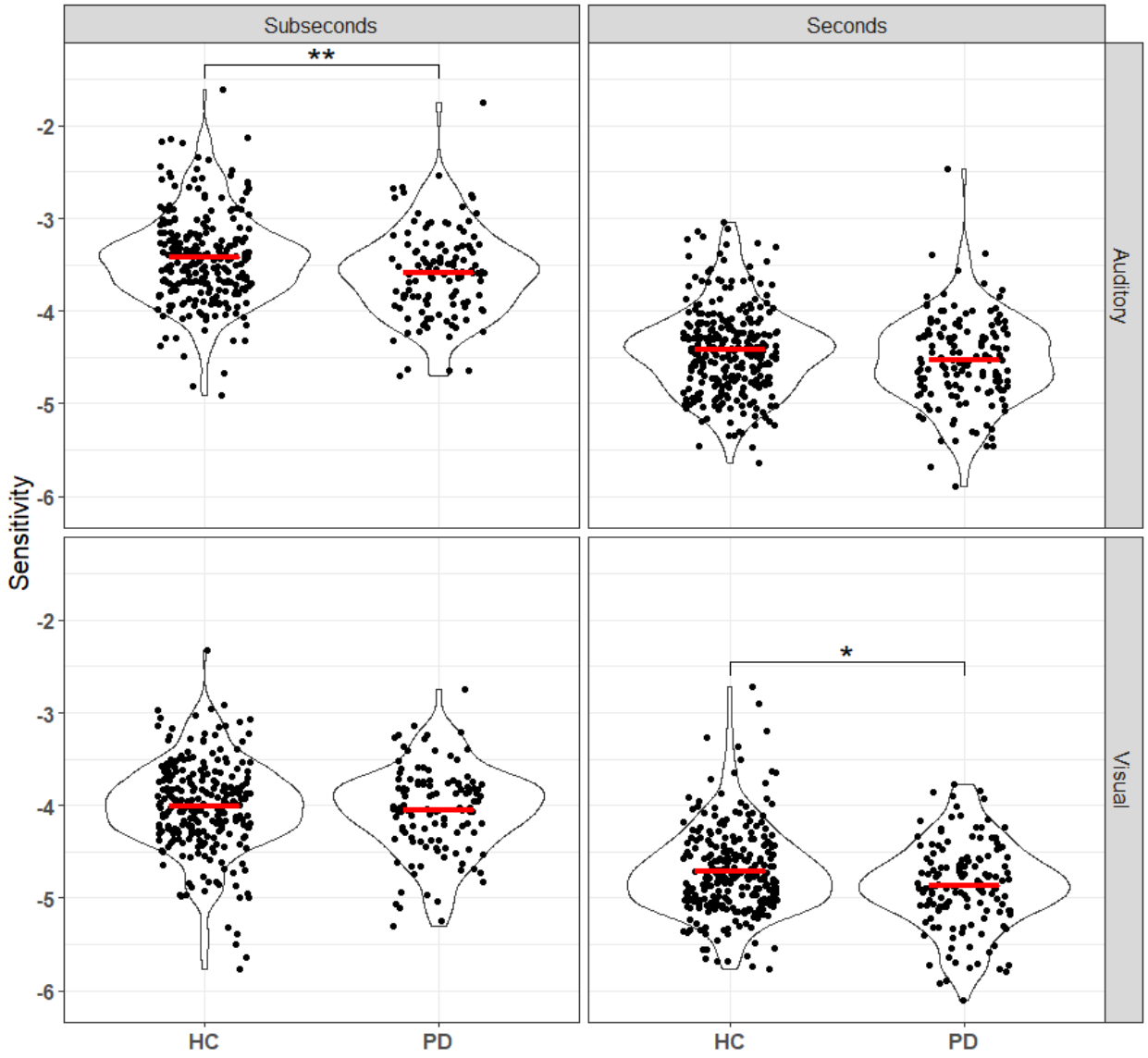


*Figure 5.4. Sensitivity calculated using equation (2), of all patients and controls to both auditory and visual stimuli in the seconds and subseconds intervals. PD patients showed impaired time perception to auditory stimuli in the subseconds range and visual stimuli in the seconds range. Annotations denote statistical significance after Bonferroni correction: adjusted *p<0.05, **p<0.01.*

PD patients' estimates differed from controls in the same way in both the seconds (p=.0065) and subseconds (p<.001) ranges (*Figure 5.5*). This shift is absent in both visual tasks. In the subseconds range, the HC group appear to on average have a perfect judgement of the duration, whereas PD patients have an error. In the seconds range, the error becomes smaller for PD than HC *(Figure 5.5).* This may be a result of PD partially offsetting time error.

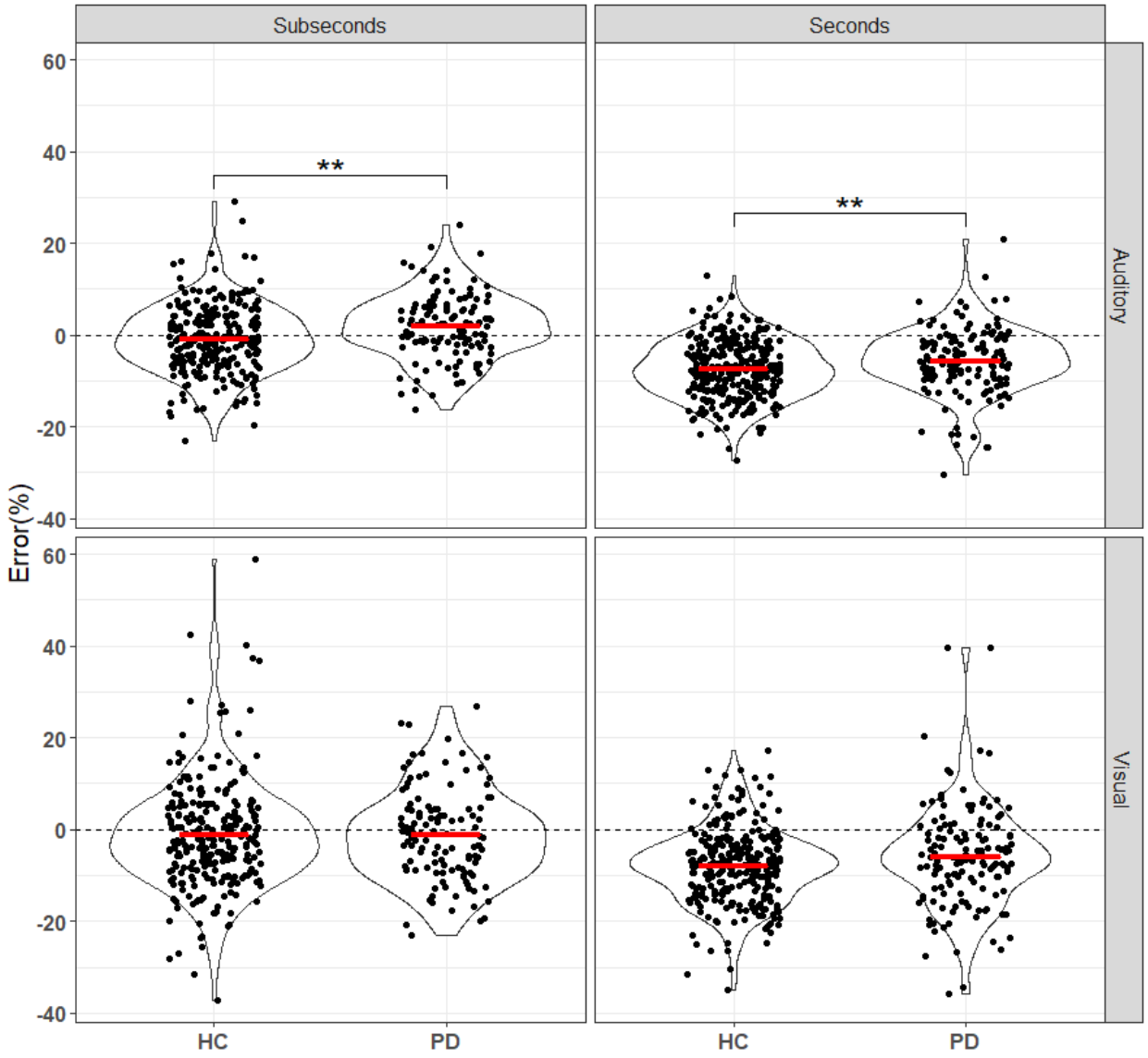


*Figure 5.5. Error of patients and controls in comparing auditory and visual stimuli in the seconds and subseconds intervals (Equation 3). No significant difference was seen between the patient and control groups for the visual stimuli. For the auditory stimuli, PD patients overestimated the standard duration compared to the controls. Annotations denote significance of adjusted p-values after Bonferroni correction: **p<.01.*

5.3.3 Intra-individual variability

Standard deviations of response times and IIV for each auditory and visual stimuli in the seconds and subseconds range are summarized in *Table 5.2*. There is no significant difference in response time variability between patient and control groups after Bonferroni correction.

Table 5.2. Standard deviation and intra-individual variability (IIV) or response time in HC and PD groups responding to auditory and visual stimuli in the seconds and subseconds range. P-values are from unpaired t-tests. There is no statistically significant difference in the variability in response time after Bonferroni correction

	Subseconds			Seconds		
	HC (N=256)	PD (N=120)	P-value	HC (N=275)	PD (N=144)	P-value
Auditory Response Time Std						
Mean (SD)	447 (310)	570 (506)	0.014	458 (327)	519 (283)	0.049
Median [Min, Max]	350 [105, 2740]	405 [115, 4100]		364 [106, 2710]	448 [148, 1470]	
Visual Response Time Std						
Mean (SD)	445 (324)	631 (918)	0.033	477 (390)	749 (1760)	0.07
Median [Min, Max]	368 [98.3, 2710]	440 [85.2, 9390]		380 [113, 3330]	508 [133, 20600]	
Auditory Response Time IIV						
Mean (SD)	8.54 (0.796)	8.73 (0.761)	0.03	8.56 (0.834)	8.65 (0.858)	0.288
Median [Min, Max]	8.60 [6.16, 9.95]	8.66 [7.21, 9.95]		8.60 [6.93, 10.0]	8.66 [6.71, 10.0]	
Visual Response Time IIV						
Mean (SD)	8.89 (0.762)	9.06 (0.775)	0.055	8.67 (0.787)	8.76 (0.814)	0.259
Median [Min, Max]	9.00 [7.14, 9.95]	9.14 [7.14, 9.95]		8.72 [6.86, 10.0]	8.77 [6.71, 10.0]	

5.4 Discussion

This study has shown that patients with PD have impaired sensitivity in discriminating between durations of both visual and auditory stimuli compared to healthy controls. This effect has not been found in previous studies[479]; likely due to the greatly increased sample sizes and thus statistical power permitted by the online approach taken here.

5.4.1 Towards an integrative model of Parkinsonian deficits in supra second time processing

There is a significant body of evidence to support the theory that time perception is mediated by different mechanisms at different timescales[206, 550], and the BG are particularly implicated in the processing of longer (supra second) durations. Per the striatal beat-frequency model[551], cortico-striato-thalamocortical loop circuits facilitate the comparison of cortical oscillations at the start and end of an interval. Based on functional neuroimaging evidence, a role for dopaminergic neurons in the SNc in this process as a "perceptual starting gun" for interval timing by resetting the phase of these oscillations has been proposed[552], which has since been backed up by a study in mice[220].

Taken together, this would predict that PD, which is characterised by degeneration of SNc dopaminergic neurons and widespread striatal pathology, produces an impairment in supra second interval perception across modalities. However, the nature of this impairment is complex, as one must consider the interacting effects of a hypodopaminergic state, the resulting chronic dysfunction (hyperexcitability) in striatal dopamine-recipient neurons, and any dopaminergic medication effects[553, 554]. Thus, we expected to see both a loss of sensitivity on average, and an increase in inter-individual variability within the PD population.

Additionally, distortions in unimodal perception at sub second timescales can be sufficient to give rise to modality-specific effects at supra second timescales in hierarchical models where supra second timekeeping is amodal[555, 556]; in light of this, it was surprising that the PD group had significant decreases in auditory sensitivity in only the sub second range in our data (*Figure 5.4*). Given the size of the difference in sample medians, it is likely that future online-only study designs would need even larger group sizes to detect subtle effects like this.

5.4.2 Perceptual bias across timescales

Biases in temporal perception have also been observed in this study, with systematic differences in the relative perceived durations of the standard (first) and comparison (second) stimuli (*Figure 5.5*). As the stimuli were not perceived simultaneously, several processes can affect this through changes in the perception of the first duration, the memory of the first duration, and the perception of the second duration.

The effect first observed by Terao et al[479], in which subjective error shifted from more positive to more negative as stimulus length increased for both groups, was replicated here (all comparisons $p < 0.001$ after Bonferroni correction; see *Supplementary Figure 5.8*). However, the observed difference between the control and PD groups was in the opposite direction, with our data suggesting a more positive error in PD patients.

Care must be taken when interpreting these effects, as perception may change based on previous stimuli or peri-stimulus sensory or motor events. For example, repetition of a stimulus shortens its perceived duration[557-559], and saccades made around the onset of a visual stimulus also compress its subjective duration[560, 561]. As the external sensory environment of

our participants was unknown, it is difficult to estimate the degree to which these effects are present in our data.

5.4.3 Developing cognitive biomarkers for Parkinson's disease

Aberrant time perception in PD could provide some insight into disease progression and severity. Perceptual error in auditory duration comparison correlated with MMSE score in a recent study[479], and should be studied longitudinally in a prospective cohort study. Additionally, these deficits may exhibit consistent treatment effects: two studies have shown improvements of STN-DBS on time perception in auditory interval discrimination at subseconds time scales, and motor time production at supra second timescales[200, 562]. These effects could potentially be exploited for treatment optimization but should be studied in greater detail as there is a degree of task dependence. While motor and sensory midpoints in an interval bisection task are indistinguishable[563], the relationship between bias and stimulus length may be reversed between motor and sensory tasks[479].

5.4.4 Limitations

To our knowledge, this is the first study of time perception in PD to have been conducted entirely online. While this has enabled us to greatly increase sample sizes, several sources of variability are also introduced by this method of delivery.

Firstly, computer hardware and software varied significantly between participants (see supplementary data). This could have affected recording of reaction times, but also stimulus delivery, *e.g.,* by slowdown due to multiple applications being open simultaneously, by variable screen refresh rates, or using wireless audio peripherals. Gorilla Experiment Builder, which

was used to deliver the experiment, is designed primarily to mitigate these inconsistencies between systems, but cannot eliminate them entirely[546]. To ensure that the type of device used does not significantly impact time perception, slopes were compared between device types across patient and interval groups. No significant difference was found, suggesting that the type of device used does not affect time perception sensitivity (See *Supplementary Figure 5.7*).

Secondly, we relied entirely on self-report measures; participants were not assessed by a clinician as part of the study, nor were any data from their medical records available. Patients on antiparkinsonian medications were asked to list their medications and estimate the number of hours since last taking medication. Thus, patients were not in a well-defined 'ON' or 'OFF' state during testing, and levodopa equivalent dose could not be estimated from this information. While a previous small study found no effect of levodopa on PD patients' ability to discriminate between durations around 50ms[562], the vastly shorter stimulus duration in that study may have probed intracortical rather than cortico-striatal processing, so the effect of this on our experiment is unknown. Furthermore, tremor and dyskinesia were not measured in this study, both of which will influence the reaction times and some of the responses.

Finally, the experimental environment cannot be controlled as tightly as is typical for in-person experiments. Factors intrinsic to the task such as stimulus luminance/loudness and contrast, which are known to affect duration perception for visual stimuli[561], would have been under control of the participant's device. In addition to the functional integrity of the above-described neural substrates responsible for measuring time, time perception can be easily distorted by emotional state and cognitive context[557, 564]. Similarly, extrinsic factors (*i.e.* distractors) would have varied widely between participants. In a hypothetical extreme case, for example, a

participant might have completed the task on a bus. This means they would have been exposed to a wide range of simultaneous auditory and visual stimuli in an environment with rapidly changing background luminance and noise, all while attending to another time perception task at a different timescale (estimating the interval of time elapsed since getting on or passing a previous stop in order to leave the bus at the right time).

Despite these limitations, online delivery of this study has permitted group sizes an order of magnitude greater than those used in previous studies, and recruitment across a far larger geographical area, leading to greater statistical power.

5.4.5 Conclusions

Our findings demonstrate modality- and stimulus length-specific differences in duration perception in patients with PD *versus* healthy controls. These differences may shed light on timekeeping systems and the pathophysiology of PD but require further study and careful examination of the effects observed as they can be sensitive to task design and experimental conditions.

5.4.6 Acknowledgements

For this chapter, we would like to acknowledge the contribution of Parkinson's UK (https://www.parkinsons.org.uk/), Canadian Open Parkinson Network (C-OPN) (https://copn-rpco.ca/), Parkinson Canada (https://www.parkinson.ca/), Parkinson's UK Oxford Branch (https://oxfordparkinsons.org.uk/), Parkinson Society British Columbia (https://www.parkinson.bc.ca/), and Parkinson Association of Alberta (https://parkinsonassociation.ca/) for helping promote the study.

Chapter 6 Discussion

This final chapter summarizes the work performed in this thesis with a conclusion relating to the major findings. Future directions which build on the work of this thesis are also discussed.

6.1 Discussion

The work presented in this thesis was primarily focussed on quantifying gait parameters in PD throughout disease progression, under medication, as well as after surgical treatments. The aim for such investigation was to find biomarkers which are both sensitive enough to pick up early progression characteristics and are also non masked by the current symptomatic treatments. The thesis started with a cross-sectional study in an effort to identify gait features altered by PD and used this as a baseline to track progression of gait (Chapter 2). The effect of the most common PD treatment, levodopa, was then examined in Chapter 3, and the effect of surgical treatment STN-DBS was the focus of Chapter 4. Intriguing results from Chapter 4 revealed rhythmicity of gait to be separately impacted by distinct working mechanisms of medication and DBS. This brought rhythmicity and time perception into attention as a potential biomarker. Chapter 5 further examined this potential underlying factor in gait irregularity through an online population study on time perception.

Chapter 2 focused on identifying gait features specific to PD progression in early PD patients (up to 8 years since diagnosis). Seven spatial features, one sway feature, seven transition features, five variability features and three asymmetry features were identified to be characteristic of PD gait (See *2.3.2*). Among these features none showed a statistically significant progression over a span of two years except for foot strike angle. Foot strike angle

showed a significant decrease at 15 months from the first visit, while MDS-UPDRS-III score showed a difference at 21 months. Reduced foot strike angle leads to less ground clearance and higher risk of falling. Reduced range of motion is a common PD symptom that is relieved by levodopa medication. The fact that progression in foot strike angle was detected in medicated patients suggest that the rate of progression is large enough to outweigh the therapeutic symptom improvement by medication, making it a more robust and sensitive biomarker than the current clinical rating scale in tracking PD progression.

Taking a closer examination at early-stage PD patients (average PD duration =3.1 years), specifically their response to dopaminergic medication, Dopaminergic medication was found to improve gait speed and amplitude but not sway and transition parameters in Chapter 3. Bilateral stride length, gait speed, lateral step variability, foot strike angle, trunk coronal ROM and arm ROM were identified with significant response to dopaminergic medication. Since the sway and transition features selected (Mean sway velocity, sway coronal path length, turn duration, turn velocity, sit to stand duration, and stand to sit duration) were significantly altered by PD and not by medication, this suggests that at least in early-stage patients, these features are not masked by the medication effect and are thus promising biomarkers to measure underlying changes in disease state for patients on dopaminergic treatment.

Chapter 4 examined the effect of medication and gait in more advanced PD patients. In this chapter, the Poincare analysis, commonly used in measuring heart rhythmicity, was adopted to segregate and quantify short- (step-to-step) and long-term variability in walking and found that STN-DBS reduced step-to-step variability in a range of lower limb gait parameters in PD while dopaminergic medication had no significant effect. This suggest that STN stimulation

and not dopaminergic medication modulates circuits that control gait rhythm and therefore that control of amplitude and rhythm may be separate. Retrograde activation of cholinergic PPN neurons by STN-DBS was proposed to be the most likely explanation of the distinct effects from treatments. PD disrupts gait variability which can be improved by DBS and not dopaminergic medication[153]. Is the change in gait variability caused by underlying defects in time perception?

Chapter 5 focuses on answering exactly this question. Both auditory and visual perception of durations in the seconds and subseconds ranges, controlled by different pathways in the brain, were examined through an online study. PD patients were found with impaired sensitivity in discriminating subseconds auditory stimuli and seconds visual stimuli, with patients showing a consistent overestimation of auditory durations. This demonstrates modality- and stimulus length-specific differences in duration perception in patients with PD *versus* HC. These differences may shed light on timekeeping systems and the pathophysiology of PD but require further study and careful examination of the effects observed as they can be sensitive to task design and experimental conditions. Study design and data collection of this chapter took place during the Covid pandemic and prompted me to bring a traditionally in-person experiment online. Although this meant several challenges including difficulties in controlling for confounding factors like screen luminosity, surrounding noise level, type of response device used, the test still captured impaired time perception in PD patients and allowed a robust sample size of over 800 participants. This chapter demonstrates the plausibility and validity in online testing for PD patients to participate in the comfort of their own homes without the stress of travelling to clinics and white-coat effect.

6.2 Future Directions

Accurate quantification of PD state and progression would require a combination of multiple factors upon single-feature investigations. In Chapter 2, progression over two years in individual biomechanical components may not be large enough or may be masked by symptomatic treatment effects. Future work should focus on factorizing and combining multiple components in building a model that can track PD progression in shorter time frames. A common theme throughout gait quantification was the intercorrelation between gait features. No single parameter can clearly categorize PD disease state, progression, or type of treatment. This finding is unsurprising, as the control of gait and balance depends on highly interconnected functional networks (See *1.2.1* and *1.2.2*). Work from this thesis examining individual parameters then set an important foundation for the logical next step of this investigation, which is building a model with selected parameters. This type of work has already begun in our group, examining PSP patients and has just been accepted for publication.

Upon identification of gait rhythm impairment that could be a result from time perception defects, results from Chapter 5 demonstrated disrupted time perception in PD patients. Online assessments were also validated as one of the effective and efficient methods to carry out future investigations. In addition to building multi-feature models, moving the data collection process from labs into the individuals' homes might also help improve accuracy of PD gait quantification.

Home monitoring of both motor and non-motor symptoms of PD is an exciting next step for continuous monitoring of gait and symptoms that enables capturing daily functions instead of lab performance. Throughout the data collection process, many patients reported themselves

consciously giving better performance (moving the arms more during walking) during the test compared to how they normally walk in their daily lives. Travelling to the clinic and making an appointment also adds on additional physical and mental stress, both known to significantly impact motor functions in PD patients. Home monitoring can easily overcome these confounding factors to give a more realistic picture of PD gait and a prolonged data collection period.

6.3 Concluding Remarks

This thesis set out to quantify Parkinsonian gait using wearable technology and was able to identify foot strike angle as a sensitive marker for PD progression and sway and transition features as promising markers not masked by medication treatment. Furthermore, medication and surgical PD treatments were compared, and the latter was found to provide additional improvement in restoring gait rhythmicity. Finally, a disrupted perception of time in the seconds and subseconds range in PD was found by an online population study, providing a new way of quantifying non-motor symptoms in addition to motor symptoms.

Supplementary figures and tables

Supplementary Table 2.7. List of gait features collected for the two-minute walk task. APA: anticipatory postural adjustment; I: ipsilateral side; C: contralateral side; CV: coefficient of variation; GCT: gait cycle time.

Anticipatory Postural Adjustment - APA Duration (s)	Gait - Lower Limb - Stance I (%GCT) [mean]
Anticipatory Postural Adjustment - First Step Duration (s)	Gait - Lower Limb - Stance I (%GCT) [CV]
Anticipatory Postural Adjustment - First Step Range of Motion (degrees)	Gait - Lower Limb - Stance C (%GCT) [mean]
Anticipatory Postural Adjustment - Forward APA Peak (m/s^2)	Gait - Lower Limb - Stance C (%GCT) [CV]
Anticipatory Postural Adjustment - Lateral APA Peak (m/s^2)	Gait - Lower Limb - Stance Asymmetry (%Diff) [mean]
Gait - Lower Limb - Cadence I (steps/min) [mean]	Gait - Lower Limb - Step Duration I (s) [mean]
Gait - Lower Limb - Cadence I (steps/min) [CV]	Gait - Lower Limb - Step Duration I (s) [CV]
Gait - Lower Limb - Cadence C (steps/min) [mean]	Gait - Lower Limb - Step Duration C (s) [mean]
Gait - Lower Limb - Cadence C (steps/min) [CV]	Gait - Lower Limb - Step Duration C (s) [CV]
Gait - Lower Limb - Cadence Asymmetry (%Diff) [mean]	Gait - Lower Limb - Step Duration Asymmetry (%Diff) [mean]
Gait - Lower Limb - Cadence Asymmetry (%Diff) [CV]	Gait - Lower Limb - Stride Length I (m) [mean]
Gait - Lower Limb - Double Support I (%GCT) [mean]	Gait - Lower Limb - Stride Length I (m) [CV]
Gait - Lower Limb - Double Support I (%GCT) [CV]	Gait - Lower Limb - Stride Length C (m) [mean]
Gait - Lower Limb - Double Support C (%GCT) [mean]	Gait - Lower Limb - Stride Length C (m) [CV]
Gait - Lower Limb - Double Support C (%GCT) [CV]	Gait - Lower Limb - Stride Length Asymmetry (%Diff) [mean]
Gait - Lower Limb - Double Support Asymmetry (%Diff) [mean]	Gait - Lower Limb - Swing I (%GCT) [mean]
Gait - Lower Limb - Double Support Asymmetry (%Diff) [CV]	Gait - Lower Limb - Swing I (%GCT) [CV]
Gait - Lower Limb - Elevation at Midswing I (cm) [mean]	Gait - Lower Limb - Swing C (%GCT) [mean]
Gait - Lower Limb - Elevation at Midswing I (cm) [CV]	Gait - Lower Limb - Swing C (%GCT) [CV]
Gait - Lower Limb - Elevation at Midswing C (cm) [mean]	Gait - Lower Limb - Swing Asymmetry (%Diff) [mean]
Gait - Lower Limb - Elevation at Midswing C (cm) [CV]	Gait - Lower Limb - Terminal Double Support I (%GCT) [mean]
Gait - Lower Limb - Elevation at Midswing Asymmetry (%Diff) [mean]	Gait - Lower Limb - Terminal Double Support I (%GCT) [CV]
Gait - Lower Limb - Gait Cycle Duration I (s) [mean]	Gait - Lower Limb - Terminal Double Support C (%GCT) [mean]
Gait - Lower Limb - Gait Cycle Duration I (s) [CV]	Gait - Lower Limb - Terminal Double Support C (%GCT) [CV]
Gait - Lower Limb - Gait Cycle Duration C (s) [mean]	Gait - Lower Limb - Terminal Double Support Asymmetry (%Diff) [mean]
Gait - Lower Limb - Gait Cycle Duration C (s) [CV]	Gait - Lower Limb - Toe Out Angle I (degrees) [mean]
Gait - Lower Limb - Gait Cycle Duration Asymmetry (%Diff) [mean]	Gait - Lower Limb - Toe Out Angle I (degrees) [CV]
Gait - Lower Limb - Gait Speed I (m/s) [mean]	Gait - Lower Limb - Toe Out Angle C (degrees) [mean]
Gait - Lower Limb - Gait Speed I (m/s) [CV]	Gait - Lower Limb - Toe Out Angle C (degrees) [CV]
Gait - Lower Limb - Gait Speed C (m/s) [mean]	Gait - Lower Limb - Toe Out Angle Asymmetry (%Diff) [mean]
Gait - Lower Limb - Gait Speed C (m/s) [CV]	Gait - Lumbar - Coronal Range of Motion (degrees) [mean]
Gait - Lower Limb - Gait Speed Asymmetry (%Diff) [mean]	Gait - Lumbar - Coronal Range of Motion (degrees) [CV]
Gait - Lower Limb - Gait Speed Asymmetry (%Diff) [CV]	Gait - Lumbar - Sagittal Range of Motion (degrees) [mean]
Gait - Lower Limb - Lateral Step Variability I (cm)	Gait - Lumbar - Sagittal Range of Motion (degrees) [CV]
Gait - Lower Limb - Lateral Step Variability C (cm)	Gait - Lumbar - Transverse Range of Motion (degrees) [mean]
Gait - Lower Limb - Lateral Step Variability Asymmetry (%Diff) [mean]	Gait - Lumbar - Transverse Range of Motion (degrees) [CV]
Gait - Lower Limb - Circumduction I (cm) [mean]	Gait - Trunk - Coronal Range of Motion (degrees) [mean]
Gait - Lower Limb - Circumduction I (cm) [CV]	Gait - Trunk - Coronal Range of Motion (degrees) [CV]
Gait - Lower Limb - Circumduction C (cm) [mean]	Gait - Trunk - Sagittal Range of Motion (degrees) [mean]
Gait - Lower Limb - Circumduction C (cm) [CV]	Gait - Trunk - Sagittal Range of Motion (degrees) [CV]
Gait - Lower Limb - Circumduction Asymmetry (%Diff) [mean]	Gait - Trunk - Transverse Range of Motion (degrees) [mean]
Gait - Lower Limb - Foot Strike Angle I (degrees) [mean]	Gait - Trunk - Transverse Range of Motion (degrees) [CV]
Gait - Lower Limb - Foot Strike Angle I (degrees) [CV]	Gait - Upper Limb - Arm Swing Velocity I (degrees/s) [mean]
Gait - Lower Limb - Foot Strike Angle C (degrees) [mean]	Gait - Upper Limb - Arm Swing Velocity I (degrees/s) [CV]
Gait - Lower Limb - Foot Strike Angle C (degrees) [CV]	Gait - Upper Limb - Arm Swing Velocity C (degrees/s) [mean]
Gait - Lower Limb - Foot Strike Angle Asymmetry (%Diff) [mean]	Gait - Upper Limb - Arm Swing Velocity C (degrees/s) [CV]
Gait - Lower Limb - Toe Off Angle I (degrees) [mean]	Gait - Upper Limb - Arm Swing Velocity Asymmetry (%Diff) [mean]
Gait - Lower Limb - Toe Off Angle I (degrees) [CV]	Gait - Upper Limb - Arm Range of Motion I (degrees) [mean]

Gait - Lower Limb - Toe Off Angle C (degrees) [mean]	Gait - Upper Limb - Arm Range of Motion I (degrees) [CV]
Gait - Lower Limb - Toe Off Angle C (degrees) [CV]	Gait - Upper Limb - Arm Range of Motion C (degrees) [mean]
Gait - Lower Limb - Toe Off Angle Asymmetry (%Diff) [mean]	Gait - Upper Limb - Arm Range of Motion C (degrees) [CV]
Gait - Lower Limb - Single Limb Support I (%GCT) [mean]	Gait - Upper Limb - Arm Range of Motion Asymmetry (%Diff) [mean]
Gait - Lower Limb - Single Limb Support I (%GCT) [CV]	Turns - Duration (s) [mean]
Gait - Lower Limb - Single Limb Support C (%GCT) [mean]	Turns - Turn Velocity (degrees/s) [mean]
Gait - Lower Limb - Single Limb Support C (%GCT) [CV]	Turns - Steps in Turn (#) [mean]
Gait - Lower Limb - Single Limb Support Asymmetry (%Diff) [mean]	

Supplementary Table 2.8. List of features collected for the 30s eyes-closed sway test. Acc: acceleration.

Postural Sway - Acc - 95% Ellipse Axis 1 Radius (m/s^2)
Postural Sway - Acc - 95% Ellipse Axis 2 Radius (m/s^2)
Postural Sway - Acc - 95% Ellipse Rotation (radians)
Postural Sway - Acc - Sway Area (m^2/s^4)
Postural Sway - Acc - Centroidal Frequency (Hz)
Postural Sway - Acc - Centroidal Frequency (Coronal) (Hz)
Postural Sway - Acc - Centroidal Frequency (Sagittal) (Hz)
Postural Sway - Acc - Frequency Dispersion (AD)
Postural Sway - Acc - Frequency Dispersion (Coronal) (AD)
Postural Sway - Acc - Frequency Dispersion (Sagittal) (AD)
Postural Sway - Acc - Jerk (m^2/s^5)
Postural Sway - Acc - Jerk (Coronal) (m^2/s^5)
Postural Sway - Acc - Jerk (Sagittal) (m^2/s^5)
Postural Sway - Acc - Mean Velocity (m/s)
Postural Sway - Acc - Mean Velocity (Coronal) (m/s)
Postural Sway - Acc - Mean Velocity (Sagittal) (m/s)
Postural Sway - Acc - Path Length (m/s^2)
Postural Sway - Acc - Path Length (Coronal) (m/s^2)
Postural Sway - Acc - Path Length (Sagittal) (m/s^2)
Postural Sway - Acc - RMS Sway (m/s^2)
Postural Sway - Acc - RMS Sway (Coronal) (m/s^2)
Postural Sway - Acc - RMS Sway (Sagittal) (m/s^2)
Postural Sway - Acc - Range (m/s^2)
Postural Sway - Acc - Range (Coronal) (m/s^2)
Postural Sway - Acc - Range (Sagittal) (m/s^2)

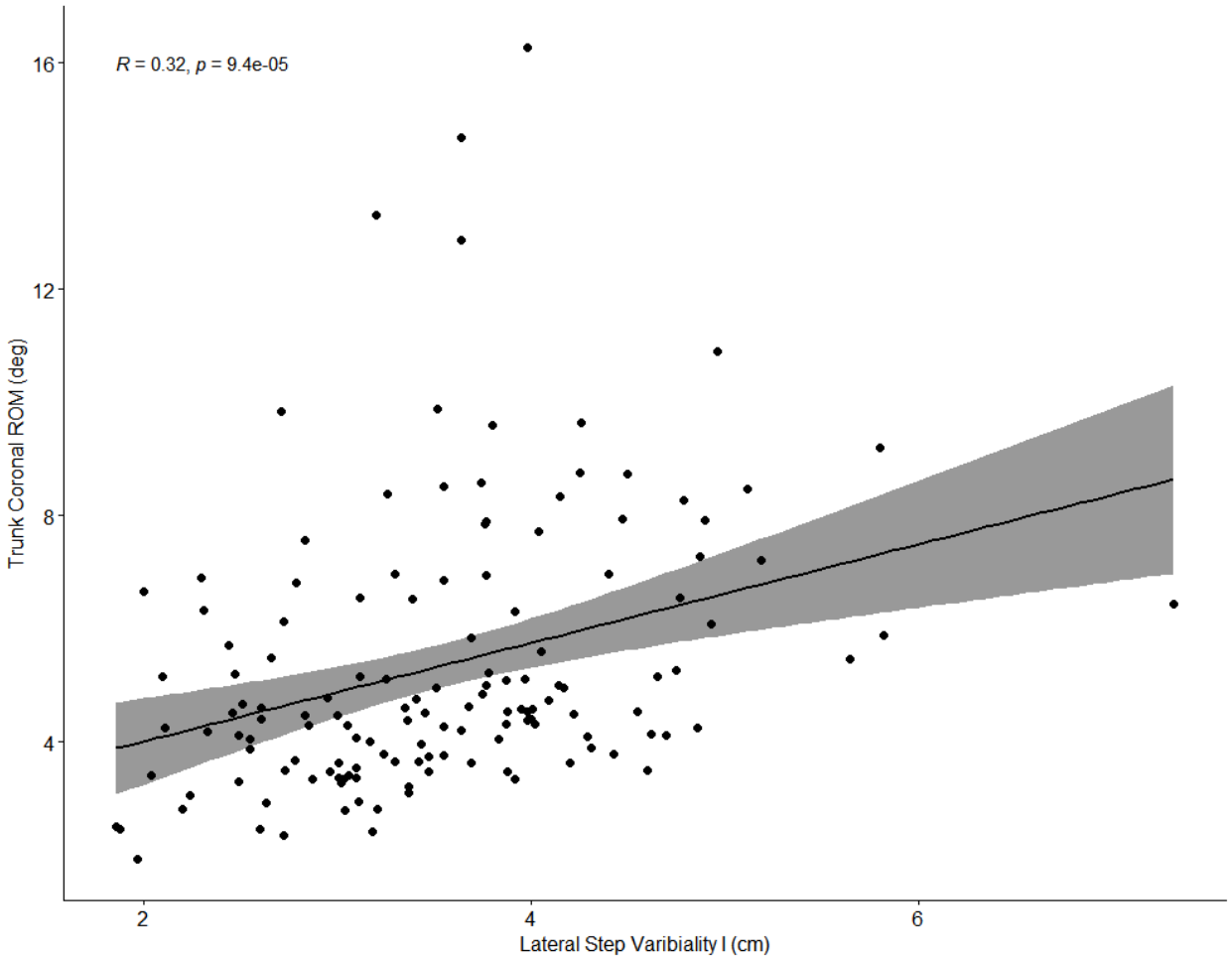
Supplementary Table 2.9. List of postural transition features collected from the Timed-Up-and-Go task

TUG Duration (s)
Sit to Stand - Duration (s) [mean]
Sit to Stand - Lean Angle (degrees) [mean]
Stand to Sit - Duration (s) [mean]
Stand to Sit - Lean Angle (degrees) [mean]
Turns - Duration (s) [mean]
Turns - Turn Velocity (degrees/s) [mean]

Supplementary Table 2.10. List of Asymmetry features collected from the two-minute walk task.

Gait-Lower Limb-Cadence Asymmetry (%Diff) [mean]

Gait-Lower Limb-Double Support Asymmetry (%Diff) [mean]
Gait-Lower Limb-Elevation at Midswing Asymmetry (%Diff) [mean]
Gait-Lower Limb-Gait Cycle Duration Asymmetry (%Diff) [mean]
Gait-Lower Limb-Gait Speed Asymmetry (%Diff) [mean]
Gait-Lower Limb-Lateral Step Variability Asymmetry (%Diff) [mean]
Gait-Lower Limb-Circumduction Asymmetry (%Diff) [mean]
Gait-Lower Limb-Foot Strike Angle Asymmetry (%Diff) [mean]
Gait-Lower Limb-Toe Off Angle Asymmetry (%Diff) [mean]
Gait-Lower Limb-Single Limb Support Asymmetry (%Diff) [mean]
Gait-Lower Limb-Stance Asymmetry (%Diff) [mean]
Gait-Lower Limb-Step Duration Asymmetry (%Diff) [mean]
Gait-Lower Limb-Stride Length Asymmetry (%Diff) [mean]
Gait-Lower Limb-Swing Asymmetry (%Diff) [mean]
Gait-Lower Limb-Terminal Double Support Asymmetry (%Diff) [mean]
Gait-Lower Limb-Toe Out Angle Asymmetry (%Diff) [mean]
Gait-Lower Limb-Arm Swing Velocity Asymmetry (%Diff) [mean]
Gait-Lower Limb-Arm Range of Motion Asymmetry (%Diff) [mean]



Supplementary Figure 3.7. Pearson correlation of Trunk coronal ROM and Ipsilateral Lateral Step Variability.

```
set       durations ← [standard_duration × [0.50 to 1.50 by 0.01 except 1.00]],
          trial_durations ← random_permutation(durations),
          responses ← [],
          β0 ← [], β1 ← [],
          cv ← [repeat NA for [1 to 50]],
          i_trial ← 1,

while i_trial ≤ 100 do
          play_stimulus(trial_durations[i_trial])
          set responses[i_trial] ← input

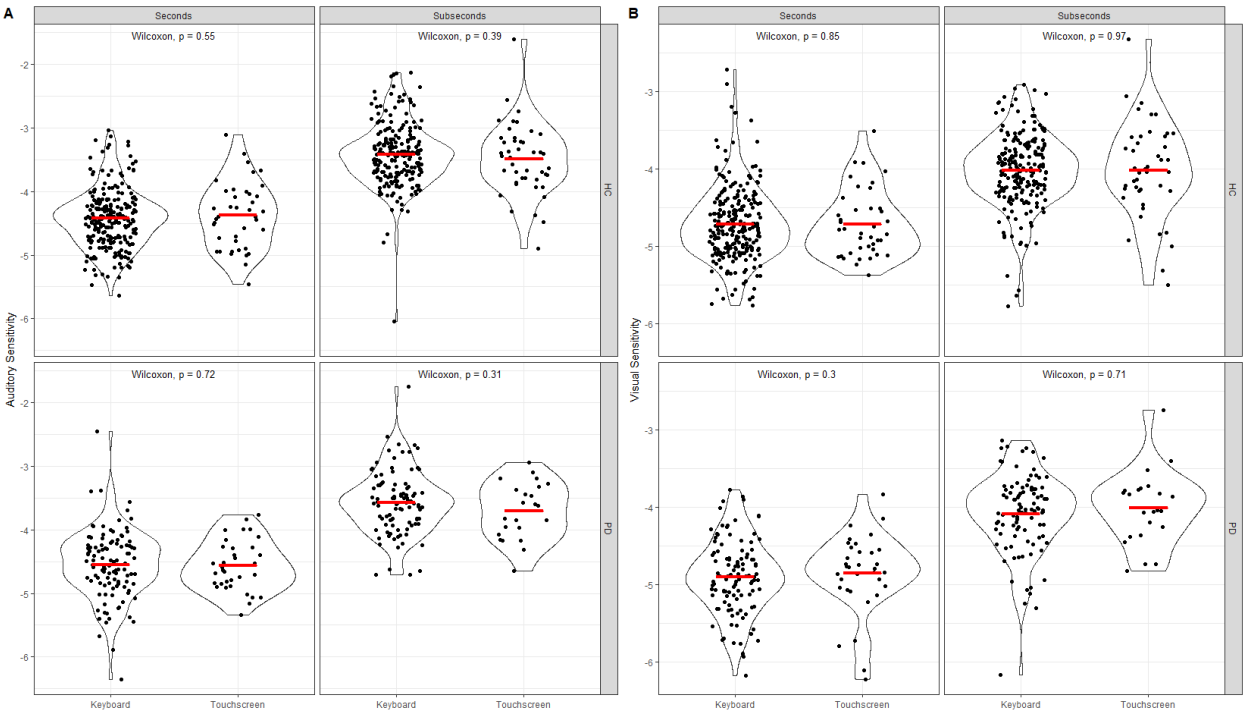
          if i_trial > 40 do
       set (β0,i_trial,β1,i_trial) ← fit_logistic_regression(trial_durations[1 to i_trial],
       responses)
          end if

          if i_trial > 50 do
                    set cv[i_trial] ← stddev(β1,[i_trial-9 to i_trial])/mean(β1,[i_trial-9 to i_trial])
          end if

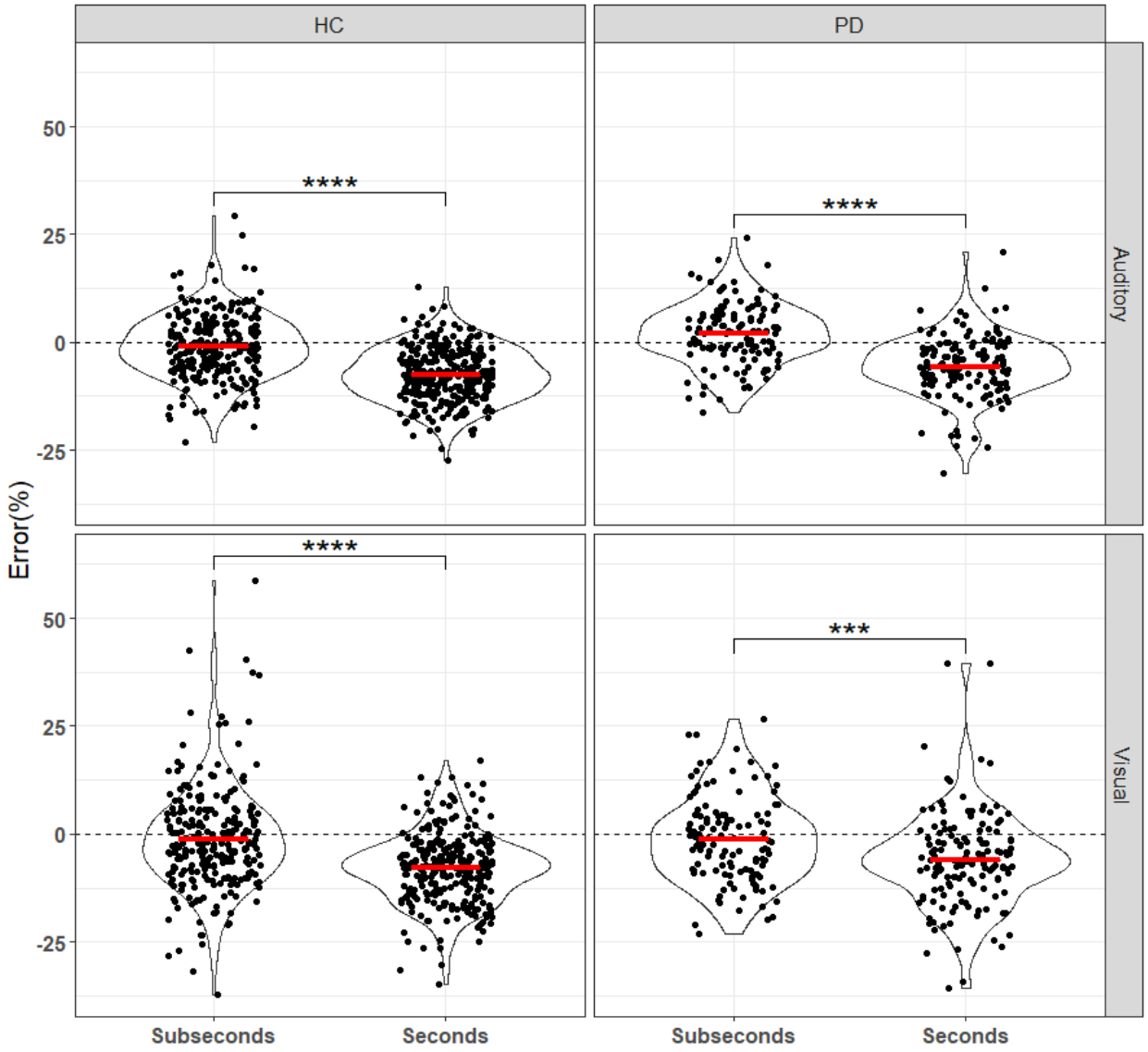
          if i_trial > 55 and all(cv[i_trial-4 to i_trial] < 0.02) then exit

          set i_trial ← i_trial + 1
end while
```

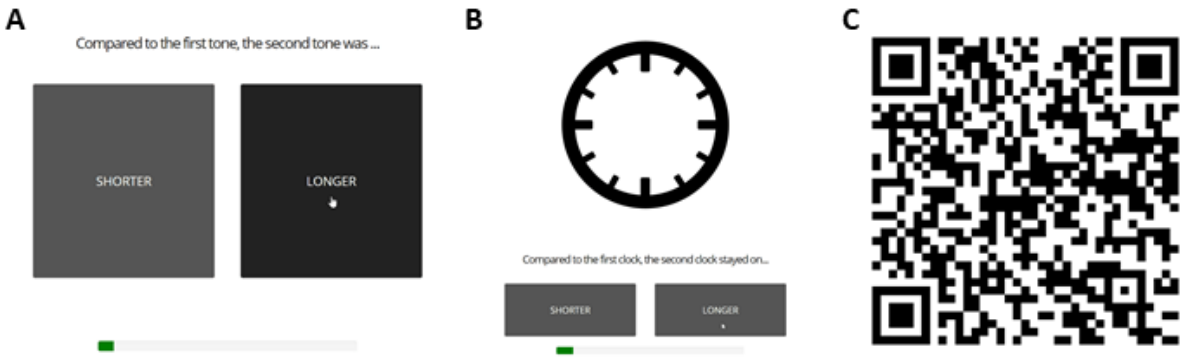
Supplementary Figure 5.6. Pseudocode used for the early exit condition.



Supplementary Figure 5.7. Sensitivity calculated using equation (2), of all patients and controls using either keyboard or touch screen response in each interval duration and stimuli settings. There was no significant difference in sensitivity and type of device used.



*Supplementary Figure 5.8. Error of patients and controls in comparing auditory and visual stimuli in the seconds and subseconds interval. Subjective error shifted from more positive to more negative as stimulus duration increased for both PD and control groups. Annotations denote significance of adjusted p-values after Bonferroni correction: ***p<.001; ****p<.0001.*



Supplementary Figure 5.9. Demonstration of the audio (A) and visual (B) task interface along with the QR code (C) to the online task.

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