Coordination deficits in Parkinson's disease: Effects of attention and medicine

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Table of Contents

List of Tables

List of Figures

List of Initialisms and Abbreviations

CRP	Continuous relative phase
DT	Dual task
DTC	Dual-task cost
GE	Gait events
HKB	Haken-Kelso-Bunz [model]
LA	Less affected
MA	More affected
PCA	Principal component analysis
PCI	Phase coordination index
PD	Parkinson's disease
PFE	Plausible freezing episode
pwPD	People with PD
RRT	Repetitive reaching task
SIPT	Stepping-in-place task
SMA	Supplementary motor area
UPDRS	Unified Parkinson's Disease Rating Scale
vGRF	Vertical ground reaction force

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Preface

Project 1

Approvals

Data previously collected by Allen Hill and Julie Nantel. Ethics approval was given by the University of Ottawa Research Ethics Boards and Ottawa Hospital Research Institute.

Research contributions[1]

Allen Hill: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing

Julie Nantel: Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – review & editing

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Project 3

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Julie N. Côté: Conceptualization, Funding Acquisition, Project Administration, Resources, Supervision, Writing – Review & Editing

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Abstract

Parkinson's disease is a progressive neurodegenerative disease that begins unilaterally in the dopaminergic neurons of the basal ganglia. This neurodegeneration results in various cognitive and motor deficits, including movement asymmetry, attentional deficits, and impairments in timing and rhythm, all of which contribute to or reflect the development of deficits in coordination. Dopaminergic medication is effective in treating some symptoms, but not all symptoms are responsive to dopamine. The purpose of this thesis was to better understand the nature and extents of coordination deficits in people with Parkinson's disease. In particular, the three objectives of this thesis were to: 1) Test measurement validity of existing (a)symmetry metrics in the literature, 2) Measure the effects of a dual task on interlimb coordination in people with Parkinson's disease while walking, and 3) Determine the effects of dopaminergic medication and auditory cueing on coordination of the upper and lower limbs in people with Parkinson's disease. **Article 1** showed that several existing symmetry metrics were equally valid and sensitive to producing findings of asymmetry, but one metric and one common transformation were found to cause or have significantly decreased sensitivity. **Article 2** found that multiple aspects of interlimb coordination in people with Parkinson's disease were not affected by a dual task, which suggests that interlimb coordination remains automatic, and not requiring attention, in Parkinson's disease. **Article 3** found that dopaminergic medication did not generally affect timing in people with Parkinson's disease, but the presence of timing deficits in comparison to healthy controls were confirmed. These findings suggest that timing deficits in people with Parkinson's disease are not directly the result of dopaminergic neurodegeneration, and alternate solutions (e.g. non-dopaminergic or non-pharmaceutical therapies) should be sought.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease originating in the dopaminergic neurons in the basal ganglia, with cascading effects in connected neural circuits (Poewe et al., 2017). PD is estimated to affect 0.05% of people in their 60s in North America and Europe, and age increases the prevalence of PD—up to 3% in 80+ year olds (Pringsheim et al., 2014). Low dopamine levels in the striatum, a part of the basal ganglia, are treated with dopaminergic medication which supplements or bolsters the action of striatal dopamine (Poewe et al., 2017). Dopaminergic medication addresses multiple motor deficits seen in PD, however unresponsive motor symptoms (e.g. time variability, aspects of coordination) provide evidence for non-dopaminergic pathologies (Almeida & Brown, 2013; Lord et al., 2011).

People with PD (pwPD) commonly exhibit postural instability and gait deficits, which are risk factors for falls (Hiorth et al., 2017). Common gait deficits in pwPD include increased spatial and temporal variability, impaired interlimb coordination, and increased asymmetry in the lower limbs when compared to healthy peers (Hausdorff et al., 2001; Lord et al., 2016; Maki, 1997; Roemmich et al., 2013). Similar changes in variability, interlimb coordination, and asymmetry have also been found in the upper limbs during gait in pwPD (Mirelman et al., 2016; Roemmich et al., 2013; Sterling et al., 2015).

As an aspect of coordination and a widely recognized feature of PD, movement asymmetry is a common focus of research in PD and other diseases with prominent asymmetry. However, current metrics for measuring asymmetry have been observed to be mutually incompatible (Patterson et al., 2010) and exhibit varying degrees of measurement validity (Sant'Anna et al., 2011). Previous comparisons of common asymmetry metrics have methodological limitations which reduces the strength of their evidence (Patterson et al., 2010; Queen et al., 2020; Sant'Anna et al., 2011); the relative strengths/weaknesses of existing metrics remains unclear.

Additionally, impairments in timing and rhythm (e.g. temporal variability, coordination accuracy and stability) may be a contributing factor to coordination deficits in pwPD (Almeida &

Brown, 2013; Erra et al., 2019; Lord et al., 2011). The basal ganglia is an active part of the central timekeeper in the brain, and studies using simple, repetitive single-joint movement tasks (e.g. finger tapping) have found deficits in central timing for pwPD compared to healthy older adults (Coull et al., 2011). Increased temporal variability is also often seen in gait (Baltadjieva et al., 2006; Cole et al., 2010; Lord et al., 2011), but a link between central timing deficits and temporal gait variability has not been established; an investigation of timing deficits in movements of intermediate biomechanical complexity (between finger tapping and gait) is lacking. Furthermore, the participation of the basal ganglia in the central timekeeper raises the possibility that timing deficits in pwPD may be due to dopaminergic neurodegeneration (versus secondary, cascading neurodegeneration), but dopaminergic modulation of timing deficits in pwPD has not been previously confirmed.

Additionally, the neurodegeneration in PD reduces gait automaticity and impairs the execution and timing of sequential movements (Calabresi et al., 2014; Yogev-Seligmann et al., 2008). PwPD compensate for these deficits with an increased attentional focus on the current task (e.g. gait, finger tapping sequence) (Wu & Hallett, 2005; Yogev-Seligmann et al., 2008). However, pwPD also demonstrate attentional deficits related to basal ganglia impairment that reduce their ability to perform secondary tasks without experiencing reduced performance in one or both tasks (Hausdorff et al., 2008; Ravizza & Ivry, 2001; Yogev et al., 2005; Yogev-Seligmann et al., 2008). The underlying mechanisms involved in interlimb coordination deficits in pwPD, and whether coordination is affected by dual-tasking, remains unclear.

1.1. Research objectives

The aims of this thesis are as follows:

1. Test measurement validity of existing symmetry metrics in the literature
2. Measure the effects of a dual task on interlimb coordination in pwPD while walking
3. Determine the effects of dopaminergic medication and auditory cueing on coordination of the upper and lower limbs in pwPD

1.2. Thesis impacts

Article 1: Previous comparisons of common asymmetry metrics only used experimental data, which are not suitable for determining metric reliability (since the lack of external ground truth prevents type I or II error detection) or sensitivity (i.e., statistical power, a probability, which cannot be measured from a single estimate based on experimental data). An experimentally validated simulation provided evidence on the reliability and sensitivity of common asymmetry metrics. This evidence may be used to increase research efficiency among future studies which assess movement asymmetry by encouraging the use of more sensitive asymmetry metrics.

Articles 2 and 3: The underlying mechanisms and extent of coordination deficits in pwPD are unclear. An assessment of a dual task and interlimb coordination showed that pwPD compensate for some coordination deficits with increased attention. Similarly, dopaminergic medication did not strongly affect timing deficits (observed for both internal and external timing) in pwPD; this supports previous research which found that timing deficits in pwPD are likely the result of non-dopaminergic neurodegeneration. Therefore, therapeutic programs developed for pwPD should include training which reinforces internal timing performance, thereby complementing the action of dopaminergic medication in pwPD.

2. Literature review

2.1. Parkinson's Disease

PD is a progressive neurodegenerative disease of the basal ganglia that causes several motor and non-motor symptoms with implications for movement and quality of life (Poewe et al., 2017). There are three cardinal motor symptoms of PD: 1) bradykinesia, defined as slowness of movement and decreased movement amplitude and/or velocity; 2) rigidity, defined as resistance to slow passive movement to relaxed major joints by an examiner; and 3) (resting) tremor, defined as a 4-6 Hz tremor in a resting limb (Postuma et al., 2015). The primary criteria for diagnosing PD include the presence of bradykinesia, at least one of the two other cardinal motor symptoms, and a positive response to dopaminergic medication (Postuma et al., 2015). In addition to the cardinal motor symptoms, postural instability and gait disturbances often emerge during the typical progression of PD and increase in prevalence and severity with time post-diagnosis (G. Alves et al., 2006; Postuma et al., 2015). PD is uncommon in people younger than 50 years, and the emergence of PD motor symptoms in people younger than 45 qualifies as early-onset PD (Poewe et al., 2017). PD prevalence increases with age, where the estimated occurrence in those over 80 is more than 3% (Poewe et al., 2017; Pringsheim et al., 2014).

In PD, the neurodegeneration begins in the dopaminergic neurons of the substantia nigra, one of the four main nuclei of the basal ganglia, and results in cascading deterioration of additional basal ganglia nuclei—including the striatum (composed of the putamen and caudate nucleus), globus pallidus, and the subthalamic nucleus—along with other nondopaminergic systems as the disease advances (Blandini et al., 2000; Dauer & Przedborski, 2003; Poewe et al., 2017). The loss of dopaminergic neurons in the substantia nigra causes dopamine depletion in the striatum (Poewe et al., 2017). PD symptomatic emergence is estimated to occur when the striatal dopaminergic depletion has reached at least 65% of healthy peers (Rakshi et al., 1999). These estimates are supported by a study of identical twins, with one twin diagnosed with PD and the other twin undiagnosed/asymptomatic, where the authors found that striatal

dopaminergic uptake in the asymptomatic cotwin is reduced compared to age-matched controls (Piccini et al., 1999).

In addition, neurodegeneration in PD exhibits bilaterally asymmetric reductions in dopaminergic activity throughout the basal ganglia, and particularly in the striatum (Bohnen et al., 2006; Lin et al., 2014; Rinne et al., 1993). Asymmetric neurodegeneration is correlated to handedness (Scherfler et al., 2012; van der Hoorn et al., 2012) and to an asymmetric presentation of motor symptoms, where one side is more affected (MA) than the other (less affected, LA) side (Bohnen et al., 2006; Lin et al., 2014). However, some participants do exhibit an MA side ipsilateral to the hemisphere with worse dopaminergic depletion (Scherfler et al., 2012).

While the asymmetric motor symptoms in PD may not be solely or directly related to asymmetric neurodegeneration, a unilateral presentation is a prominent feature of the disease and considered diagnostically important (Djaldetti et al., 2006; Postuma et al., 2015). A large proportion of people with PD (up to 85%) exhibit asymmetric motor symptoms (Uitti et al., 2005; Yust-Katz et al., 2008). Some evidence suggests that which side is more affected may influence the disease progression (Munhoz et al., 2013) and predict cognitive differences, with pwPD with a left MA side showing greater deficits in visuospatial domains, while pwPD with a right MA side have larger deficits in language and verbal memory domains (Verreyt et al., 2011). Movement asymmetry is greatest in early PD, and decreases with disease progression as the LA side movement degenerates to match the MA side (Djaldetti et al., 2006; Mirelman et al., 2019). Therefore, consideration of the MA side in PD is important to control a known factor in the heterogeneity of PD presentation and progression.

The basal ganglia participate in multiple parallel thalamocortical circuits, where each circuit funnels neuronal projections from an area of the cortex to functionally and anatomically distinct areas within the basal ganglia, which integrate the cortical inputs and project to distinct areas within the thalamus, and then project back to the input cortical areas; these circuits form a core,

semi-“closed” loop, where a particular basal ganglia-thalamocortical circuit receives projections from and sends projections back to a particular cortical area, while not excluding the presence of other inputs/outputs throughout that loop (Alexander et al., 1986; Draganski et al., 2008).

In the “motor” basal ganglia-thalamocortical circuit, the striatum serves as the input stage and receives somatotopically organized projections from sensorimotor cortical areas, including the supplementary motor area, which is also the primary recipient of the circuit outputs from the thalamus (Alexander & Crutcher, 1990). Dopaminergic activity in the substantia nigra and striatum has a reinforcing action on movements initiated in the motor cortex, which contributes to a “gating” action, whereby the basal ganglia modulates preparation and initiation of motor sets (movements), and inhibits inactive motor sets (Alexander & Crutcher, 1990; Calabresi et al., 2014; Graybiel et al., 1994). Therefore, impaired basal ganglia activity may lead to deficits in action selection and inhibition of competing motor plans, which has been observed in pwPD (Coxon et al., 2010; Kraft et al., 2007; Wu et al., 2010). Studies that investigated coordination, including movement asymmetry, in pwPD found deficits in coordination compared to healthy controls (Huang et al., 2012; Plotnik et al., 2007; Roemmich et al., 2013; Swinnen et al., 1997). In addition, these deficits in action selection and inhibition appear to be related to attentional deficits which are also seen in PD (Hausdorff et al., 2006; Horstink et al., 1990; Ravizza & Ivry, 2001).

The various motor and non-motor symptoms exhibited by pwPD are ultimately the result of the dopaminergic degeneration in the basal ganglia (Poewe et al., 2017), and some symptoms can be improved by dopaminergic medication, most commonly L-dopa which supplements striatal dopamine levels, and otherwise bolsters dopaminergic activity in the brain (Curtze et al., 2015; Stocchi et al., 2003). Dopaminergic medications primarily improve motor symptoms, observed in Unified Parkinson’s Disease Rating Scale (UPDRS) scores (Espay et al., 2011; Pavese et al., 2006; Schaafsma et al., 2003; Zach et al., 2020) and some gait characteristics (Curtze et al., 2015). However, some motor symptoms (Wright et al., 2007) and gait

characteristics (Lord et al., 2011; Rochester et al., 2011), are termed dopa-resistant for their lack of response to medication. Some non-motor symptoms are responsive to dopaminergic treatment (e.g. depression, anxiety, etc.), but cognitive dysfunction and attention deficits may not be improved (Chaudhuri & Schapira, 2009). The underlying mechanisms that contribute to dopa-resistant movement impairments are not well understood.

2.2. Coordination

Coordination can be described as the organization of many degrees of freedom into a smaller number of independent variables; in the context of the human body, this requires the control of 792 muscles to manipulate over 100 mechanical degrees of freedom (Turvey, 1990). Krasovsky and Levin proposed a quantifiable, practical definition of locomotor coordination as “an ability to maintain a context-dependent and phase-dependent cyclical relationship between different body segments or joints in both spatial and temporal domains” (Krasovsky & Levin, 2010); movements are cyclic in the context of steady-state locomotion.

At a neural level, coordination is produced and modified at multiple levels, from the spine to the cerebrum (Swinnen, 2002). Within the spine, central pattern generators act semi-autonomously to coordinate uni- and bimanual movements, and have been observed to contribute to quadrupedal coordination in decerebrate and decorticate felines and other vertebrates (Grillner, 1985). Some evidence in humans is consistent with task dependent action of central pattern generators (i.e. during gait, but not standing with arm swing or sitting) which may indicate residual quadrupedal locomotion pathways (Dietz et al., 2001; Dietz, 2002). More centrally, in the brainstem, the lateral corticospinal tract crosses in the medulla and primarily provides precise contralateral end-effector control, while the ventral corticospinal tract terminates bilaterally in the spinal cord and provides control of proximal and axial muscles (Brinkman & Kuypers, 1972; Shinoda et al., 1994).

Finally, in the cerebrum, a distributed network contributes to interlimb coordination including the sensorimotor cortex, premotor cortex, and supplementary motor area (SMA) (Debaere et al.,

2001). Bimanual synchronization does not appear to be solely mediated by the corpus callosum, as indicated by preserved synchronization tendency for symmetric/mirror movements following callosal transection (Berlucchi et al., 1994; Wiesendanger et al., 1994). The SMA shows high activity during learning of motor sequences (Halsband & Lange, 2006; Hardwick et al., 2013), and phasic activity before movement (sub)sequences, which is thought to reflect a role of the SMA in initiating movements (Iansek et al., 1995). The SMA also contributes to coordination timing and synchronization, as revealed by deficits in reproduction rhythm and motor sequences from memory after lesions to the SMA (Halsband et al., 1993). However, unilateral SMA lesions on either side did not transiently or permanently interfere with bimanual (temporal) synchronization (Wiesendanger et al., 1994), likely reflecting a distributed nature of the motor network used in bimanual coordination (Debaere et al., 2001).

The basal ganglia are a natural possible element of this distributed motor network, due to its extensive innervation of the SMA via thalamic outputs. Different areas of the putamen showed prominent activity during motor learning and performance of the learned movements, which likely indicates activity of different basal ganglia-thalamocortical circuits (Lehéricy et al., 2005). In particular, the basal ganglia showed increased activation when learning sensorimotor (defined as involving novel movement kinematics/dynamics) tasks (Hardwick et al., 2013), and when performing well-learned tasks (Seitz et al., 1990). In healthy adults, the putamen shows increased activation during motor task initiation which scales with coordinative difficulty (Kraft et al., 2007). Due to activity in the basal ganglia during movement coordination, neurodegeneration seen in PD may be expected to lead to deficits in coordination.

Indeed, pwPD exhibit decreased coordination accuracy and stability compared to healthy controls, and a decreased ability to perform more difficult coordination modes, which is thought to reflect a central deficit in coordination (Serrien et al., 2000; Swinnen et al., 1997). These findings of decreased ability to perform and maintain simple and challenging coordination modes in comparison to healthy age-matched controls are well supported by multiple studies

(Byblow et al., 2002; Johnson et al., 1998; Ponsen et al., 2006; van den Berg et al., 2000). Findings of coordination deficits in pwPD are supported by direct neuromotor measurements and neuroimaging: PwPD exhibit weaker motor synergies during multi-finger coordination (J. Park et al., 2012), and functional magnetic resonance imaging revealed that people with PD showed abnormal shifts in activity away from the basal ganglia and SMA towards primary motor and premotor cortices and the cerebellum during a challenging bimanual coordination task (Wu et al., 2010). Furthermore, motor symptom severity is also correlated with coordination performance: Swinnen et al. (1997) noted a correlation between Hoehn and Yahr scores and a decreased ability to perform more difficult coordination modes. Similarly, Almeida and Brown (2013) found a correlation between UPDRS scores and reduced coordination stability. Difficulty in coordinating fast bimanual movements by pwPD may logically thought to be related to bradykinesia (Serrien et al., 2000), but some studies suggest that the reduced coordinative performance, in terms of phase accuracy and variability, is independent of bradykinesia (Roemmich et al., 2013; van den Berg et al., 2000).

The large number of dopaminergic neurons in the striatum raises the possibility of dopaminergically mediated deficits in coordination. Administration of L-dopa in pwPD increases striatal dopamine (Pavese et al., 2006), which leads to increased cortico-striatal connectivity (Gao et al., 2017; Jahanshahi et al., 2010). In addition, Williams et al. (2002) noted a dopaminergic modulated degree of connectivity between the subthalamic nucleus and the cerebral cortex, in particular the supplemental motor area, when comparing pwPD ON and OFF medication. Dopaminergic medication led to more consistent organization of muscle synergies when maintaining postural stability in PD (Falaki et al., 2017). However, for dynamic tasks such as bimanual coordination, two studies on pwPD found that coordination accuracy and stability were not affected by medication (Almeida & Brown, 2013; Daneault et al., 2016). In contrast, Crenna et al. (2008) found that medication improved the arm-leg coordination during gait in pwPD. Although manipulation of dopaminergic medication could be an insightful method to

better understand the nature of coordination deficits in PD, existing literature investigating the influence of dopaminergic medication on coordination in PD is limited.

2.2.1. Measuring coordination

The coordination dynamics approach seeks to discover the underlying principles of interlimb coordination by characterizing the behavior of the system, which cannot be understood from its individual components (Amazeen et al., 1998; Swinnen et al., 1994; Turvey, 1990). Therefore, most methods for measuring coordination are rooted in the concept of relative phase, which is the (temporal) relationship between periodic elements, also known as oscillators. “Absolute” coordination occurs when multiple limbs oscillate at the same frequency (or multiples of), even when their natural frequencies may be different (Turvey, 1990); this leads to consistent (i.e. stationary) relative phase over time.

The Haken-Kelso-Bunz (HKB) model uses the relative phase between two oscillators as a “order parameter”—which characterizes the state of the system—to predict behavior such as spontaneous phase transitions, differential stability between coordination modes (anti-phase vs. in-phase), and critical fluctuations (i.e. variability) in the relative phase as the system nears a transition point (Haken et al., 1985). The HKB model explains previous observations that only two coordination modes are naturally stable for a pair of oscillators: in-phase, with a 0° phase offset between the oscillators, and anti-phase, with a 180° phase offset between the oscillators, and that in-phase oscillation is more stable than anti-phase (Haken et al., 1985; Kelso, 1984). Using relative phase, coordination can be characterized during bilateral oscillatory tasks which include in-phase and/or anti-phase movements, and many studies have observed results which match predictions of the HKB model (e.g. spontaneous phase transitions from anti-phase to in-phase, differential stability of coordination modes, and critical fluctuations prior to phase transitions) in simulations and experiments across multiple bilateral oscillatory tasks (e.g. finger or wrist oscillations, and gait) (Haken et al., 1985; Jeka & Kelso, 1995; Kelso, 1984; Lamoth et al., 2009; van Emmerik & Wagenaar, 1996). Furthermore, the greater stability of in-phase

versus anti-phase coordination appears to be reflected at a neural level, as evidenced by increased brain activity for anti-phase coordination modes for both real and imagined movements (Debaere et al., 2001; Oullier et al., 2005).

Relative phase can be calculated as a single point (discrete) or continuously. Discrete relative phase has been frequently used to assess coordination and has the benefit of providing a more immediately intuitive result than continuous relative phase. A natural, but incorrect, interpretation is that continuous relative phase is a continuous measure of the phase offset between (frequency-matched) signals, which intuitively should be constant throughout a period (assuming signals are stationary). However, continuous relative phase of non-sinusoidal signals (i.e., most real world signals) varies over a period, while only the average of continuous relative phase over a period is equivalent to the phase offset between signals (Lamb & Stöckl, 2014). Discrete relative phase will not detect intracycle changes in coordination, which may be undesirable (Krasovsky & Levin, 2010; Peters et al., 2003).

Discrete relative phase is calculated using the following equation:

$$\phi = 360° \times \frac{t_{Ai} - t_{Bi}}{t_{B(i+1)} - t_{Bi}} \quad (1)$$

where t_{Ai} and t_{Bi} are consistent points in the period (e.g. the identified beginning of a period) of two oscillators.

The phase coordination index (PCI) is a variant of discrete relative phase, originally applied specifically to swing time, but theoretically applicable to other signals, that sums the phase accuracy (discrete relative phase deviation from 180°) and variability (coefficient of variation of relative phase) of swing time (Plotnik et al., 2007).

To calculate continuous relative phase (CRP), the continuous phase of two continuous (timeseries) signals must first be calculated. The original method for calculating the continuous phase of a signal was published by Scholz and Kelso (1989) and used the equation

$$\phi = \tan^{-1}[(dX/dt)/X] \quad (2)$$

where the signal X has been normalized by rescaling to a range of ± 1. This method remains in common use; however, some authors have noted issues with this method because it is substantially affected by the signal normalization method (of which there are several), and is only valid for sinusoidal signals—where a signal and its derivative accurately recreate the phase plane (Lamb & Stöckl, 2014; Peters et al., 2003). Lamb and Stöckl (2014) recommended normalizing a signal by amplitude centering on zero, as in Eq. (3), and then calculating the instantaneous phase, which is defined as the angle of the (complex) analytic signal comprised of a signal and its Hilbert transform as the real and imaginary parts, respectively, in Eqs. (4) and (5) (Lamb & Stöckl, 2014).

$$X_{cent} = X - \min(X) - [\max(X) - \min(X)]/2 \quad (3)$$

$$\zeta = X + i\,H(X) \quad (4)$$

$$\phi = \tan^{-1}[H(X)/X] \quad (5)$$

CRP is regularly summarized in two ways: First, the relative phase of the system is found by averaging CRP, which gives a similar result as discrete relative phase, and indicates the overall coordination accuracy, typically near 0° or 180°, where departures may indicate imbalanced natural frequencies of the oscillators and other abnormal characteristics of the system (Schmidt et al., 1993). Second, according to the HKB model, critical fluctuations in relative phase indicate loss of stability that may precede a spontaneous transition in relative phase (Haken et al., 1985). These critical fluctuations can be measured as cycle–to–cycle variability in continuous relative phase (Hamill et al., 2000, 2012; van Emmerik & Wagenaar, 1996), and are interpreted as reduced coordinative stability.

While CRP is limited to comparing bi-joint coordination patterns, principal component analysis (PCA) enables the study of multi-joint coordination modes (Forner-Cordero et al., 2005). PCA is a linear transformation of multi-dimensional data into uncorrelated orthogonal

dimensions, known as principal components, sorted by variance from high to low (Daffertshofer et al., 2004). Analyses involving PCA commonly focus on the highest–variance dimensions, and, the remaining, lower–variance, principal components may be investigated as the residual error from the main signal or indications of instability in coordination (Daffertshofer et al., 2004; Forner-Cordero et al., 2005). Some authors assert that intermediate and higher–order principal components can contain discriminatory information indicative of subtle changes in movement (Phinyomark et al., 2015). Previous studies of PCA on multiple joint angle data revealed intersegmental coordination patterns and behavior that are consistent with continuous relative phase (Forner-Cordero et al., 2005). However, PCA may not be accurate for non-sinusoidal signals and/or relative phase relationships that differ from in-phase or anti-phase; this limitation may contribute to the low adoption of this method.

2.2.2. Movement asymmetry

Movement (a)symmetry is an outcome of interlimb coordination; where the presence and magnitude of bilateral movement asymmetry is movement and context dependent (Krasovsky & Levin, 2010). Theoretical models assert that the most naturally stable coordination modes between two or more oscillators (e.g. arms and/or legs during gait, etc.) will be temporally symmetric, where oscillatory peaks will occur simultaneously (Haken et al., 1985; Schöner et al., 1990). Tendencies towards spatial symmetry can also be inferred, during straight line walking, from typical bilateral symmetry about the sagittal plane. Therefore, symmetric movement, spatial or temporal, is a characteristic trait of typical coordination. In healthy gait, implicit or explicit assumptions of symmetric gait patterns are common in large amounts of gait research (Sadeghi et al., 2000); however, varying degrees of asymmetry are present in several bilateral gait characteristics (Vagenas & Hoshizaki, 1992; Sadeghi et al., 1997; Sadeghi, 2003; Plate et al., 2015; Killeen et al., 2018). Some authors have noted that these natural asymmetries in healthy adults suggest that asymmetry should be considered as an incomplete indicator of coordination (Krasovsky & Levin, 2010; Haddad et al., 2010). This view suggests that asymmetry is primarily

only relevant in comparison to “normal” levels of (a)symmetry, such as what is exhibited by healthy adults. However, although asymmetry is considered a fundamental, pathological characteristic of PD (Djaldetti et al., 2006), research on the presence or degree of asymmetry in various aspects of Parkinsonian gait and movement is under-represented in the literature.

Reduced and/or otherwise altered arm swing is a frequently recognized characteristic of PD gait (Knutsson, 1972; Nieuwboer et al., 1998). Asymmetry in arm swing magnitude is present to some extent in healthy young and older populations (Killeen et al., 2018; Kuhtz-Buschbeck et al., 2008; Plate et al., 2015), but multiple studies have noted increased arm swing asymmetry in early PD participants compared to healthy, age-matched controls. Mirelman et al. (2016) noted that carriers of the LRRK2-G2019S mutation, which increases the risk of PD, displayed higher arm swing asymmetry independent of PD diagnosis. Another study observed a progression of bradykinesia-related asymmetry in arm movements, and their extrapolations suggested that this asymmetry may be present before diagnosis (Louie et al., 2009). However, reduced and/or asymmetric arm swing is not always found in PD, which may indicate that asymmetry in the upper limbs is an example of the heterogenous presentation and progression of PD (Roemmich et al., 2013; Baron et al., 2018).

In the lower limbs, higher levels of asymmetry in various aspects of movements during gait (including hip, knee, and ankle joint motion, and swing time) have been observed in pwPD compared to healthy elderly and/or young adults (K. Park et al., 2016; Roemmich et al., 2013; Baltadjieva et al., 2006; Plotnik et al., 2007). Increased PCI (which is, in part, a measure of swing time asymmetry) has been seen in pwPD compared to controls among some studies. However, similar to findings of asymmetry in the upper limbs, other studies on pwPD found no difference in asymmetry of lower limb movements compared to healthy controls (Grajić et al., 2015; Vervoort et al., 2015). In addition to heterogeneity of PD, different choices in limb dichotomization (left/right vs LA/MA) between studies may also contribute to inconsistent findings of asymmetry (Baudendistel et al., 2022). Furthermore, conceptualization and

measurement of asymmetry vary across studies, which may lead to additional inconsistencies in findings of asymmetry in pwPD.

2.2.3. Measuring asymmetry

Similar to relative phase, measurements of (a)symmetry can be discrete or continuous, by comparing two discrete numbers (e.g. stride length) or comparing the similarity between two continuous signals (Viteckova et al., 2018). Although continuous measures of (a)symmetry are capable of detecting intra-cycle changes in (a)symmetry, discrete symmetry metrics are more common according to a review by Viteckova et al. (2018). Research on movement asymmetry is complicated by inconsistent definitions and measures of (a)symmetry within the literature (Sadeghi et al., 2000; Viteckova et al., 2018). Multiple commonly compared discrete symmetry metrics have unique measurement scales for the same concept (“asymmetry”), which leads to numerically incompatible results. Additionally, differences in the sensitivity of various metrics to detect a difference in (a)symmetry (e.g. between experimental conditions or groups) have been observed when using the same data to calculate asymmetry with different metrics (Błażkiewicz et al., 2014; Patterson et al., 2010; Sant’Anna et al., 2011). The explicit purpose of multiple previous studies is to compare common discrete (a)symmetry metrics with the intent to encourage a standardized method of measuring asymmetry (S. A. Alves et al., 2020; Patterson et al., 2010; Queen et al., 2020). Furthermore, several of these studies have discussed that previous similar papers comparing symmetry metrics have limitations that undermine their recommendations (S. A. Alves et al., 2020; Błażkiewicz et al., 2014; Queen et al., 2020).

Indeed, methodological issues weaken the strength of previous analyses and recommendations, even among studies which acknowledged and addressed some of the methodological weaknesses of their predecessors. A common weakness of several studies is the use of indirectly defined asymmetric references (e.g. stroke, PD, torn anterior cruciate ligament, or mechanically induced asymmetry) to provide an asymmetric “standard” (S. A. Alves et al., 2020; Patterson et al., 2010; Sant’Anna et al., 2011). The term “gold standard” is

commonly used to describe a method that is recognized to be the best (in whichever sense of "best" is most relevant) method, which is used as a reference when assessing or compare all other methods. Experimentally, there is no widely recognized "gold standard" for measuring or defining asymmetry; nevertheless, some form of measurement standard that can provide a reference level of asymmetry is needed to compare the accuracy, precision, or other qualities of asymmetry metrics. Ideally, a reference standard should be defined directly (e.g. in terms of asymmetry), but previously used asymmetric standards have only been defined using indirectly correlated characteristics (experimental or demographic), which are not directly and extrinsically known, and are potentially inconsistent (i.e. a heterogenous population like stroke survivors likely encompasses a wide range of gait asymmetry, depending on stroke severity and recovery). Such standards cannot be used to validate the performance of a metric. Additionally, the use of experimental data does not allow the sensitivity (from a frequentist[2] perspective) of metrics to be measured.

Patterson et al. (2010) classified a group of stroke survivors as asymmetric using a 95% CI based on a healthy control sample, and found no difference in classification among four asymmetry metrics; the authors recommended using the symmetry ratio based on ease of interpretation rather than on methodological criteria. (Calculations of Cohen's d effect size using the results of Patterson et al. (2010) indicate that a ratio, which the authors recommended, had one of the smallest effect sizes in every measured gait characteristic.) Sant'Anna et al. (2011) based analyses and recommendations on the assumed presence of increased asymmetry in a PD group compared to healthy controls. Błażkiewicz et al. (2014) incorrectly attempted to compare symmetry metrics by directly comparing the numerical results, thereby ignoring that every metric has its own scale (i.e. essentially "units", although many metrics are technically unitless) and therefore cannot be directly compared. Another study employed a similar analysis

[2] Frequentist statistical tests are focused on controlling the type I and type II error rates (Neyman, 1977)

on a protocol which directly compared the results of three symmetry metrics and had no asymmetric reference standard; the authors were unable to recommend a symmetry metric based on their results (Jafarnezhadgero et al., 2018). Queen et al. (2020) attempted to validate a newly proposed symmetry metric using a group of ACL patients as a reference standard. Finally, Alves et al. (2020) recognized that analyses performed by previous studies were methodologically weakened due to the use of assumed "asymmetric" standards and such data were therefore insufficient to adequately validate the performance of different symmetry metrics. The authors proposed a set of rules by which to assess the behavior of symmetry metrics and then used a dataset—which included a mechanically induced (via a crutch) asymmetric gait as the reference standard—to validate a newly proposed symmetry metric which adhered to their proposed rules (S. A. Alves et al., 2020). Although the authors acknowledge a stronger guarantee of asymmetry in the data, the magnitude of their asymmetric reference is not extrinsically known and potentially not consistent among participants (i.e. participants may react and adapt to the crutch differently, leading to inconsistent experimentally induced asymmetry); therefore, it is still an imperfect standard[3].

While the incompatibility between existing asymmetry metrics can often be mitigated by mathematically converting between metrics (similar to converting between metric and imperial units; although this has never been done to my knowledge), no previous paper has used an asymmetric standard which has an extrinsically guaranteed magnitude. In addition, as S.A. Alves et al. (2020) determined that multiple asymmetry metrics are functionally equivalent according to a set of rules for desired characteristics, alternate criteria are necessary to base recommendations for a symmetry metric; the sensitivity of various asymmetry metrics to

[3] A similarly limited experimental manipulation would be if researchers studying the effects of drunkenness on gait were to define the "drunk" experimental condition categorically ("We gave participants 2 alcoholic drinks"), but didn't control for alcohol tolerance. A stronger protocol might be to define the "drunk" condition based on blood alcohol levels.

different levels of asymmetry is a relevant criteria, but metric sensitivity has not previously been investigated.

2.3. Time perception and reproduction

The predictive power of relative phase in coordination suggests that timing plays a critical role in coordination (Swinnen et al., 1994). Under a framework proposed by Coull and Nobre (2008), there are two main forms of timing: explicit, where perception or reproduction of a remembered interval is required, and implicit, where sensorimotor information is predictive of the timing of impending events. While there has been much debate over appropriate models for an internal clock and their relative neurobiological feasibility, few deny that there must exist a central timekeeper which is active for intervals in the range of seconds to minutes (Matell & Meck, 2004). Functional neuroimaging provides strong evidence for localized activation of the dorsal striatum (putamen, caudate nucleus, globus pallidus) in the basal ganglia during explicit timing, independent of various task modalities (Coull et al., 2011). Alongside activity in the basal ganglia, the SMA and pre-motor cortex also show activity which may correspond with activity within parallel basal ganglia-thalamocortical loops (Alexander et al., 1986; Coull et al., 2011). In combination with evidence from pwPD, the basal ganglia is thought to be part of the central timekeeper for explicit timing (Coull et al., 2011; Matell & Meck, 2004).

A common protocol to characterize explicit timing is the synchronization–continuation paradigm, where a participant synchronizes a movement (typically finger tapping) to an auditory, metronomic cue during the first part of a trial, while during the second part of the trial, the participant must continue following the recalled cadence (Collyer & Church, 1998). Temporal perception and reproduction can be measured using the synchronization and continuation phases of this paradigm. In pwPD, explicit timing performance is often found to be disrupted (Coull et al., 2011).

During the synchronization phase, pwPD often exhibit higher variability compared to healthy controls in the “inter–response intervals” across multiple cue frequencies (Freeman et al., 1993),

and when on or off medication (Cerasa et al., 2006; Elsinger et al., 2003; Joundi et al., 2012); although, increased variability is not always found (Jahanshahi et al., 2010). During the continuation phase, pwPD typically tap slightly faster than the cueing frequency (Harrington et al., 1998; Ivry & Keele, 1989; Jahanshahi et al., 2010), and often exhibit increased inter–response interval variability, on and/or off medication (Harrington et al., 1998; O'Boyle et al., 1996; Elsinger et al., 2003; Hausdorff et al., 2006; Jahanshahi et al., 2010; Joundi et al., 2012). However, increased inter–response interval variability in pwPD during the continuation phase is also not always found (Cerasa et al., 2006; Ivry & Keele, 1989; Spencer & Ivry, 2005). While these null findings may be the result of false negative (type II) errors, other factors may contribute.

First, one study found increased inter-response interval variability in the MA side compared to the LA side (O'Boyle et al., 1996). Asymmetric response timing between the MA and LA sides could contribute to inconsistent findings, depending on protocol methodologies (e.g. which side, left/right or MA/LA, was tested, whether both sides were tested and averaged) and cohort characteristics (e.g. distribution of handedness and more affected side, degree of asymmetry). Second, some evidence suggests that heterogeneity in disease presentation[4] may result in subgroups in PD with differing levels of timing deficits; these subgroups may be distinguished by known symptomatic and/or demographic characteristics (e.g. freezing) (Tolleson et al., 2015; Vercruysse et al., 2012) or by timing deficits alone (Merchant et al., 2008).

In addition, Wing & Kristofferson (1973) proposed a model of interval timing variability which incorporates variability due to a central, internal timekeeper and variability due to motor responses. Using this model, some authors have found that pwPD exhibited increased central "clock" variability, even when ON medication (Harrington et al., 1998; Joundi et al., 2012;

[4] pwPD can be characterized by a number of subtypes and dominant symptoms, such as "tremor dominant", "postural instability and gait deficits", or "freezing of gait", which may also evolve over the course of the disease (G. Alves et al., 2006; Jankovic et al., 1990; Rajput et al., 2009; van Rooden et al., 2011)

O'Boyle et al., 1996), and when overall variability is not different than controls (O'Boyle et al., 1996).

Finally, given the function of the basal ganglia in timing, dopaminergic medication could be expected to modulate timing deficits. Evidence in support of dopaminergically mediated timing deficits is mixed, with both positive (O'Boyle et al., 1996) and negative (Elsinger et al., 2003; Jahanshahi et al., 2010; Spencer & Ivry, 2005) results; however, all these studies were relatively small (i.e. only statistically powered to detect large effects), with groups sizes of 8–12.

Most of the previously cited studies investigating coordination and timing deficits in pwPD used simple tasks (e.g. single–joint oscillation, finger tapping). During gait, a relatively complex biomechanical task, pwPD also typically exhibit increased temporal variability (e.g. step/stride time variability (Cole et al., 2010; Plotnik et al., 2007), single/double support variability (Baltadjieva et al., 2006; Lord et al., 2016), etc.) compared to healthy controls. Increased gait variability is associated with reduced stability and falling status in PD (Cole et al., 2010; Lord et al., 2016; Schaafsma et al., 2003); however, it is unclear what (if any) role timing deficits play at this complex scale (vs. simple single–joint tasks). Short and medium-term (4–week) physical training with metronomic cues reduced step and stride time variability in pwPD, which suggests that central timing deficits may play a role in gait variability (Fernández-Del-Olmo & Cudeiro, 2005; Hausdorff et al., 2007). Interestingly, after the 4–week training (which did not include finger tapping), self-paced finger tapping variability reduced (vs. pre–training) in pwPD to similar levels as controls (Fernandez del Olmo et al., 2006); this study lacked a functional control group (i.e. a PD group on a similar training program without rhythmic cues to exclude the possibility of improved finger tapping variability due to other neuromuscular improvements), but the evidence suggests that central timing deficits in pwPD may contribute to gait variability. However, directly attributing reduced coordination during gait to timing deficits is challenged by the large number of degrees of freedom in gait, where both spatial and temporal aspects of movement can be adjusted to accommodate task demands (Morris et al., 1998). Instead, a more constrained

motor task, but with similar complexity, could provide some evidence towards the relative contribution of timing deficits to dyscoordination in pwPD.

2.4. Dual-tasking

Dual task (DT) paradigms are often used to investigate automaticity—where a learned task can be performed without attention and with little to no interference from a secondary task (Logan, 1979). In healthy adults, simultaneous production of two (or more) novel, independent motor tasks is nearly impossible, and often results in unintended interactions between the tasks (Heuer, 1991). pwPD exhibit decreased abilities in shifting attention between motor tasks, which appears to be related to basal ganglia dysfunction (Ravizza & Ivry, 2001).

Dual tasking creates a context in which the cognitive demands of a secondary task may interfere with the primary task (e.g. gait or postural balance) and can thereby support the presence or absence of automaticity in the primary task (Woollacott & Shumway-Cook, 2002). Although gait has traditionally been considered an automatic task, the use of DTs have shown that gait has measurable cognitive demands, even in healthy adults (Woollacott & Shumway-Cook, 2002). Woollacott and Shumway-Cook (2002) acknowledge that although the accuracy in estimating attentional demand is limited, due to mutual interference between the two tasks, DT methodologies are still a valuable tool to investigate cognitive demands and loss of automaticity. Additionally, increased DT interference during gait can be predictive of fall risk (Verghese et al., 2002; Yogev-Seligmann et al., 2008).

There are three theories of the mechanism behind DT interference: resource sharing, bottleneck theory, and the multiple resource model (Yogev-Seligmann et al., 2008). First, resource sharing asserts that attentional resources are finite and shared, so the addition of a second task may oversubscribe the attentional resources, causing decreased performance in at least one task (Yogev-Seligmann et al., 2008). Bottleneck theory suggests that when two tasks require the same neural resource, one will be delayed until the first task is no longer using the contended resource (Yogev-Seligmann et al., 2008). Third, the multiple resource model

proposes that tasks may require multiple cognitive resources, and the tasks will only interfere if there are common resource requirements between the two tasks (Yogev-Seligmann et al., 2008). Yogev-Seligmann et al. (2008) noted that studies have supported each theory, but that a unified theory is still lacking.

Several reviews of the effects of dual tasking on gait have noted that there is a minimal DT cost (DTC) in healthy young adults, which increases with age (Al-Yahya et al., 2011; Woollacott & Shumway-Cook, 2002; Yogev-Seligmann et al., 2008). Similar to how cognitive tests target a particular cognitive domain, dual tasks can also be categorized. Al-Yahya et al. (2011) used five classes in their review of DT interference in gait: reaction time tasks, discrimination and decision-making tasks, mental tracking tasks, working memory tasks, and verbal fluency tasks. Different DT categories have been found to have different DTC among different populations and for different gait characteristics. A meta-analysis noted that healthy young and old participants experienced the greatest DTC for gait speed with verbal fluency tasks, while those with neurological disorders experienced the greatest DTC for gait speed with mental tracking tasks (Al-Yahya et al., 2011). Further, Beauchet et al. (2005) were one of the first authors to note that gait characteristics are responsive in varying degrees to different tasks: stride time of elderly adults was reduced by both mental tracking and verbal fluency tasks, while stride time variability was only increased by the mental tracking task. In PD, Penko et al. (2018) found generally worse spatiotemporal gait performance in DT categories of discrimination/decision-making, mental tracking, working memory, and verbal fluency, but noted that the mental tracking task affected the largest number of gait characteristics. However, when comparing cognitive and motor tasks, O'Shea et al. (2002) found no differences in DTC for gait speed, stride length, or cadence between a mental tracking and a motor task. Amidst the unique population and gait-characteristic susceptibilities to DT interference among different DT categories, there is no general framework within the literature which explains the observed effects (with respect to why different movements are affected by specific DTs and DT categories).

In pwPD, several studies have observed similar DTC between pwPD and healthy older controls across numerous aspects of gait and posture (Rochester et al., 2011; Yogev-Seligmann et al., 2013). However, mediolateral stability (step width and width variability) was more affected by DT in PD than healthy older controls (Rochester et al., 2014); increases in step width variability between single-task and DT in PD was reported by Siragy and Nantel (2020). Additionally, some studies reported changes in arm swing in PD, but not controls, between single-task and DT (Mirelman et al., 2016; Baron et al., 2018). Arm swing during gait is the result of passive and active coupling between the arms and legs which serves to minimize angular momentum about the vertical axis (Collins et al., 2009; Dietz et al., 2001); therefore, any changes in arm swing that are independent of changes in gait speed indicate a change in coordination for level straight walking (van Emmerik & Wagenaar, 1996).

Several studies have noted correlations between DTC and some gait characteristics linked to fall risk, such as PCI, gait variability, and gait asymmetry (Plotnik et al., 2009; Plotnik, Giladi, et al., 2011; Yogev et al., 2005, 2007). However, evidence that increased DTC is predictive of fall risk in PD is limited and conflicting. Hausdorff et al. (2002) noted that gait variability under single-task conditions, but not DT, was correlated with fall risk in PD. In a cross-sectional study, Plotnik et al. (2011) noted an increased DTC for gait variability and PCI in PD fallers compared to non-fallers, using a mental tracking task. Additionally, Jacobs et al. (2014) found that pwPD were more susceptible to falling due to a postural perturbation than healthy controls when performing a verbal fluency DT.

Studies have shown that coordination of bimanual movement patterns can be stabilized by an attentional focus, but a DT serving as an attentional distractor interferes with coordinating the motor task (Lee et al., 2002; Temprado et al., 1999). Since gait while dual tasking may be more similar to gait in the real world than typical laboratory recordings of steady–state gait (Hillel et al., 2019), dual tasking during gait may offer an ecologically valid method of manipulating attention to highlight coordinative deficits (McFadyen et al., 2017). Studies of coordination-

related metrics in pwPD show declines in some aspects of upper- and lower-limb coordination during DT (Baron et al., 2018; Mirelman et al., 2016; Plotnik et al., 2009), and the DTC of some metrics distinguishes PD fallers from PD non-fallers (Plotnik, Giladi, et al., 2011). These results suggest that loss of automaticity for movement coordination in pwPD (i.e. noted by presence of significant DTC) may provide insight into the progression of motor impairments and may not always be apparent without experimental manipulation.

3. General methods

3.1. Research design

3.1.1. Article 1

A Monte Carlo random sampling-based simulation was used to estimate the power of discrete symmetry metrics for application to gait. Simulation plausibility was supported by experimental data from a previous study with a within-subjects design (Hill & Nantel, 2019) which included tied and split-belt walking conditions (i.e. experimentally imposed asymmetric gait of known magnitude).

3.1.2. Article 2

This data was previously collected as part of a larger research program “Early Detection of Postural Impairments and Gait Disturbances phenotype in individuals with Parkinson’s disease: new strategies to detect and slow the progression of postural instability and gait disturbances.” A within-subjects repeated measures design was used to examine the effects of a dual-task on interlimb coordination during steady-state walking in pwPD.

3.1.3. Article 3

This data was previously collected as part of a larger research program “Freezing mechanisms of upper and lower limbs in PD.” A between and within-subjects design was used to examine the effect of auditory cueing and medication on interlimb coordination during repetitive reaching or stepping in place tasks in people with PD and healthy controls.

3.2. Data analysis and reduction

3.2.1. Gait events (Articles 1 & 2)

Gait events (GE) were required for articles one and two. An instrumented split-belt treadmill (i.e. integrated force plates beneath each belt) was used in articles one and two, and vertical ground reaction force (vGRF) is the gold standard for detecting the GE of heel strike and toe–off. However, participants occasionally wandered mediolaterally until both feet were stepping on one force plate (more common in participants with PD). In addition, the complete data collection

on which article's 1 and 2 were based featured trials designed to perturb (e.g. slip or trip) the participant's gait, which induced high–impulse recovery steps by the participants that resulted in a baseline drift in the vGRF signal. The mediolateral wandering and baseline drift prevented accurate automatic identification of GE from the vGRF signal. Therefore, GE were manually identified from vGRF on a subset of the gait trials used in each article (1 & 2) to be used as gold standard data for evaluating the accuracy/precision of alternative automatic GE identification algorithms. GE were only manually identified when participants unambiguously stepped wholly on the correct force plate (i.e. steps that bridged the force plates were excluded).

The first algorithm to be evaluated was published by Roerdink et al. (2008). Heel strikes are identified by local minima in vertical heel marker position, and toe-offs are identified by the local maxima in the vertical heel marker velocity. The window for local extrema was set to 0.1 s. Minima in position (for heel strike) were required to have a minimum (topographic) prominence[5] of 3 cm, and maxima in velocity were required to have a minimum prominence of 1.2 m/s. For the gait trials used in article 1, heel strikes were identified 5.75 ms, 95% CI [5.5, 6.0], (*N*=10,019) after the reference heel strikes, and toe–offs were identified 34.6 ms, [34.8, 34.4], (*N*=9,995) before the reference toe-offs. The CI of stride time error was 0.33 ms, [-0.028, 0.70], (*N*=4,982). In the case of the gait trials used in article 2, heel strikes were identified 3.95 ms, 95% CI [2.3, 5.6], (*N*=9,370) after the reference heel strikes, and toe–offs were identified 48.0 ms, [49.5, 46.5], (*N*=9,234) before the reference toe–offs. The CI of stride time error was 1.2 ms, [-0.46, 2.9], (*N*=4,608). The accuracy and precision of this GE identification method were deemed acceptably small in consideration of typical step time and step time variability in healthy older adults (Brach et al., 2007) and people with PD (Baltadjieva et al., 2006; Frenkel-Toledo et al., 2005), and in consideration that stride time variability would not be included as a

[5] Topographic prominence is the height of a peak, relative to neighboring peaks and valleys. Prominence is technically defined as the absolute difference between a given peak and the next highest valley within the span of larger peaks (or signal bounds) on either side of the given peak.

dependent variable in either article. Therefore, no other GE algorithms were evaluated, and the Roerdink et al. (2008) GE algorithm was chosen. The code and notebook for evaluating the GE are on Zenodo (Hill, 2024).

4. Articles

4.1. Sensitivity of discrete symmetry metrics: implications for metric choice

4.1.1. Summary

Background:

- Gait and movement asymmetry is a characteristic of multiple pathological populations, including those with Parkinson's disease, Huntington's disease, and stroke survivors
- Asymmetry of discrete (i.e. scalar as opposed to vector/time-series) variables, such as step time, has been calculated in multiple ways.
- Previous studies suggest that different symmetry metrics are numerically incompatible (preventing direct comparison without unit conversion), and show different sensitivity to detect asymmetry, when used on the same data

Findings:

- Several common discrete symmetry metrics exhibit practically similar (reaching 80% power within 0.1 of asymmetry magnitude R of other metrics) levels of sensitivity
- A bilateral difference (e.g. $\mathrm{left} - \mathrm{right}$) is the most sensitive discrete symmetry metric
- A ratio (e.g. $\frac{\mathrm{left}}{\mathrm{right}}$) is susceptible to loss of sensitivity due to large group variability
- Asymmetry should not be transformed with an absolute value: two metrics defined with an absolute value transformation exhibited worse sensitivity (increased false negative error rate) compared to the same, but untransformed, metrics

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RESEARCH ARTICLE

Sensitivity of discrete symmetry metrics: Implications for metric choice

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Abstract

Gait asymmetry is present in several pathological populations, including those with Parkinson's disease, Huntington's disease, and stroke survivors. Previous studies suggest that commonly used discrete symmetry metrics, which compare single bilateral variables, may not be equally sensitive to underlying effects of asymmetry, and the use of a metric with low sensitivity could result in unnecessarily low statistical power. The purpose of this study was to provide a comprehensive assessment of the sensitivity of commonly used discrete symmetry metrics to better inform design of future studies. Monte Carlo simulations were used to estimate the statistical power of each symmetry metric at a range of asymmetry magnitudes, group/condition variabilities, and sample sizes. Power was estimated by repeated comparison of simulated symmetric and asymmetric data with a paired t-test, where the proportion of significant results is equivalent to the power. Simulation results confirmed that not all common discrete symmetry metrics are equally sensitive to reference effects of asymmetry. Multiple symmetry metrics exhibit equivalent sensitivities, but the most sensitive discrete symmetry metric in all cases is a bilateral difference (e.g. left—right). A ratio (e.g. left/right) has poor sensitivity when group/condition variability is not small, but a log-transformation produces increased sensitivity. Additionally, two metrics which included an absolute value in their definitions showed increased sensitivity when the absolute value was removed. Future studies should consider metric sensitivity when designing analyses to reduce the possibility of underpowered research.

Introduction

Assumptions of bilateral symmetry in the lower limbs during healthy gait are implicit to much of gait research, and many studies collect and report data from only one side of the body, or report the average both sides [1]. Nevertheless, Sadeghi et al. [1] found evidence for the presence of both symmetric and asymmetric characteristics of kinematic and kinetic aspects of gait among healthy people. Furthermore, several populations, including those diagnosed with Parkinson's disease (PD) or who have experienced stroke, have unilateral neural pathologies which cause distinct gait asymmetries compared to healthy controls [2–6]. These gait asymmetries are of interest in pathological populations for tracking disease progression or rehabilitation progress [6–8].

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Measurements of gait asymmetry can be grouped into two classes, discrete and continuous metrics, which either compare two scalar numbers or two continuous time-series. In this paper, we will focus primarily on the more common class of symmetry measures: discrete symmetry metrics (DSM). Sadeghi et al. [1] and Viteckova et al. [9] published reviews of literature analyzing gait symmetry which identified five discrete symmetry metrics commonly used in the literature [10–14].

The first of these five discrete symmetry metrics, a ratio, was introduced by Seliktar and Mizrahi [10] for analyzing asymmetry of ground reaction forces. Robinson et al. [11] also measured symmetry in ground reaction forces with a new metric, commonly referred to as the symmetry index. Vagenas and Hoshizaki [12] introduced a third discrete symmetry metric while analyzing the asymmetry of lower limb kinematics. Plotnik et al. [13] introduced a new metric to assess the relationship between gait asymmetry and freezing of gait in PD. Another metric was proposed by Zifchock et al. [14] to address issues of previous DSMs related to the choice of reference value [11]. Additionally, a research group from Newcastle University uses another metric on a number of spatiotemporal gait variables [15, 16], and two new DSM have been recently proposed by Queen et al. [17] and Alves et al. [18]. Despite their conceptual equivalence, the different defining equations for all of these DSM produce unique numeric results which are not directly comparable [19].

Likewise, these metrics produce different standardized effect sizes and findings of significance for the same underlying effect of asymmetry [17–20]; these results suggest that metrics are not equally powered to detect effects of asymmetry [21]. Achieving adequate power (e.g. power > 0.8) is an important factor in experimental design [21], therefore, understanding the differences in DSM sensitivity to effects of asymmetry may allow the design of better powered experiments. No previous studies comparing common DSM were designed to directly assess metric sensitivity, in terms of power to detect an effect of asymmetry.

Statistical power is a function of sample size, significance criterion, and the effect size [21]. A power analysis known as "sensitivity power analysis" in G*Power [22] can analytically calculate power for many statistical tests given a significance criterion, sample size, and effect size. However, symmetry metric sensitivity cannot be assessed in this way because it remains unclear how a given underlying effect of asymmetry translates to standardized effect sizes for each symmetry metric [18]. Additionally, the sensitivity of various symmetry metrics cannot be precisely assessed using (finite) experimental data as a reference effect of asymmetry because observed effect sizes have inherent error, as point estimates, which would propagate to estimates of sensitivity [21]. Data from observational studies which lack known true effects, as in some previous studies [17, 19, 20], are particularly ill-suited for comparing symmetry metric sensitivity because false positives could overestimate metric sensitivity.

To ensure applicability to a range of populations and study designs, the sensitivity of symmetry metrics should be assessed on a wide range of effects. Precise estimates of power require large amounts of data that could be prohibitive to collect experimentally. A Monte Carlo simulation is a convenient method to generate the large volume of data needed to accurately estimate power while ensuring that a broad range of factors of effect size (e.g. mean difference and group/condition variability) are evaluated.

Therefore, as previous studies have covered the literature with respect to the validity of general assumptions about the degree of asymmetry present in gait [1], and with respect to the breadth of commonly used symmetry metrics and data analyzed for gait symmetry [9], the purpose of this study is to provide a comprehensive assessment of the sensitivity of common discrete symmetry metrics using power simulations and unreported data from a previous study [23] to validate simulation assumptions. This study will aid the design of future studies

by informing authors which metric(s) are appropriate to maximize the power to detect asymmetry for their experimental design.

Materials and methods

Power simulation

Discrete symmetry metrics are all mathematical functions which accept two arguments (which can be any set of bilateral variables, e.g., left and right step swing time, affected and unaffected joint range of motion, etc.). We represent a generic symmetry function as $S(x, y)$. We assume that the inputs x and y are independent, normally distributed (an assumption made by many parametric tests), have the same sign, and have the same shape with a variability σ (e.g., group, condition):

$$\begin{aligned} \boldsymbol{\mathcal{X}} &\sim x\boldsymbol{\mathcal{N}}(1, \sigma^2) \\ \boldsymbol{\mathcal{Y}} &\sim y\boldsymbol{\mathcal{N}}(1, \sigma^2) \end{aligned} \tag{1}$$

$$S(\boldsymbol{\mathcal{X}}, \boldsymbol{\mathcal{Y}}) = S\big(x\boldsymbol{\mathcal{N}}(1, \sigma^2),\ y\boldsymbol{\mathcal{N}}(1, \sigma^2)\big) \tag{2}$$

As noted by Alves et al. [18], a key characteristic of symmetry metrics is the relative difference between x and y, the ratio y/x. Therefore, Eq (2) can be simplified to

$$S\big(x\boldsymbol{\mathcal{N}}(1, \sigma^2),\ y\boldsymbol{\mathcal{N}}(1, \sigma^2)\big) = S\big(\boldsymbol{\mathcal{N}}(1, \sigma^2), R \cdot \boldsymbol{\mathcal{N}}(1, \sigma^2)\big) \tag{3}$$

Where $R = y/x$ and represents the asymmetry magnitude. Eq (3) describes the general form that was used for randomly sampling data (parameterized by R and σ) and subsequent evaluation by a symmetry metric S.

Discrete symmetry metrics from eight previously published papers [10–14, 16–18] were included, based on presence in previous reviews, number of citations, or if recently proposed as improvements on previous metrics. Two metrics [13, 16] are defined with absolute values and solely assess asymmetry magnitude; to enable consistent comparisons between metrics, these two metrics were assessed with and without the absolute value applied. As well, Alves et al. [18] proposed a weighting factor for their metric based on the standard deviation of the input data; the weighted and unweighted metric were evaluated. The standard deviation used in the weighting factor was the σ value from the set of parameters for a given test, which will produce a best-case estimate of power, as the true standard deviation would not be known for real data.

Simulated data was randomly sampled with standard deviation $\sigma = [0.01,1]$, and with an asymmetry magnitude of $R = [1,5]$. This range of parameters is expected to be sufficient to extrapolate metric behavior to untested parameters. Statistical power can be estimated as the proportion of significant test results when comparing simulated symmetric data (where $R \cong 1$) to asymmetric data (where $R \neq 1$) using a paired t-Test. Significance was defined as $\alpha = .05$, and test sample sizes of $N = [10,100]$ were evaluated. For every combination of testing parameters (R, σ, sample size N), all metrics were tested on the same randomly sampled data, to prevent extreme values from unevenly affecting metrics, and power was estimated from the proportion of 20 million tests. The rate at which metrics' power increases versus asymmetry magnitude distinguishes metric sensitivity. Sufficient power was defined as >0.8, and a difference between metrics of >0.1 in R at the 0.8 power threshold was deemed a practically significant difference in metric sensitivity.

Experimental data

A previously published study from these authors used a split-belt treadmill to mechanically induce asymmetric gait [23]. Kinematic data were collected at a frequency of 100 Hz using the Computer Assisted Rehabilitation Environment (CAREN; CAREN-Extended, Motekforce Link, Amsterdam, NL) which includes an instrumented split-belt treadmill (Bertec Corp., Columbus, OH) and a 12 camera Vicon motion capture system (Vicon 2.6, Oxford, UK). Gait speed during tied-belt walking was set at 1.2 m/s, while during split-belt walking, the left belt maintained the 1.2 m/s speed and the right belt was slowed to 80% of the left belt, 0.96 m/s. Gait trials lasted 200 s, and the first 25 s were ignored to ensure participants had reached a steady-state. Gait events were calculated using an algorithm based on the local extrema of the vertical position and velocity of the heel marker [24]. Swing time was calculated in units of percent stride; future references to swing time will omit mention of the units. Swing time asymmetry was compared between tied and split-belt walking, as previous studies show that split-belt walking causes immediate changes in stance and swing time [25]. Swing time asymmetry was evaluated using all metrics. For comparison to modelling assumptions made in the power simulations, normality of left and right swing times were assessed using the Anderson-Darling test, and Bartlett's test was used to test equality of variances between left and right sides. Tied and split-belt conditions were compared using a paired t-Test. All statistical tests used $\alpha = 0.05$. All simulations and analyses were performed using the Julia programming language [26] using custom code [27].

Results

General metric characteristics

All discrete symmetry metrics evaluated here are shown in Table 1, including their defining equations and important characteristics (the value for perfect symmetry, the limits of the functions for positive inputs, and whether the metric has a directional output—an output which uniquely signifies which input, x or y, is larger/smaller). The order of x and y arguments have been adjusted, when necessary, such that a larger y always produces a positive asymmetry

Table 1. Discrete symmetry metrics.

Metric	Definition	Perfect symmetry	Limits† (x→∞,y→∞)	Directional
Seliktar and Mizrahi (Sel86) [10]	$S(x,y) = \frac{y}{x}$	1	0,∞	Y
Robinson et al. (Rob87) [11]	$S(x,y) = \frac{y-x}{y+x} \cdot 200$	0	-200,200	Y
Vagenas and Hoshizaki (Vag92) [12]	$S(x,y) = \frac{y-x}{\max(x,y)} \cdot 100$	0	-100,100	Y
Plotnik et al. (Plo05) [13]	$S(x,y) = \lvert\ln\left(\frac{y}{x}\right)\rvert \cdot 100$	0	0,∞	N*
Zifchock et al. (Zif08) [14]	$S(x,y) = \left(\frac{45^\circ - \text{atand}\left(\frac{x}{y}\right)}{90^\circ}\right) \cdot 100$	0	-50,50	Y
Rochester et al. (Roc14) [16]	$S(x,y) = \lvert y - x\rvert$	0	∞,∞	N*
Queen et al. (Que20) [17]	$S(x,y) = \frac{y-x}{\max(0,x,y)-\min(0,x,y)}$	0	-1,1	Y
Alves et al. (Alv20) [18]	$S(x,y) = \frac{y-x}{\sqrt{2\left(x^2+y^2\right)}}$	0	-1,1	Y
Alves et al. (Alv20b) [18]	$S(x,y,\sigma) = \frac{y-x}{\sqrt{2\left(x^2+y^2\right)}} \cdot \left(1 - \frac{\sqrt{2}\sigma}{\sqrt{2\sigma^2+x^2+y^2}}\right)$	0	-1,1	Y

*Removing the absolute value enables directional output.

†These limits are accurate for inputs of the same sign, however, many of the discrete symmetry metrics can produce larger values for inputs of differing signs (not including Plotnik et al. [13], where the logarithm requires identically signed inputs).

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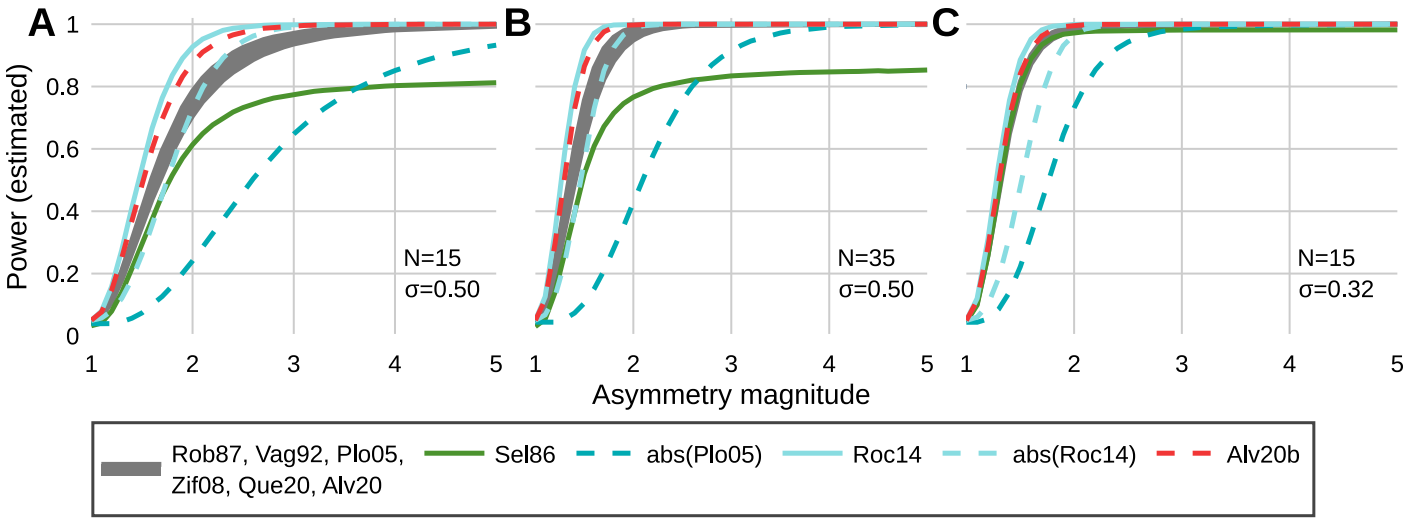

Fig 1. Estimated power vs. asymmetry magnitude. Estimated power for (A) a sample size of 15 and a variability of 0.50. (B) a sample size of 35 and a variability of 0.50. (C) a sample size of 15 and a variability of 0.32.

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value for every metric. Symmetry metrics are abbreviated as the first three letters of the first author followed by the last two digits of the publication year, and metrics with an absolute value are distinguished by an absolute value function annotation, e.g. "abs(Plo05)".

Power simulation

As sample size increases and group/condition variability decreases, all metrics reach sufficient power at a lower asymmetry magnitude (Fig 1A vs 1B and 1A vs 1C). When $R = 1$ (a true null effect), average power was approximately equal to the critical alpha, $0.049 \cong \alpha$. Six metrics (Rob87, Vag92, Plo05, Zif08, Que20, and Alv20) display practically equivalent sensitivity for all variabilities and sample sizes (Fig 1). The ratio (Sel86) ceases to asymptotically approach 100% power for variability greater than 0.25, regardless of sample size; at the largest sample size (100) and variability (1.0), sufficient power was not reached for the largest asymmetry magnitude (power = 0.79). In contrast, the abs(Plo05) metric approached 100% power for the entire range of variabilities, but increased in power much slower than the ratio. The slow increase in power of the Sel86 and abs(Plo05) metrics compared to all other metrics was practically significant for all sample sizes, and increased with variability (Figs 1 and 2). The abs(Plo05) and abs (Roc14) metrics both show large decreases in power compared to their respective non-absolute valued versions and increase in power with asymmetry magnitude much slower in comparison (Fig 1). The Roc14 and Alv20b metrics reached sufficient power quicker than other metrics for all variabilities and sample sizes, however meaningful differences between these and other metrics only exist for variability greater than 0.25. The Alv20b metric (with the weighting factor) increases in power faster than the unweighted (Alv20) version, however, this difference is only practically relevant for variabilities greater than 0.5.

Experimental results

Gait trials from fifteen healthy, young adults (7 female, 23.4 ± 2.8 years (mean ± s.d.); 72.3 ± 13.5 kg; 170.2 ± 8.1 cm) were analyzed [23]. Table 2 reports the average and standard deviation of the swing time, calculated from 140 strides per trial, and the equivalent magnitude

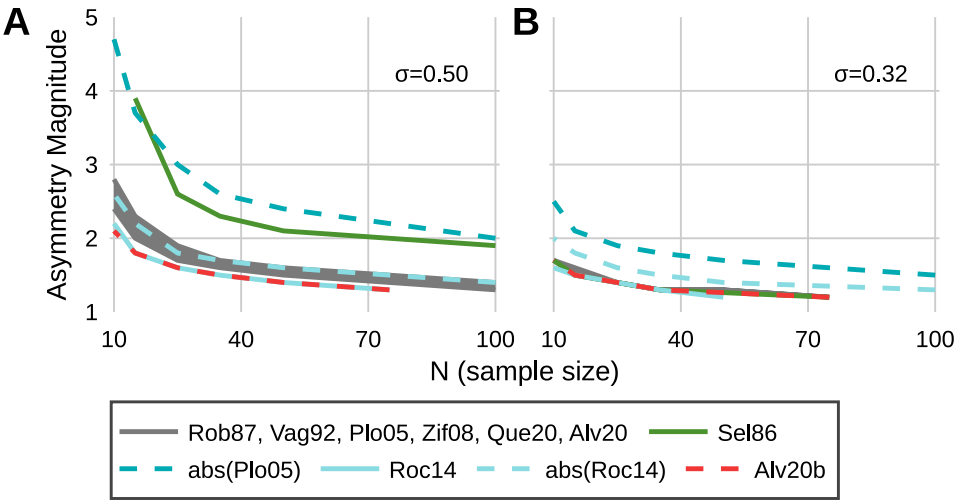

Fig 2. Minimum sample size to achieve sufficient power (80%). Shown at a variability of (A) 0.50 and (B) 0.32. The maximum and minimum sample tested were 100 and 10, respectively. Lower asymmetry magnitude and smaller N (i.e. closer to the bottom left corner) represents higher sensitivity.

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asymmetry and variability in the format used in the power simulations. Left and right swing times for both tied and split-belt conditions passed the Anderson-Darling test of normality ($p > 0.46$). Both tied and split-belt conditions passed Bartlett's test of equality of variances between the left and right sides ($p > 0.44$). Results for swing time asymmetry evaluated with all metrics are reported in Table 3. All metrics produced significant differences ($p < .001$).

Discussion

The results of the power simulation follow several basic principles of statistical power: power for a true null effect is equivalent to the critical alpha, power increases with effect size (e.g. increases in asymmetry magnitude and decreases in variability) and sample size [21]. Our results confirm that symmetry metrics assessed in this study exhibit different power for the same underlying effects of asymmetry, particularly for small effects. Two metrics (Roc14 and Alv20b) were highly sensitive and robust to increased variability, two metrics (Sel86 and abs (Plo05)) show poor sensitivity to small effects and high variability. Finally, six metrics (Rob87, Vag92, Plo05, Zif08, Que20, Alv20) exhibited similar sensitivity, at slightly less than the non-absolute value Roc14 and Alv20b metrics. Additionally, the swing time asymmetry results validated assumptions made for the power simulation (independent and normally distributed inputs with equal variances) and were situated within the range of asymmetry magnitudes, variabilities, and sample sizes tested in the power simulation.

The use of the split-belt treadmill to mechanically induce asymmetric changes in swing time prevents the occurrence of false positive test statistics and allows greater confidence in assessing sensitivity based on differences in findings of significance among the metrics. Despite

Table 2. Swing time.

Condition	Left (%)	Right (%)	Asymmetry magnitude (R)	Variability (σ)
Tied-belt	38.6 ± 0.67	38.9 ± 0.67	1.01	0.017
Split-belt	40.5 ± 1.3	36.2 ± 1.1	1.12	0.033

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Table 3. Swing time asymmetry.

Metric	Mean difference*	95% CI		t(15)	$d_{unbiased}$
		Lower	Upper		
Seliktar and Mizrahi [10]	-0.114	-0.131	-0.0963	-14.2	4.03
Robinson et al. [11]	-12.0	-14.0	-10.0	-13.0	3.80
Vagenas and Hoshizaki [12]	-11.3	-13.1	-9.61	-14.1	4.03
Plotnik et al. [13]	-12.0	-14.0	-10.0	-12.9	3.79
Plotnik et al. [13] (abs)	10.1	7.47	12.7	8.29	3.25
Zifchock et al. [14]	-3.82	-4.44	-3.19	-13.0	3.81
Rochester et al. [16]	-4.61	-5.39	-3.82	-12.6	3.71
Rochester et al. [16] (abs)	3.86	2.83	4.88	8.09	3.17
Queen et al. [17]	-0.113	-0.131	-0.0961	-14.1	4.03
Alves et al. [18]	-0.0599	-0.0697	-0.0501	-13.1	3.82
Alves et al. [18] (weighted)	-0.0575	-0.067	-0.0481	-13.0	3.82

*Mean difference refers to the average of the pair-wise group difference between tied- and split-belt walking conditions.

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this, several aspects of the swing time results demonstrate the need for power simulations to assess metric sensitivity. First, the large effect sizes demonstrate that every metric was highly powered to detect the effect of asymmetry in swing time, and the unanimous findings of significance for this large effect of asymmetry does not preclude disagreement at smaller effect sizes (i.e. any differences in metric sensitivity are ambiguous in this data). This ambiguity in metric sensitivity due to large effect sizes is similarly apparent when effect size (Cohen's d) is manually calculated from several gait variables in the results of Patterson et al. [19, Table 1]. Second, all things being equal (sample size, significance criterion), power is a direct function of effect size [21]. However, the inherent uncertainty of observed effect sizes is emphasized by the mismatch between the order of effect sizes in Table 3 and the general results of the power simulation: The abs(Plo05) and Roc14 metrics exhibit the two smallest effect sizes for swing time, despite the power simulation showing large differences in power between these metrics for small asymmetry magnitudes with non-negligible variability. Similarly, the ratio (Sel86) produced the largest effect size, which could falsely support an interpretation of high sensitivity, but a key behavior of the ratio (lack of robustness to high variability compared to other metrics, see Fig 1) is not apparent in the swing time results, due to the low group variability in swing time. The poor sensitivity of the Sel86 metric in the presence of non-negligible variability is due to the definition of symmetry as a ratio. The distribution of a ratio of two normally distributed random variables is a Cauchy distribution—which has an analytically undefined variance. In practice, this can lead to a large variance that obscures mean differences that might otherwise be significant.

In contrast, the power simulation suggests that the Rochester et al. [16] metric without the absolute value, a simple difference, is the most sensitive, with a caveat that it is the only metric which is not normalized by a reference value. The weighted Alves et al. [18] metric is a normalized alternative that has practically equivalent sensitivity. All other symmetry metrics evaluated here produce relative bilateral differences, such that the asymmetry of $S(x, y) \neq S(x + c, y + c)$; this is also called "scale invariance" by Alves et al. [18] who asserted that symmetry metrics should display this behavior. The lack of scale invariance by the Roc14 metric may be mitigated in some cases via the addition of a covariate to a statistical test. Alternately, all the other metrics assessed here [11, 12, 14, 17, 18] are scale invariant, practically equivalent in sensitivity

to effects of asymmetry, and only slightly less sensitive than the metric proposed by Rochester et al. [16].

A strength of this study is that the parameters (asymmetry magnitude and variability) of the power simulation are the major factors in effect sizes, and therefore the power simulation essentially simulated different effect sizes. This allows the results of the power simulation to generalize to more statistical tests than the paired t-test used here. However, real data may not exhibit all the characteristics (asymmetry magnitudes and variability) and assumptions (independent and normally distributed inputs with equal variances, asymmetric data compared to symmetric baseline). Our simulation code and results are available in Zenodo and can be further explored or expanded to test characteristics or assumptions not made here [27].

Recommendations

The results of this study show that multiple symmetry metrics demonstrate sufficient sensitivity for a broad range of data. However, several practices may reduce the isolation of results based on the numeric differences in the results of various symmetry metrics. First, reporting of bilateral data in addition to symmetry metric results enables the direct calculation of asymmetry with alternate symmetry metrics and aids in comparisons to other studies and/or populations. Second, in the context of a population analyzed using affected/unaffected sides instead of left/right, reporting the bilateral data for both affected/unaffected and left/right, along with the correlation between affected side and limb dominance, communicates valuable information that cannot be otherwise inferred. Third, in agreement with the conclusions of Patterson et al. [19], a ratio is a more intuitive format for reporting results than other metrics. To improve the communication of results while maintaining a higher power for statistical testing, a metric with good sensitivity could be used for the statistical analysis, and then the results of the analysis—means and confidence intervals—could be transformed to ratios for reporting; such an approach would combine the strengths of a more sensitive metric and the intuitiveness of a ratio. Confidence intervals would need to be used because the lower and upper bounds can be exactly transformed between metrics, while differences in how each metric affects variability prevents the conversion of standard deviations between metrics.

Conclusion

In this study, we compared commonly used discrete symmetry metrics using power simulations and real data to demonstrate that metrics exhibit different sensitivities to the same underlying effects of asymmetry. Two metrics, published by Rochester et al. [16] (when used without an absolute value) and Alves et al. [18], display excellent sensitivity to a broad range of data characteristics. However, some metrics display very poor sensitivity when data is highly variable, therefore we suggest that future studies consider metric sensitivity to reduce the possibility of underpowered research.

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Formal analysis: Allen Hill.

Funding acquisition: Julie Nantel.

Investigation: Allen Hill.

Methodology: Allen Hill.

Project administration: Julie Nantel.

Resources: Julie Nantel.

Software: Allen Hill.

Supervision: Julie Nantel.

Validation: Allen Hill.

Visualization: Allen Hill.

Writing – original draft: Allen Hill.

Writing – review & editing: Allen Hill, Julie Nantel.

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4.1.3. Additional methods

The simulation was performed on a custom-built computer with an AMD Ryzen 9 3900X 12-core, 24-thread processor equipped with 32 Gb of RAM. The simulation took 13.5 hours to run using 20 threads. Random numbers were generated by a single-precision (32 bit) MersenneTwister random number generator initialized with a constant seed. Thread iteration order is non-deterministic; therefore the simulation is non-deterministic (i.e. multiple simulation runs do not produce bit-for-bit identical results) despite the consistently seeded random number generator. However, the large number (20M) of simulation iterations ensures that different simulation results produce approximately the same results: across all varied parameters (symmetry magnitude, sample size, ratio, and standard deviation), the reproducibility between two simulation runs was tested to exhibit an average absolute difference in power of 9.6e-5 and a maximum absolute difference in power of 0.005. A pseudocode summary of the complete Monte Carlo simulation can be found in Algorithm 1.

Statistical power is the probability of rejecting the null hypothesis ($H_0: \boldsymbol{X} = \boldsymbol{Y}$) when the alternate hypothesis ($H_a: \boldsymbol{X} \neq \boldsymbol{Y}$) is true. The design of the simulation tests for differences between two samples which are different by design (i.e. the alternate hypothesis is true), therefore the statistical power can be estimated as the proportion of test results which correctly reject the null hypothesis. Theoretically, the power estimates from different symmetry metrics are binomial proportions that could be compared using Binomial tests and confidence intervals (CIs). However, with the sample size (20M) of the power estimate (i.e. binomial proportion), CIs would be so narrow as to be uninformative (e.g. any comparison would always yield a significant difference due to the high power from the large sample size). The CI of a binomial proportion is largest when the proportion is 0.5; at that probability, a binomial proportion with 20M samples would have a CI of ±0.0003. For this reason, the functionally significant difference in sensitivity between metrics was chosen as 10%.

Algorithm 1 Monte Carlo Simulation. *A pseudocode depiction of the complete Monte Carlo simulation used to estimate power of symmetry metrics at given parameters*

Inputs:

σ: The standard deviation of the random variables

R: The asymmetry magnitude as a ratio $\frac{y}{x}$ which is the relative difference between the two arguments, x and y, of the symmetry metrics

N: The sample size of the current simulation

Output:

$\widehat{\boldsymbol{Power}}\{\boldsymbol{S}\}$: The estimated power of symmetry metric S

$\widehat{\boldsymbol{Power}}\{\boldsymbol{S}\} = \mathbf{0}$ for all $\boldsymbol{S} \in [\mathbf{Sel86}, \mathbf{Rob87}, \mathbf{Vag92}, \mathbf{Plo05}, \mathbf{abs}(\mathbf{Plo05}), \mathbf{Zif08}, \mathbf{Roc14}, \mathbf{abs}(\mathbf{Roc14}), \mathbf{Que20}, \mathbf{Alv20}, \mathbf{Alv20b}]$

while i < 20M

$\boldsymbol{X} = \{\boldsymbol{x}_1, \boldsymbol{x}_2, \dots, \boldsymbol{x}_N\}$ where $\boldsymbol{x}_j \overset{\boldsymbol{i.i.d.}}{\longrightarrow} \boldsymbol{\mathcal{N}}(1, \sigma^2)$

$\boldsymbol{X'} = \{\boldsymbol{x'}_1, \boldsymbol{x'}_2, \dots, \boldsymbol{x'}_N\}$ where $\boldsymbol{x'}_j \overset{\boldsymbol{i.i.d.}}{\longrightarrow} \boldsymbol{\mathcal{N}}(1, \sigma^2)$

$\boldsymbol{Y} = \{\boldsymbol{y}_1, y_2, \dots, \boldsymbol{y}_N\}$ where $\boldsymbol{y}_j \overset{\boldsymbol{i.i.d.}}{\longrightarrow} R \cdot \boldsymbol{\mathcal{N}}(1, \sigma^2)$

for S = [Sel86, Rob87, Vag92, Plo05, abs(Plo05), Zif08, Roc14, abs(Roc14), Que20, Alv20, Alv20b]

$t = \text{t-test}\big(S(\boldsymbol{X}, \boldsymbol{X'}) - S(\boldsymbol{X}, \boldsymbol{Y})\big)$

$p = \text{p-value}(t)$

if $p < 0.05$

$\widehat{Power}\{S\} \mathrel{+}= 1/20\text{M}$

end

end

increment i

end

The ranges of simulation parameters (symmetry metric, sample size, ratio, and standard deviation) were chosen such that the minimum and maximum of individual parameters were sufficiently “extreme” to indicate the behavior of metrics beyond what was simulated (e.g. power will increase for all metrics as asymmetry magnitude increases; past a sufficiently large value, all metrics that will/can reach 100% power should be expected to have done so).

4.2. Interlimb coordination in Parkinson's Disease is minimally affected by a visuospatial dual-task

4.2.1. Summary

Background:

- PwPD exhibit coordination deficits in the upper and lower limbs in Parkinson's disease
- Increased attentional demands of some aspects of gait coordination in pwPD are suggested by dual-task interference
- The nature of inter- and intra-limb coordination deficits in PD gait are unclear, in particular, the role of MA and LA sides

Findings:

- A visuospatial dual task reduced some aspects of interlimb coordination in Parkinson's disease
- Reduced interlimb coordination occurred only on the less affected side
- LA and MA hip range of motion responded differently to the dual task, while intralimb leg coordination was similar between MA and LA sides

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Interlimb coordination in Parkinson's Disease is minimally affected by a visuospatial dual task

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Abstract

Parkinson's disease (PD) leads to reduced spatial and temporal interlimb coordination during gait as well as reduced coordination in the upper or lower limbs. Multi-tasking when walking is common during real-world activities, and affects some gait characteristics, like gait speed and variability. However, the impact of a dual task (DT) on intra and interlimb coordination of both lower and upper limbs when walking in people with PD remains unknown. Seventeen volunteers with mild to moderate PD (11 males, 65 $\pm$ 8 years, 173 $\pm$ 8 cm, 74 $\pm$ 20 kg, Unified Parkinson's Disease Rating Scale motor section 10 $\pm$ 5) participated in gait trials in an Extended-CAREN system, which includes a treadmill, 12-camera Vicon motion capture system, and a 180° field-of-view virtual reality projection screen. Participants completed a 3 min walking trial and a 2 min visuospatial word recognition DT trial at their preferred walking pace. Single and DT were compared with a paired t-test, and the less and more affected (LA, MA) sides were tested for equivalence in sensitivity to the DT. During the DT, we found the LA shoulder ROM decreased by 1.5°, and the LA shoulder peak flexion decreased by 1.1° ($p<.028$, $g_{av}>.12$). The LA and MA hip ROM were differently affected by the dual task (p=.023), and intralimb coordination was affected by dual tasking equivalently between sides (p=.004). These results suggest that during normal single-task gait, people with PD use attentional resources to compensate for reduced arm swing. Furthermore, our results indicate that any effect of DT on lower intralimb coordination is not meaningfully different between the LA and MA sides.

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Introduction

Parkinson's disease (PD) is a multisystem neurodegenerative disease characterized by the loss of dopaminergic neurons in the substantia nigra with cascading effects in other regions, including those involved in cholinergic systems (Yarnall et al., 2011; Poewe et al., 2017). The neurodegeneration in PD begins unilaterally and progresses bilaterally, and motor symptoms mirror this unilateral emergence and bilateral progression, commonly resulting in one side being more affected than the other (Djaldetti et al., 2006). In addition to the three cardinal motor symptoms of PD—bradykinesia, rigidity, and tremor—people with PD develop further motor deficits, such as hypokinesia (reduced movement amplitude), increased movement variability, gait asymmetry, and postural instability, all of which may contribute to or reflect impairments in coordinating the upper and lower limbs during locomotion (van Emmerik & Wagenaar, 1996; Yogev et al., 2007; Plotnik et al., 2007; Mirelman et al., 2019). Coordination of the upper and lower limbs is required to maintain dynamic gait stability in the presence of major and minor perturbations (Marigold & Misiaszek, 2009; Krasovsky et al., 2012). In addition, gait tasks involving speed modulation require adaptations in interlimb coordination. Such tasks have shown kinematic differences in older adult fallers compared to non-faller peers (Barak et al., 2006; Shishov et al., 2017).

Coordination is defined as the context- and phase-dependent control of spatial and temporal cyclical relationships between body segments (Krasovsky & Levin, 2010). One prominent feature of normal gait coordination is the frequency-matched anti-phase swing (180 deg phase offset) between the arms, legs, and ipsilateral arm-leg pairs, while contralateral arm-leg pairs swing in phase with each other (Wagenaar & van Emmerik, 2000). (One-to-one arm and leg swing frequencies are expected for gait speeds above 0.8 m/s, while slower gait sometimes exhibits 2:1 arm swing to stride frequencies (Wagenaar & van Emmerik, 2000).) These phase relationships result in gait which is generally temporally and spatially symmetric in healthy adults (Sadeghi et al., 2000; Killeen et al., 2018). In contrast, asymmetry in spatial or temporal gait characteristics is recognized as a disruption in the coordination of normal gait and occurs in several pathological populations, including those with PD (Yogev et al., 2007; Huang et al., 2012; Park et al., 2016).

One approach to measuring coordination is based on dynamical systems theory and uses the continuous relative phase (CRP) between coupled oscillators to characterize the state of the system (Haken et al., 1985). Previous studies using CRP have found that, compared to healthy peers, people with PD have reduced coordination stability and increased average phase error (from anti- or in-phase) for upper and lower interlimb coordination during gait and for upper limb coordination during bimanual tasks (van Emmerik & Wagenaar, 1996; Winogrodzka et al., 2005; Almeida & Brown, 2013). Other studies support the presence of reduced interlimb coordination stability in PD (Roemmich et al., 2013), and increased phase error in some upper and lower limb pairs compared to healthy peers and comparing PD freezers to non-freezers (Nanhoe-Mahabier et al., 2011).

Homologous limb coordination is decreased in PD as well. Plotnik and collaborators (2007) reported worse lower limb coordination in people with PD compared to healthy controls using the phase coordination index (PCI), a combined measure of accuracy and consistency in the anti-phase coordination of step timing during gait. Coordination between the upper limbs is also reduced or altered in people with PD compared to healthy controls (Huang et al., 2012; Sterling et al., 2015).

Although there is support for coordination deficits in PD, the more and less affected (MA and LA) sides may contribute differently to interlimb coordination amidst the predominantly unilateral symptoms of early PD. However, the relative nature of coordination makes it difficult to separately characterize coordination between the MA and LA sides. Some studies have found that the LA side maintains an ability to adapt to and compensate for task requirements, such as split-belt walking (Roemmich et al., 2014) or dual-tasking during gait (Siragy & Nantel, 2020); despite the potential benefits of adaptation, this may appear as "worse" coordination due to the decreased similarity between sides. Other studies have found that people with PD showed increased PCI (ie less accurate and/or consistent coordination) when asked to use non-preferred step lengths and times, or when asked to adapt to external mechanical constraints, such as walking on split-belt treadmills (Williams et

al., 2013; Fasano et al., 2016); the authors suggest that the increased PCI indicates a generally reduced ability to adapt (lower limb) coordination in PD. However, adaption to split-belt walking differed between MA and LA sides, depending on which side was sped up (Fasano et al., 2016), and therapy focused on the LA side may be more effective than a balanced or MA-side focus (Ricciardi et al., 2015). In addition, two studies have found that ipsilateral arm-leg coordination is reduced on the MA side (Nanhoe-Mahabier et al., 2011; Roemmich et al., 2013). CRP can be used to measure coordination stability within individual limbs (i.e. intralimb coordination), which could contribute to a better understanding of coordination deficits in specific limbs (Barela et al., 2000; Byrne et al., 2002). However, we are not aware of previous studies having investigated this in people with PD.

Performing a secondary task during gait adds an attentional stressor that can reveal the loss of automaticity for some aspects of gait (e.g. gait speed, gait variability), and this is measured as a change in performance while dual tasking, often referred to as the dual-task cost (Yogev-Seligmann et al. 2008). In addition, experimental studies have shown that coordination of bimanual movement patterns can be stabilized by an attentional focus, but a dual task serving as an attentional distractor interferes with the stabilization (Temprado et al., 1999). Since gait while dual tasking may be more similar to gait in the real world than typical laboratory recordings of steady state gait (Hillel et al., 2019), dual tasking during gait may offer an ecologically valid method of manipulating attention to highlight coordinative deficits. Studies of coordination and dual tasking in people with PD show a larger decline in lower limb coordination, measured by PCI, during a dual task compared to healthy controls, and PCI in PD fallers and freezers is more affected by a dual task than PD non-fallers and non-freezers (Plotnik & Hausdorff, 2008; Plotnik et al., 2009; Plotnik, Giladi, et al., 2011). In addition, studies have found reduced arm swing during gait in people with PD during a dual task compared to single task gait (Mirelman et al., 2016; Baron et al., 2018). These results suggest that loss of automaticity in coordination may be associated with the progression of PD to more severe outcomes.

While effects of dual tasking on bilateral coordination and asymmetry have been found (Plotnik, Dagan, et al., 2011), as well as differences in spatiotemporal and movement characteristics between the MA and LA limbs in the upper and lower body (Mirelman et al., 2016; Siragy & Nantel, 2020), the effect of motor symptom presentation (i.e. MA and LA sides) in coordination within and between the upper and lower limbs has not been sufficiently explored. Differential dual-task cost between sides in interlimb coordination in people with PD could provide evidence of how the asymmetric presentation of the disease affects coordination in the upper and lower limbs. Therefore, the purpose of this study is to investigate MA/LA side differences in coordination deficits in people with PD by observing interlimb coordination within and between the upper and lower limbs during single and dual-task gait.

Methods

Participants

Volunteers with mild to moderate PD (between I-III Hoehn & Yahr) were recruited from the Ottawa-Gatineau area. Exclusion criteria included any additional neurological impairment, a recent orthopedic injury or surgery that could interfere with gait, the use of a walking aid, or any discomfort with using a projected virtual reality system. Participant characteristics for sex, age, height, weight, handedness, Unified Parkinson's Disease Rating Scale (UPDRS) motor section (III), freezing and falling status, and interval since diagnosis of PD were recorded. The MA side was defined as the side where PD motor symptoms first occurred, as reported by participants. Falling status was self-reported based on conservative criteria of having fallen at least once in the past year, including non-injurious falls. Participants were tested when optimally medicated ("ON") by their normal medication. All participants provided written informed consent, and the study was approved by local ethics review boards.

Protocol

Data was collected using the CAREN system (CAREN-Extended, Motekforce Link, Amsterdam, NL). The CAREN system consists of an instrumented split-belt treadmill (Bertec Corp., Columbus. OH) embedded in a six

degree-of-freedom motion platform, a 12-camera motion capture system (Vicon, Oxford, UK), and a 180 deg field of view projection screen. The participants wore a safety harness attached to an overhead frame on the motion platform to prevent falls without restricting movement.

Participants were allowed an initial familiarization period with the CAREN system for several minutes until they reported being comfortable; the familiarization period was also used to determine their preferred walking speed for the gait trials. The single task trial was 3 min long, while the dual task trial was 2 min long. The dual task consisted of a visuospatial word recognition and acknowledgement task where a word was shown at eye level at a random position between 20-70 deg to the left or right of center; participants were asked to notice and acknowledge the word by reading it aloud. Twelve words were randomly drawn from a standard list of 16 possible words in the native language of the participant (English or French). The dual task began 20 s into the trial, and a new word was shown for 3 s every 2-4 s for 80 s. The dual task was designed to be an ecologically valid recreation of common daily life situations (e.g. public transportation terminal, etc.) requiring perception and comprehension of visual cues (Siragy & Nantel, 2020; Ahmadi et al., 2021). The dual task trial occurred after the single task trial. Participants were allowed to rest between trials when requested.

Data reduction

A set of 57 markers (Wilken et al., 2012) was used to capture full-body kinematics at 100 Hz; marker data was then filtered using a 4^{th} order dual-pass Butterworth low-pass filter with a cutoff frequency of 12 Hz. Low pass filter cutoff frequency was chosen based on a residual frequency analysis of marker data using an RMS noise of 0.5 mm measured from static markers fixed to the motion platform (Winter, 2009). Gait events were calculated using an algorithm based on the local extrema of the vertical position and velocity of the heel marker (Roerdink et al., 2008). OpenSim was used with the Rajagopal et al. (2016) model to perform inverse kinematics to extract bilateral knee, elbow, shoulder, and hip flexion/extension angles (Delp et al., 2007). The wrist pronation/supination range of motion of the model was expanded from 90 deg to 160 deg to better match normative biomechanical characteristics (Shaaban et al., 2008).

To detect changes in spatial coordination, range of motion (ROM), ROM coefficient of variation (COV), and peak flexion were measured on the MA and LA sides for the shoulder and hip joints. Similarly, changes in temporal coordination were assessed using average intercycle phase variability of CRP (interpreted as coordination stability) to measure for ipsilateral shoulder and hip interlimb joint pairs and intralimb (shoulder and elbow, hip and knee) joint pairs. Continuous phase was calculated as the angle of the complex analytic signal produced by the Hilbert transform after centering the original signal (Lamb & Stöckl, 2014).

Statistics

Effects of dual tasking on individual variables were tested using paired t-tests. Additionally, a TOST procedure was used to test for equivalence between sides for changes due to dual tasking (DTC); this was done for all lateral variables (e.g. shoulder ROM, which was measured on both LA and MA sides) (Lakens, 2017). Dual task cost was defined as the difference between single and dual task for a given variable. All tests were performed with $\alpha = 0.05$. Unless otherwise noted, equivalence bounds were set per variable using unstandardized values (i.e. the original units/scale, without normalizing to group error) to reduce bias (Lakens, 2017) and estimated from previously published results for healthy older adults. The maximum bilateral difference in DTC for shoulder ROM and peak flexion was estimated to be 3.5° (Plate et al., 2015, tbl. 1; Killeen et al., 2018, fig. 2). The maximum bilateral difference in DTC for shoulder ROM COV was estimated at 6° (Mirelman et al., 2016, tbl. 2). Bounds for hip ROM and peak flexion were set as 0.5°, based on changes in DTC between left and right limbs in PD (Ribeiro et al., 2019, tbl. 2). Lower intralimb phase variability bounds were set to 0.85° (Ghanavati et al., 2014, fig. 2A). Appropriate reference data could not be found for the remaining variables (hip ROM COV, ipsilateral phase variability, and upper intralimb phase variability), and the equivalence bound was set at Cohen's d=0.36, estimated from the maximum bilateral difference in change in arm swing ROM due to DT in healthy older adults (Plate et al., 2015, tbl. 1).

Effect sizes were calculated using Cohen's dav with a Hedge's g correction, noted as gav (Cumming, 2011; Lakens, 2013). A sensitivity power analysis for a two-tailed t-test was conducted in G*Power (Faul et al., 2007)

to find that the minimum detectable effect size with 80% power is $d_z = 0.72$ when $\alpha = .05$ and the sample size is 17. A sensitivity power analysis for a TOST equivalence test using the TOSTER package in R showed that the minimum bounds that would be rejectable with 80% power is $d = .90$ when $\alpha = .05$ and the sample size is 17. Arm swing for a given shoulder was treated as functionally absent when ROM was less than 5 deg. No meaningful coordination was expected between a shoulder with functionally absent arm swing and either the ipsilateral hip or the contralateral shoulder; therefore, the ipsilateral and intralimb CRP variables for affected subjects/shoulders were removed as outliers—3 subjects at most, depending on the variable. Circular statistics (circular mean and standard deviations) were used for the variables with angular units (Fisher, 1993). All data reduction and statistical analyses were performed with the Julia language using open-source libraries and code (Bezanson et al., 2017; Hill & Nantel, 2023).

Results

Participant demographics are reported in Table 1. Twenty subjects who met the inclusion criteria were recruited. Two participants with severe dyskinesia were excluded from this study, and a third participant was excluded for moving their hands while talking during a significant portion of a trial; both behaviors produce movements (Jankovic, 2005) which are disruptive to the normal coordination patterns of steady state gait. Subjects were diagnosed with PD an average of 7.4 ± 4.5 years prior to study participation.

Table 1 - Participant demographics

Characteristic	Mean ± SD	Range
Sex (n)	11 M, 6 F	
Age (years)	64.8 ± 7.7	48-79
Height (cm)	173.3 ± 7.6	165-188
Weight (kg)	74.2 ± 19.9	52-128
Handedness	14 R, 3 L	
More affected side	9 R, 8 L	
UPDRS III	10.2 ± 5.3	0-20
Freezers (n)	5	
Fallers (n, <1yr)	10	

Single and dual task results were calculated using an average of 139 ± 19 and 74 ± 6 steps, respectively (dual task trial length was shorter than the single task trial). Preferred gait speed was 1.0 ± 0.2 m/s among subjects.

Unilateral effects of DT

Spatial coordination results are reported in Table 2. The LA shoulder ROM and peak flexion decreased by 1.5 deg 95% CI [−2.8,−0.2] and 1.1 deg [−2.1,−0.1], respectively, during dual task compared to single task walking. Temporal coordination results are reported in Table 3; no significant differences were detected (p>.061).

Bilateral difference in DTC

Equivalence tests for difference in DTC between sides are reported in Table 4. Hip ROM DTC was significantly different between sides, M=-0.967°, and was not equivalent (p=.88), preventing a conclusion of equivalence to a healthy older adult population (See Fig. 1). Lower intralimb phase variability DTC was not significantly different between sides, and was statistically equivalent (p=.004).

Table 2 - Spatial coordination in the more and less affected sides during single and dual task

Variable		Single task	Dual task	*t*-test	p-value	g_{av}
Shoulder ROM (deg)	LA	21.2 ± 13.3	19.7 ± 12.4	t(16)=−2.44	**0.027**	−0.12
	MA	17.9 ± 12.6	19.7 ± 14.8	t(16)=0.69	0.501	0.13
Shoulder ROM COV (%)	LA	17.2 ± 9.1	25.0 ± 38.5	t(16)=1.01	0.329	0.32
	MA	22.1 ± 14.8	16.4 ± 6.6	t(16)=−1.55	0.141	−0.51
Shoulder peak flexion (deg)	LA	15.3 ± 8.6	14.2 ± 8.2	t(16)=−2.41	**0.028**	0.47
	MA	13.3 ± 7.7	14.1 ± 9.3	t(16)=0.48	0.64	0.05
Hip ROM (deg)	LA	38.5 ± 4.1	37.6 ± 3.9	t(16)=−1.61	0.127	−0.22
	MA	37.6 ± 5.1	37.6 ± 5.3	t(16)=0.14	0.892	0.01
Hip ROM COV (%)	LA	4.2 ± 1.4	4.7 ± 1.8	t(16)=1.82	0.087	0.27
	MA	4.5 ± 1.6	4.6 ± 1.8	t(16)=1.12	0.278	0.10
Hip peak flexion (deg)	LA	22.7 ± 3.9	22.4 ± 4.4	t(16)=−0.92	0.374	−0.01
	MA	20.4 ± 5.1	20.5 ± 5.0	t(16)=0.10	0.923	−0.18

ROM = range of motion, MA/LA = more/less affected side, g_{av} = Cohen's d_{av} effect size corrected with Hedge's g.

Table 3 - Temporal coordination (PCI and phase variability) in and between the more and less affected sides during single and dual task

Variable		Single task	Dual task	*t*-test	p-value	g_{av}
PCI (deg)		6.6 ± 3.0	7.6 ± 4.0	t(16)=1.70	0.109	0.28
Shoulder interlimb (deg)		20.1 ± 9.9	21.4 ± 14.3	t(13)=0.41	0.688	0.1
Hip interlimb (deg)		7.1 ± 2.7	7.1 ± 2.1	t(16)=−0.13	0.895	−0.02
Ipsilateral shoulder-hip (deg)	LA	18.1 ± 15.5	22.1 ± 17.5	t(15)=1.49	0.157	0.24
	MA	16.6 ± 9.1	14.6 ± 6.0	t(13)=−0.43	0.675	−0.15
Contralateral shoulder-hip (deg)*	LA	17.9 ± 15.4	21.9 ± 17.7	t(15)=1.48	0.16	0.24
	MA	16.3 ± 8.9	14.0 ± 6.0	t(13)=−0.57	0.581	−0.2
Upper intralimb (deg)	LA	22.5 ± 10.2	26.3 ± 16.0	t(15)=2.03	0.061	0.28
	MA	31.5 ± 21.6	26.8 ± 13.5	t(13)=−0.58	0.573	−0.16
Lower intralimb (deg)	LA	6.6 ± 2.5	7.1 ± 2.5	t(16)=1.62	0.126	0.21
	MA	6.8 ± 2.4	7.1 ± 1.9	t(16)=0.87	0.396	0.11

PCI = phase coordination index (Plotnik et al., 2007), MA/LA = more/less affected side, g_{av} = Cohen's d_{av} effect size corrected with Hedge's g. *LA/MA refers to the shoulder of the contralateral shoulder-hip pair. Arm swing for three subjects was treated as functionally absent in one or both shoulders, which reduced the degrees of freedom for the t-tests of some variables.

Table 4 - Tests of equivalence in DTC between sides

DTC Variable	LA side	MA side	95% CI	Difference *t*-test	p-value	TOST p-value	g_{av}
Shoulder ROM (deg)	-1.5 ± 2.6	1.8 ± 11	[-8.8, 2.2]	t(16)=-1.26	0.225	0.467	-0.49
Shoulder ROM COV (%)	7.8 ± 32	-5.6 ± 15	[-4.1, 31]	t(16)=1.62	0.125	0.808	0.56
Shoulder peak flexion (deg)	-1.1 ± 2	0.78 ± 6.8	[-5.5, 1.7]	t(16)=-1.13	0.276	0.177	-0.42
Hip ROM (deg)	-0.92 ± 2.3	0.051 ± 1.5	[-1.8, -0.15]	t(16)=-2.52	**0.023**	0.88	-0.49
Hip ROM COV (%)	0.45 ± 1	0.16 ± 0.6	[-0.23, 0.81]	t(16)=1.17	0.26	0.378	0.35
Hip peak flexion (deg)	-0.21 ± 0.96	0.027 ± 1.2	[-0.96, 0.49]	t(16)=-0.69	0.502	0.223	-0.22
Ipsilateral shoulder-hip (deg)	5 ± 11	-1.1 ± 9.6	[-1.9, 14]	t(13)=1.64	0.124	0.614	0.59
Upper intralimb (deg)	2.1 ± 5.2	-2.8 ± 18	[-6.4, 16]	t(13)=0.93	0.369	0.342	0.41
Lower intralimb (deg)	0.53 ± 1.3	0.24 ± 1.1	[-0.11, 0.68]	t(16)=1.53	0.146	**0.004**	0.22

MA/LA = more/less affected side, g_{av} = Cohen's d_{av} effect size corrected with Hedge's g. Arm swing for three subjects was treated as functionally absent in one or both shoulders, which reduced the degrees of freedom for the t-tests of some variables.

Discussion

In this study, we found that few aspects of coordination are unilaterally affected by a visuospatial dual task in a cohort of mild to moderate PD. Furthermore, few aspects of coordination exhibit a significant bilaterally different sensitivity to dual tasking, however, most variables do not support a conclusion of equivalent sensitivity of coordination between the MA and LA sides. During the dual task, the LA shoulder ROM and peak

flexion decreased compared to single task performance (Table 2), but the change in shoulder ROM and peak flexion due to dual tasking were not significantly different between the LA and MA sides. A significant difference was noted in hip ROM DTC between MA and LA sides, but neither side was affected by dual tasking. Lower intralimb phase variability was not affected by dual tasking and was not different and equivalent between sides at $\pm 0.85°$ bounds.

Our results are generally inconclusive, as null findings for both t-tests and equivalence tests prevent meaningful conclusions about the presence or absence of meaningful (i.e. clinically relevant) effects. Reduced arm swing during dual tasking on the LA side is similar to previous studies (Mirelman et al., 2016; Baron et al., 2018). Additionally, gait asymmetry present in people with PD often results in LA ROM and coordination that are more similar to—but not always matching—healthy peers, while the MA side is less similar to healthy peers (Roggendorf et al., 2012; Roemmich et al., 2013). Qualitatively, the single task shoulder ROM in our data showed that the arm swing was fairly symmetric (Table 2), and slightly reduced on both sides compared to normative arm swing data for healthy older adults at similar gait speeds (Plate et al., 2015; Killeen et al., 2018).

However, we note that the absence of a significant effect of dual tasking on the MA shoulder ROM should not be interpreted as evidence for differing behaviors/responses to dual tasking between the MA and LA shoulder ROM, as Gelman and Stern (2006) have previously stated, “comparisons of the sort ‘X is statistically significant and Y is not’ can be misleading”. Indeed, we directly compared the unilateral DTC and found no difference between sides for shoulder ROM. Since equivalence at the tested bounds was not reached, there remains the possibility of a bilateral difference in DTC at an effect size that is smaller than we were powered to detect but too large to reject at our chosen equivalence bounds. Similarly, while there were no significant differences between single and dual task for unilateral hip ROM, there was a significant difference in DTC between sides; see Fig. Figure 1.

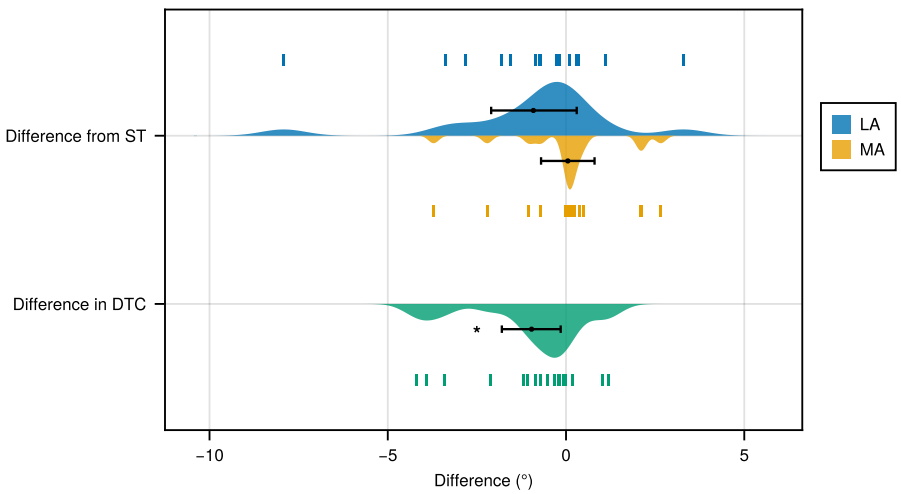

Figure 1 - Distribution and CIs of changes in unilateral hip ROM due to dual-tasking. Error bars represent the 95% CIs. On top, the LA and MA hip ROM did not significantly change between single and dual task conditions. On bottom, the asterisk denotes that the difference in DTC for hip ROM was significantly different between LA and MA sides.

Lower intralimb phase variability was not affected by the dual task used in this study, and the difference in responses of each side to dual tasking was equivalent to estimated responses in healthy older adults. Different dual tasks have been found to have population specific effects (i.e. task interference) (Al-Yahya et al., 2011), and previous studies on gait and dual tasks in PD suggests that fallers and/or freezers may be more sensitive to dual task interference (Plotnik, Giladi, et al., 2011; Bekkers et al., 2018). More research is needed to determine whether such increased sensitivity for PD fallers or freezers would apply to the novel visuospatial task—intended to mimic an ecologically realistic scenario—that was used in this study.

Limitations

Due to the absence of a control group, we are only able to quantify the response of a mild PD group to the DT, and are unable to discuss how responses to the DT in a group of healthy controls might differ from this group of people with PD. In addition, the participants in this study had mild to moderate PD, and the arm swing ROM and ROM asymmetry within our cohort is markedly different compared to previously reported PD cohorts (Roggendorf et al., 2012; Isaias et al., 2012; Sterling et al., 2015; Mirelman et al., 2016); it is unclear how coordination would respond in people with similarly mild PD—but with larger levels of arm swing asymmetry, or in people with more severe PD—which have more symmetric arm swing but reduced ROM (Roggendorf et al., 2012). Similarly, the severity of PD—in terms of UPDRS III scores—may be correlated with dual task interference, however the sparse range of UPDRS III values in our cohort prevented the use of statistical tests that might detect any such interactions.

Additionally, different tasks are known to have unique and specific effects on different aspects of gait which may limit the generalizability of our results (Al-Yahya et al., 2011; Rochester et al., 2014), and the visuospatial dual task in this study was simple (12/17 participants demonstrated perfect performance, and the remaining 5 participants responded to 10 ± 1.5 words out of 12). However, Baron et al. (2018) found that arm swing kinematics were sensitive to multiple common dual tasks.

Finally, treadmill walking is different from overground walking and may prevent some common responses in PD, such as reducing gait speed when distracted. However, our results are still informative about the nature of coordination deficits in PD and the methods they use to compensate for coordination deficits when optimally medicated and walking in this specific environment.

Conclusion

Our results show that in a group of mild PD, a visuospatial dual task during gait contributes to decreased arm ROM on the LA side, but only hip ROM is differently affected by a dual task on the MA and LA sides. Furthermore, with the exception of coordination within the lower limbs, tests of equivalent sensitivity to dual tasking on the MA and LA sides were inconclusive. Despite the inconclusive tests, these results support cumulative science by providing reference data useful in calculating effect sizes for power analyses of future studies on the topic (Lakens, 2013). More research is needed to support or dispute the existence of differences in coordination between the MA and LA sides, and whether any differences are moderated by medication.

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Competing interests

The authors declare they comply with the PCI rule of having no financial conflicts of interest. They have no non-financial conflicts of interest to disclose.

Ethics approval

This study was performed in accordance with the Declaration of Helsinki. Approval was granted by the Ottawa Health Science Network Research Ethics Board (No. 20170291-01H) and the University of Ottawa Office of Research Ethics and Integrity (No. A06-17-03).

Consent to participate

Written informed consent was obtained from all study participants.

Data and code availability

The software and data produced and analyzed for this study are openly available from the Zenodo data repository at https://doi.org/10.5281/zenodo.8364708 (Hill & Nantel, 2023)

Author contributions

Allen Hill: Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – Original Draft. **Julie Nantel:** Investigation, Resources, Writing – Review & Editing, Supervision, Project administration, Funding acquisition

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4.2.3. Additional methods

The filter cutoff frequency used on the marker data was chosen using a modified version of the residual analysis method proposed by Winter (2009). The method proposed by Winter constructs a residual curve as the RMS error between a filtered and unfiltered signal across a range of frequencies (see Figure 1). The noise within the signal is estimated as the DC (0 Hz) intercept of a line section *de* on the residual curve, where *de* is a linear region in the higher frequencies of the residual curve. The cutoff frequency is then selected as the highest frequency where the value of the residual curve equals the noise.

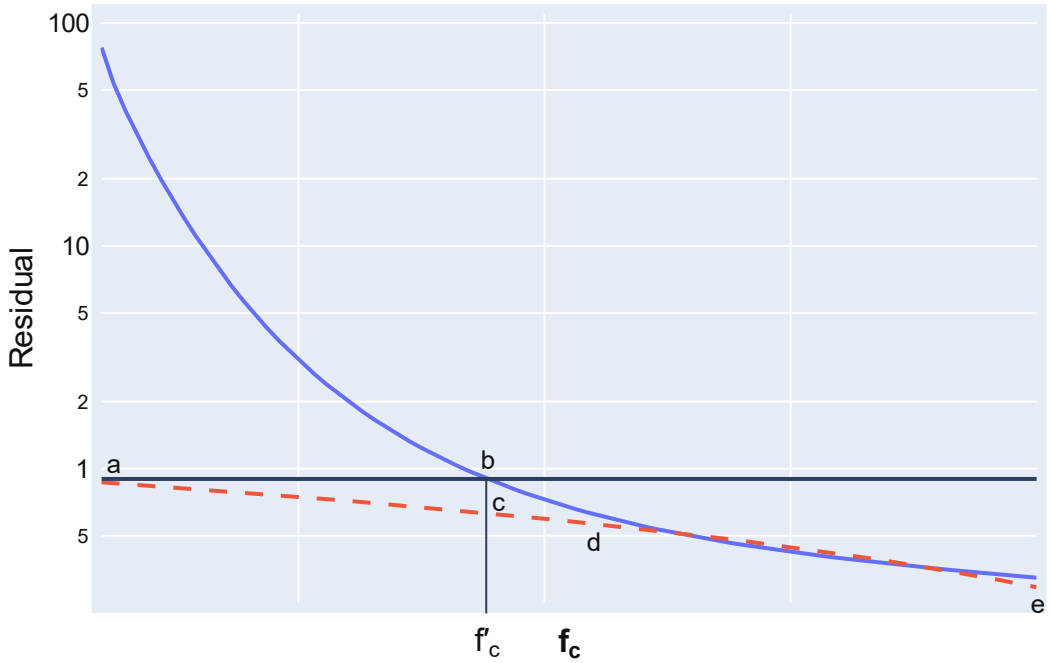

Figure 1 Residual (RMS) error between a raw and filtered signal at various cutoff frequencies. *The chosen cutoff frequency is f'c, where the level of residual error is equal to the DC intercept (*ab*) of the line section* de *fit to the residual curve. Replication of (Winter, 2009, Figure 3.20).*

The method proposed by Winter is under specified in several aspects. First, the range of frequencies used to construct the residual curve is not described[6] other than being “wide”

[6] Winter (2009, Figure 3.20) was used for illustrative purposes and the range of evaluated frequencies is not given in the figure or the text (as replicated in Figure 1). Winter (2009, Figure 3.21) subsequently gives the line *de* as the linear regression of the residual curve from harmonics 11 to 20, however, the fundamental frequency of a signal is ill-specified and is often not defined exclusively from characteristics of the signal itself (i.e. using external knowledge or data, such as defining the fundamental frequency as the stride frequency, which depends on the existence of gait events, which themselves may rely on the existence of filtered data).

(Winter, 2009, p. 70). Similarly, the frequencies *d* and *e*, used to define the line segment *de*, are not described in the text, and although Winter (2009, Figure 3.21) later reports the extent of line segment *de* as harmonics 11 to 20, no further guidelines or justification for that choice is given. In practice, these two undefined characteristics (frequency *e*, which is inferred to be the highest evaluated frequency, and frequency *d*) have a substantial impact on the resulting least squares line fit to the residual curve, and subsequently the estimated DC noise magnitude and the chosen cutoff frequency (see Figure 2A).

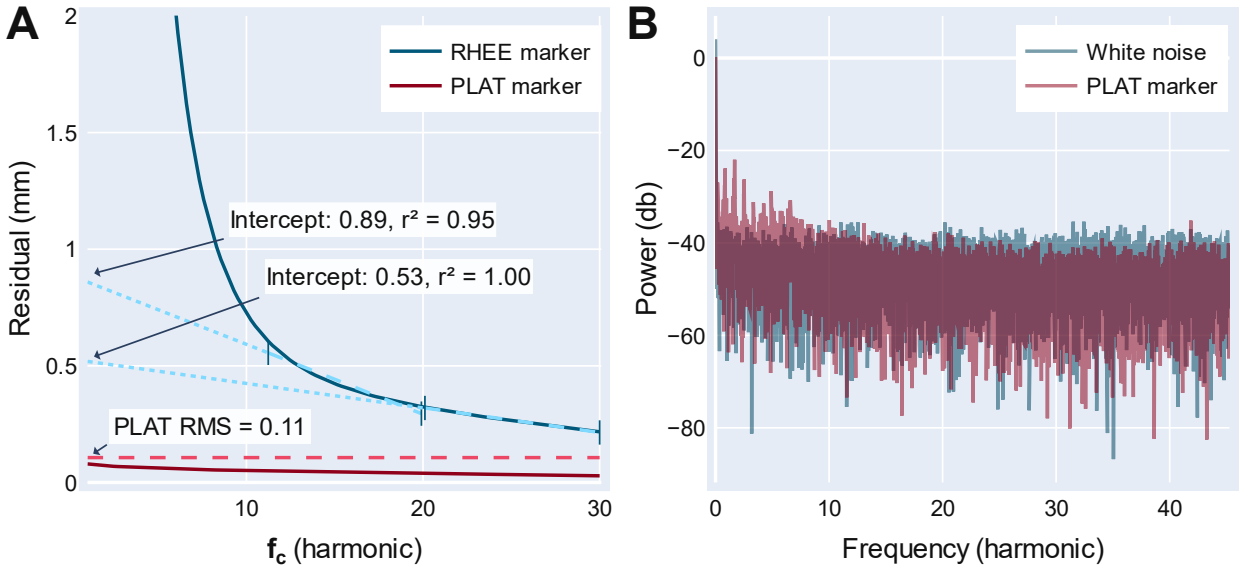

Figure 2 Residual curves of two markers mounted on the body and platform (A) and a spectrogram of the platform mounted marker vs. white noise (B)*. Panel* **A** *shows two light blue lines calculated from a least squares fit of the* RHEE *marker residual (dark blue line) for harmonics 11-20 and 20-30, which have intercepts of 0.89 and 0.53 mm, respectively. The dashed, light red line is the RMS noise of the platform mounted marker* PLAT*. In panel* **B***, the spectogram of the* PLAT *marker is visually similar to white noise; differing spectral behavior reflects system noise (e.g. marker reconstruction error, platform movement due to resonance in hydraulic actuators, etc.)*

As the goal of filtering is to remove “noise” which cannot be part of the intended data (i.e. motion) (Winter, 2009), a conservative approach is to only filter aspects which can be attributed to system/instrument error (e.g. digitization error, etc.). An alternative method was developed to directly estimate the noise of the motion capture system, using the RMS error of multiple stationary markers attached to the floor/treadmill platform during a static motion capture trial (see Figure 2). The cutoff frequency is then chosen, following Winter (2009), as the frequency

where the level of the residual error is equal to the system noise; see Figure 2 for typical curves. Noise estimates and residual analysis for the data used in this paper are detailed in a Zenodo repository (Hill & Nantel, 2023). The optimal cutoff frequency was highest for the feet markers and was rounded up to the nearest integer frequency (12 Hz) to be used as the final cutoff frequency for all markers.

4.3. Theme 3: Reaching and stepping respond differently to medication and cueing in Parkinson's disease

4.3.1. Summary

Background:

- Timing is a fundamental component to coordination
- The basal ganglia (particularly the striatum) are active during explicit timing, and pwPD exhibit deficits in explicit/interval timing
- Dopaminergic medication may modulate timing deficits in PD via increased striatal dopamine, but existing evidence is conflicting and limited to small studies

Findings:

- Overall timing variability is not noticeably different from healthy peers or affected by medication when reaching or stepping at a maximal rate
- Clock (i.e. central) variance in PD for repetitive reaching was worse ON medication when uncued in comparison to uncued and/or OFF medication
- PD timing during stepping in place was less responsive to cueing than for repetitive reaching

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Reaching and stepping respond differently to medication and cueing in Parkinson's disease

Allen Hill[1], Hiram Cantú[2,3,4,5], Julie N. Côté[2,4,5] & Julie Nantel[1]✉

The basal ganglia contribute to internal timekeeping, and dopaminergic medication has been observed to moderate timing deficits associated with Parkinson's Disease (PD) during single joint movements. However, it is unclear whether similar effects can be observed in multi-joint movements. Twenty-five people with PD and twelve healthy peers performed repetitive reaching and stepping-in-place tasks with and without auditory cues at their self-selected maximal cadence. The PD group was measured ON and OFF medication. Reduced cadence error was found for both groups and tasks when cued, and ON PD exhibited decreased cadence compared to OFF PD. Overall timing variability was no different from controls, but differences were found in estimates of clock and motor variance using the Wing-Kristofferson model of interval timing. A medication and cueing interaction during the reaching task produced increased clock variance in uncued, ON PD. During the stepping task, clock and motor variance of the PD group were unaffected by cues, in contrast to the control group. Serial lag-one correlation was reduced in both groups for cued reaching, but was unaffected by cueing or medication in the PD group when stepping-in-place. These findings suggest that overall timing variability may not capture timing deficits in PD.

Parkinson's disease (PD) is caused by multisystem neurodegeneration of dopaminergic neurons in the basal ganglia (BG), with cascading effects in other regions[1]. The neurodegeneration begins unilaterally in the substantia nigra and progresses bilaterally[2,3]. Motor symptoms mirror the unilateral emergence and bilateral progression, which commonly results in one side being more affected (MA) than the other (less affected, LA) until later stages of PD, when both sides have become similarly impaired[4]. Compared to healthy peers, people with PD (pwPD) exhibit deficits in movement coordination related to the unilateral neurodegeneration and symptoms[5].

Time perception and reproduction are core aspects of coordination, where coordination is defined as the context- and phase-dependent control of spatial and temporal relationships between body segments[6]. Functional imaging provides evidence that the BG serve a role in time perception and reproduction[7]. The substantia nigra is active for both internally cued (self-paced) and externally cued movements[8], and the putamen is involved in the internal timing of sequential movements[8,9]. Additionally, a study of timing reproduction in pwPD found that brain activation patterns in the putamen were partially normalized after administration of L-Dopa[10].

Neurological processes underlying timing have previously been investigated using paced finger tapping tasks, often in the form of a synchronization-continuation paradigm, where an auditory cue is removed during the latter half of a trial[11]. Under this paradigm, temporal perception and reproduction can be measured as the accuracy and variability of inter-response intervals during the continuation phase[11]. Freeman et al.[12] found a lower accuracy and a reduced range of speed in pwPD compared to controls, where tapping intervals were faster than the slowest (1 Hz) and slower than the fastest (5 Hz) cue frequency. This pattern of frequency-dependent changes in accuracy is common, and faster tapping frequencies are particularly revealing of timing impairments in PD[13,14]. PwPD can also exhibit higher timing variability compared to controls[10,15,16], but increased variability is not always found[17,18]. This may be due to heterogeneity in PD caused by the presence of subgroups, including previously known groups—such as freezers and non-freezers[19,20], or late-stage PD and early, medication naïve PD[13]—as well as groups that have been found using cluster analysis which are otherwise demographically similar[15].

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However, Wing and Kristofferson[21] proposed a model to distinguish interval timing variance due to variance in the internal timekeeping process (central or "clock" variance), and variance due to delays in the activation of motor responses (motor variance, e.g. finger movements when tapping). O'Boyle et al.[16] examined unilateral tapping in people with PD when OFF and ON dopaminergic medication, and found increased overall timing variability when OFF medication; a second group of medicated PD showed differences in timing variability (total, clock, and motor delay variance under the Wing-Kristofferson model) between the MA and LA sides. In contrast, Elsinger et al.[10] found no effect of medication on total variability in PD for the same synchronization-continuation paradigm, but did not use the Wing-Kristofferson model to partition the variance. An alternative explanation of the inconsistent findings of impaired interval timing in PD is that impairments are only apparent after taking into consideration the potential structure of timing variability, such as with the Wing-Kristofferson model.

Timing deficits in PD have been found using other single-joint oscillation tasks. Swinnen et al.[22] found reduced accuracy and variability in medicated PD for synchronized oscillation of elbow-knee joint pairs, and that PD exhibited less accurate continuous coordination as well. Almeida and Brown[23] found reduced temporal accuracy in a wrist oscillation task compared to healthy controls, but dopaminergic medication was not found to affect timing. A group of OFF medication PD showed no difference in timing accuracy regardless of cueing when compared to healthy controls for an ankle flexion/extension task[24]. These results across different contexts support the presence of central timing deficits in PD.

Additionally, Bernstein's perspective of "degrees of freedom" in coordination predicts that bilateral and/or multi-joint coordination should impose additional complexity in timing and motor control (i.e. degrees of freedom) compared to unilateral and/or single-joint tasks, or require additional synergies to simplify the movement[25,26]. Some functional imaging research supports this expectation; Whitall et al.[27] found additional activation in the supplementary motor area when performing bilateral arm movements compared to identical unilateral movements. In addition, a study using fMRI detected distinct activations of the supplementary motor area proper and primary motor cortex when finger movements were compared to repetitive flexion/extension of the elbow or knee[28]. Electromyographic recordings and loss of automaticity detected via dual-tasking provide direct and indirect support for generally deteriorating motor synergies in PD[29,30], which may not be engaged by simple unilateral and/or single-joint tasks. Increased gait variability is often observed in pwPD and is associated with reduced stability and falling status[31–33]; however, it is unknown whether timing deficits observed with simple single-joint tasks are related to disturbed gait timing, given the large difference in biomechanical complexity (e.g. degrees of freedom).

Therefore, the purpose of this study was to measure the dopaminergic modulation of timing in the coordination of bilateral, multi-joint movements in people with PD. The somatotopic organization of motor circuits in the basal ganglia-thalamocortical circuits allows for potential differences in the behavior of the upper and lower limbs[34]. Therefore, we used specific tasks to separately evaluate the upper and lower limbs to explore how cueing affects (multi-joint) coordination differently in PD compared to controls, and how medication moderates the effects of cueing on (multi-joint) coordination in PD.

Methods

Participants

Healthy volunteers and people with PD were recruited from the Montreal, Quebec area. Exclusion criteria for the PD group were (1) any additional neurological, orthopedic, or muscular disorder; (2) previous deep brain stimulation; (3) additional balance affecting medication besides dopaminergic medication; (4) diabetes. Healthy, age matched controls were excluded using the same criteria as the PD group. Ethics approval was given by the Research Ethics Board of the Center for Interdisciplinary Research in Rehabilitation of Greater Montreal, and the study was conducted in accordance with the Declaration of Helsinki. All subjects gave written informed consent prior to participating in the study.

Clinical evaluation

Members of both groups participated in two sessions, roughly separated by one week. Most members of the PD group were optimally medicated ("ON") for the first session and were at least 12 h withdrawn from dopaminergic medication ("OFF") for the second session. Both sessions were scheduled for the same time of day, and participants performed the same protocol each time. During the first session, all participants completed a medical history questionnaire (including self-reports of the more affected side by PD participants), the Montreal Cognitive Assessment (MoCA), and the PD group completed the Freezing of Gait Questionnaire (FOGQ) and answered a question intended to detect freezing in the upper limbs; see Supplemental Note S1 for freezing status and descriptive statistics. At each session, the PD group was evaluated using the Hoehn & Yahr (H&Y) scale and the Unified Parkinson Disease Rating Scale motor section (UPDRS-III).

Protocol

All participants performed a bilateral repetitive reaching task (RRT)[35] and a stepping in place task (SIPT)[36]; each task was performed with and without a metronomic cue. For the RRT, a cylindrical touch sensitive target (6 cm long, 0.5 cm radius, Quantum Research Group Ltd) was centered in front of the participant, horizontally level with their sternal notch, and at a distance equal to 50% of their arm length. Participants began the task with both index fingers resting near the sternal notch and with elbows elevated. Participants alternately reached to touch the target with left and right index fingers, while returning the contralateral hand to rest at the sternal notch. The RRT was performed standing. For the SIPT, participants stepped in place over two force platforms. A metronome played continuously during the cued trials. For the uncued trials, a metronome played 10 beats of the target movement cadence immediately before the trial began, and participants were instructed to remember

and match the target cadence during the trial. For both RRT and SIPT, participants were given two 20 s practice trials to perform the task at the fastest pace that could be safely and comfortably sustained for the duration of the protocol. The cadence of the fastest practice trial was used to set the beat frequency of the metronome. The RRT and SIPT tasks were performed for 120 s[37] by most participants, but the trial length was shortened for some participants who were unable to perform the task for the complete time. Task and cue order were block randomized by task. Participants wore a safety harness attached to the ceiling to arrest falls without restricting movement, and no participants fell.

Data acquisition

A six-camera Vicon motion capture system (VICON Motion Systems Ltd., Oxford, UK) was used with a kinematic sampling frequency of 100 Hz. A set of 40 markers was used to capture upper and lower body kinematics. For the upper body, markers were placed on the head (4 markers), sternal notch, on the spine at C7, and bilaterally at the acromion, upper arm, elbow lateral epicondyle, forearm, distal radial and ulnar processes, index metacarpal, and distal phalanx of the index finger. For the lower body, markers were placed on the pelvis—bilaterally on the ASIS and PSIS—and bilaterally on the lateral mid-thigh and mid-shank, the lateral epicondyles of the knee and ankle, and on the heel, fifth metatarsal, and distal phalanx of the big toe. Ground reaction forces under each foot were measured with force plates (AMTI Inc., Watertown, USA) sampled at 1000 Hz by the Vicon motion capture system.

Data reduction

Steps and reaches were identified from the data to calculate timing characteristics as a function of side (MA and LA, with the left side used as MA for control group and any bilaterally affected PD). A complete cycle is defined as three consecutive contralateral steps or reaches; a half-cycle refers to two consecutive contralateral events, where the step/reach side is defined by the (temporally) leading side (e.g. a MA event after a LA event would be a MA step). PD freezers were not excluded from participating, but the focus of this analysis is the timing characteristics during continuous cycling in the SIPT or RRT, regardless of a participant's freezing status; any interruptions in continuous cycling (e.g. freezing) would interfere with characterizing normal task performance. Therefore, we used an automatic multi-stage process to identify all possible steps/reaches, while excluding any interruptions in task cycling that could plausibly be the result of a freezing episode (plausible freezing episode, PFE).

During the SIPT, participants did not always maintain their position over both force plates, therefore, steps in the SIPT were initially identified by the local peaks in vertical foot position. Peaks in vertical foot position were determined using the 3 foot markers and the ankle marker; peaks were required to be at least 8 mm above stance marker height and separated by at least 150 ms. (8 mm minimum step height was chosen to balance uncertainty in stance marker height estimates and to limit false negatives, such as missed steps, that needed further confirmation based on unreliable—due to wandering—force plate data.) For the RRT, reaches were initially identified using the signal from the touch sensitive target. Marker data was used to identify the stepping/reaching side of each event for both SIPT and RRT, as the touch target signal and force plates were incapable of, or insufficient for, indicating side.

The first stage of PFE identification considered consecutive step/reach intervals greater than 1.5 times the median interval as unexpected interruptions—which could be caused by either freezing or unobserved steps/reaches (e.g. due to step height peaks less than 8 mm, gaps in the markers, etc.). For some interruptions in the initially identified steps in the SIPT, force plate data could be used to confirm functional unloading (defined as more than 90% body weight on the loaded leg and less than 5% body weight on the unloaded leg) when participants' feet were within the bounds of their respective force plate. For the RRT, interruptions in the initially identified reaches could be caused by issues with the touch target signal or due to participants missing the touch target, despite making complete reaches. Marker data (wrist and hand markers) were used to identify reaches when the touch target signal was insufficient. The second stage PFE identification considered premature stopping (more than 5 s before end of a trial), and any remaining intervals longer than 1.75 and 2 times the median interval, for the SIPT and RRT, respectively, as PFE. PFE were excluded from future analysis by setting a minimum sequence length of three consecutive steps/reaches, where all inter-step/reach intervals in a sequence are shorter than the PFE threshold. All identified steps, reaches, and PFE in the SIPT and RRT were visually confirmed to be reasonable, with minimal false positive PFE's[38].

Timing deficits were assessed using several metrics. Cadence was calculated as the average steps/reaches per minute. Cadence error was then calculated as the percent difference in achieved and prescribed cadence, normalized by the prescribed cadence; positive cadence error represents a faster achieved cadence than the prescribed. The Wing and Kristofferson model[21] of timing of repetitive, discrete movements was used to estimate internal clock variance and variance due to motor delays; see Fig. 1 for model diagram and derivation. Lag-one serial correlation of steps/reaches was also calculated. The phase coordination index (PCI) was used as a measure of temporal coordination accuracy and variability[39] for both the SIPT and RRT. Finally, in recognition that the MA and LA sides can behave differently, step/reach time coefficient of variability (COV) was calculated for both sides for the PD group, but was calculated over all steps/reaches on both sides for the controls.

Statistics

Independent variables were *group* (Control, PD), *meds* (OFF, ON), and *cued* (false, true). The partial nesting of medication in *group* was collapsed into a single variable *group_meds* (Control, PD_OFF, PD_ON). Dependent variables (for both tasks) were prescribed cadence, cadence error, clock and motor variance, lag-one correlation, PCI, and bilateral (LA/MA) step/reach time COV. The RRT and SIPT were evaluated separately, and dependent variables were not compared between tasks. A linear mixed effects model was defined with main and interaction effects for

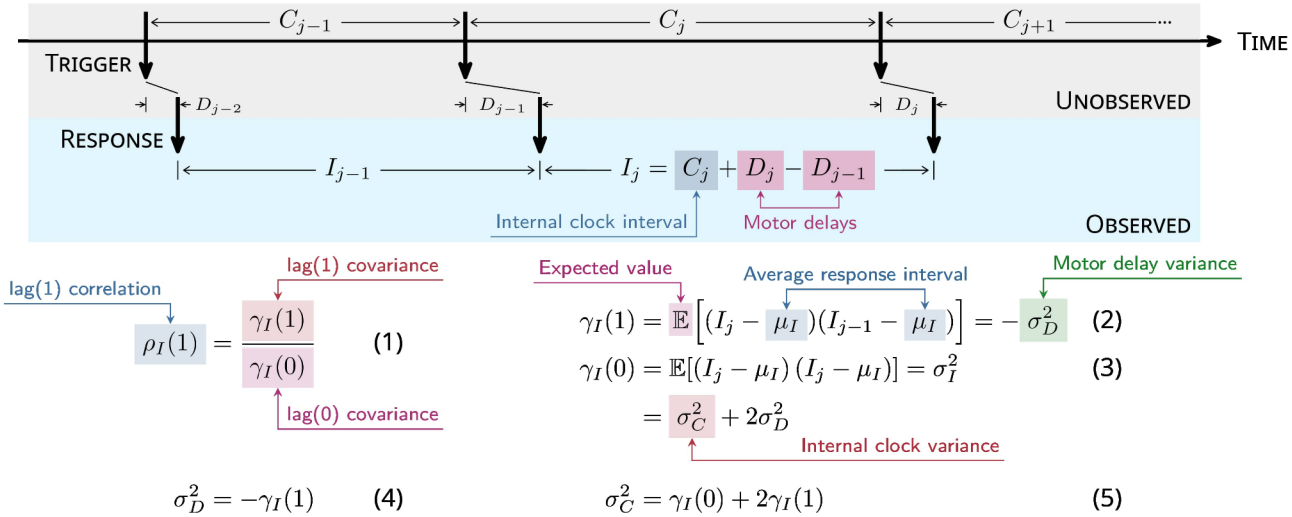

Fig. 1. Schematic and model for the Wing-Kristofferson model of the timing of repetitive, discrete motor responses. It is assumed that an internal clock process generates trigger pulses at intervals C_j. A response occurs an independent delay, D_j, after each trigger to account for e.g. neuromuscular transmission time, movement time, etc. Neither C_j or D_j are directly observable from response timing, however, the clock and motor variance, σ_C^2 and σ_D^2, can be estimated from the characteristics of the interresponse intervals I_j. The lag-one serial correlation $\rho_I(1)$, which measures dependence of consecutive interresponse intervals, can be negative without explicit negative feedback in the system. For example, a zero variance internal clock (e.g. if perfectly following an external metronome cue, and generally when $\sigma_D^2 \gg \sigma_C^2$) would lead to $\rho_I(1) = -1/2$. See Wing and Kristofferson[21] for derivations and further details.

group_meds and *cued*, and with a maximal random effects structure of random intercepts and slopes for subject and sample (to account for the repeated observations per control participant due to the two sessions)[40]. The full model formula is $Y \sim \text{group\_meds} * \text{cued} + (1 + \text{group\_meds} * \text{cued}|\text{subject}) + (1 + \text{group\_meds} * \text{cued}|\text{sample})$ (given in the common syntax of the R *lme4* and Julia *StatsModels.jl* packages[41,42]). The model with maximal random effects was then reduced to find a parsimonious model for each dependent variable[43]; fully simplified models and regression coefficients for each variable are available in our accompanying code and data repository[38]. Prespecified contrasts were used to test for differences at the between-group level $H_0 : \mu_{control} = 1/2\left(\mu_{PD_{ON}} + \mu_{PD_{OFF}}\right)$ and at the within-subject level in the PD group, $H_0 : \mu_{PD_{ON}} = \mu_{PD_{OFF}}$ Model coefficients were interpreted as significant when the parametrically bootstrapped (10,000 samples) 95% confidence intervals did not include zero. Mixed model fitting, evaluation, and bootstrapping were done in the Julia language using MixedModels.jl[44,45]. Significant interactions were tested in R using the *emmeans* package to run post-hoc tests; degrees of freedom were calculated using the Kenward-Roger method and p-values were adjusted using the Holm procedure. Observations were considered outliers when visually identified as potentially deviant, and when follow-up models were significantly different after removing the suspect observation[46].

Results

A total of 40 participants were recruited, but data issues prevented the analysis of three participants, leaving thirty-seven remaining participants; group demographics are given in Table 1. Of the remaining 37 participants, some withdrew after the first session (n = 2), were unwilling to withdraw from medication (n = 1), or were not normally medicated (n = 1); the partial data from these subjects were included in the analyses. When ON medication, the PD group showed a significant 2.8 point decrease ($t(20) = -4.53$, $p < 0.001$) in the sum of bradykinesia related UPDRS III items (finger taps, hand movements, pronation-supination, leg agility, arising from chair, gait, and body bradykinesia; a similar set of items was used in Zach et al.[47], but that study used the MDS-UPDRS).

RRT

The average number of analyzed reaches was 123 ± 49 (mean ± s.d.) for the control group (1 PFE removed from 1 trial among all trials in group), 103 ± 35 for the PD group OFF medication (4 PFE removed from 4 trials), and 100 ± 36 when ON medication (1 PFE removed from 1 trial). Significant main effects are also reported in Table 2. Prescribed reaching cadence in PD decreased 5 bpm 95% CI [−10, −1] ON medication compared to OFF; there was no significant group difference. Post-hoc tests found no significant change in cadence between the two repeated sessions within the control group [−9.9, 15.5]. Prescribed cadence error was −3.6% [−6, −1] lower when cued compared to uncued conditions.

Clock variance was greater in PD compared to controls, 0.017 s^2 95% CI [0.004, 0.03], and decreased when cued, −0.0059 s^2 [−0.009, −0.003]; an interaction between medication and cueing in PD (−0.0087 s^2 [−0.02, −0.0006]) moderated an effect of increased variance when ON medication (0.0090 s^2 [0.003, 0.01]). Post-

Characteristic	Parkinson's (n = 25)		Control (n = 12)	
	Mean (SD)	Range	Mean (SD)	Range
Sex (n)	18 M, 7 F		7 M, 5 F	
Age (years)	67 (6.6)	54–80	70 (8.8)	51–78
Height (cm)	172 (8.0)	156–185	165 (12)	146–185
Weight (kg)	75.9 (14.9)	53.0–117.2	73.0 (11.1)	57.0–93.1
MoCA	28 (1.5)	24–30	28 (1.6)	25–30
MA side	15 L, 10 R			
Years Dx	7.7 (5.7)	0–21		
UPDRS-III				
OFF (n = 21)	33 (11)	12–54.5		
ON (n = 24)	25 (9.7)	9–47		
H&Y				
OFF (n = 21)		1–4		
ON (n = 24)		1–4		

Table 1. Participant demographics. *MoCA* Montreal Cognitive Assessment, *H&Y* Hoehn & Yahr, *UPDRS-III* unified parkinson disease rating scale motor section.

Variable	Effect of PD vs. controls		Effect of cueing		Effect of ON medication	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Cadence (bpm)	n.s.		N/A		−5	[−10, −1]
Cadence error (%)	n.s.		−3.6	[−6, −1]	n.s.	
Clock variance (s^2)	0.017	[0.004, 0.03]	−0.0059	[−0.009, −0.003]	0.0090	[0.003, 0.01]
Motor variance (s^2)	n.s.		−0.0017	[−0.003, −0.0008]	n.s.	
Lag-one correlation*	0.31	[0.04, 0.6]	−0.27	[−0.4, −0.2]	n.s.	
MA CoV (%)	n.s.		−1.1%	[−2.0, −0.4]	n.s.	
LA CoV (%)	4.2%	[1.0, 7.0]	−1.3%	[−2.0, −0.7]	n.s.	

Table 2. Significant main effects for the RRT. *Lag-one correlation is unitless.

hoc tests revealed that uncued, ON medication PD had larger clock variance compared to all other conditions ($p < 0.017$); see Fig. 2. Motor delay variance decreased −0.0017 s^2 [−0.003, −0.0008] during cued trials. Lag-one correlation was 0.31 [0.04, 0.6] greater in PD compared to controls and decreased −0.27 [−0.4, −0.2] when cued; see Fig. 3a. Cueing reduced reach time CoV by −1.1% [−2.0, −0.4] and −1.3% [−2.0, −0.7] for MA and LA sides, respectively. LA side reach time CoV was 4.2% [1.0, 7.0] larger in PD compared to controls.

SIPT

The average number of analyzed steps was 237 ± 35 for the control group (3 PFE removed from 2 trials), 236 ± 71 for OFF medication PD (108 PFE removed from 13 trials), and 246 ± 62 (78 PFE removed from 8 trials). Significant main effects are also reported in Table 3. Prescribed stepping cadence was 27 bpm 95% CI [0.2, 50.0] faster in PD, and medication caused a 13 bpm [−20.0, −5.0] decrease in target cadence. Post-hoc tests found no significant change in cadence between the two repeated sessions within the control group [−11.2, 10.5]. Cadence error decreased when cued, −6.5% [−8.0, −4.0]; both groups appeared to step faster, relative to the target cadence, when uncued. For PCI, a significant interaction between group and cueing, −2.1° [−4.0, −0.05], moderated a 3.7° [1.0, 6.0] increase in PD compared to controls, and a 0.057° [−0.4, 0.5] increase due to cueing. Post-hoc tests for PCI were not significant.

Clock variance showed an interaction between group and cueing 0.00081 s^2 95% CI [0.0002, 0.001]; post-hoc tests were not significant. Motor delay variance showed a significant interaction between group and cueing, −0.00055 s^2 [−0.0008, −0.0002] that moderated an 0.00035 s^2 [3.0e−5, 0.0007] increase in PD compared to controls, and increased variance, 7.5e−5 s^2 [5.0e−6, 0.0001], during cued conditions. Post-hoc tests showed that cueing increased motor delay variance in the control group ($p = 0.001$). Lag-one correlation showed a significant interaction between group and cueing, 0.50 [0.3, 0.7], that moderated findings of decreased correlation in PD compared to controls, −0.36 [−0.6, −0.09], and decreased correlation when cued, −0.073 [−0.1, −0.02]. Post-hoc tests showed that cueing decreased lag-one correlation in the control group ($p < 0.001$); see Fig. 3b.

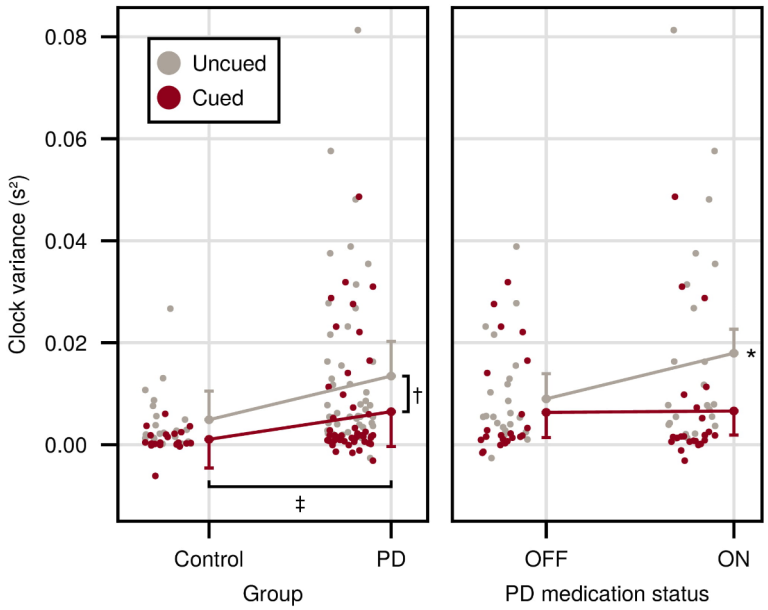

Fig. 2. Estimated variance of the internal timekeeping process during the repetitive reaching task. † Simple main effect of decreased variance when cued, −0.0059 s^2 95% CI [−0.009, −0.003]. ‡ Simple main effect of increased variance in PD, 0.017 s^2 [0.004, 0.03]. * Post-hoc tests showed that uncued, ON medication PD had larger clock variance compared to all other conditions in the PD group ($p < 0.017$).

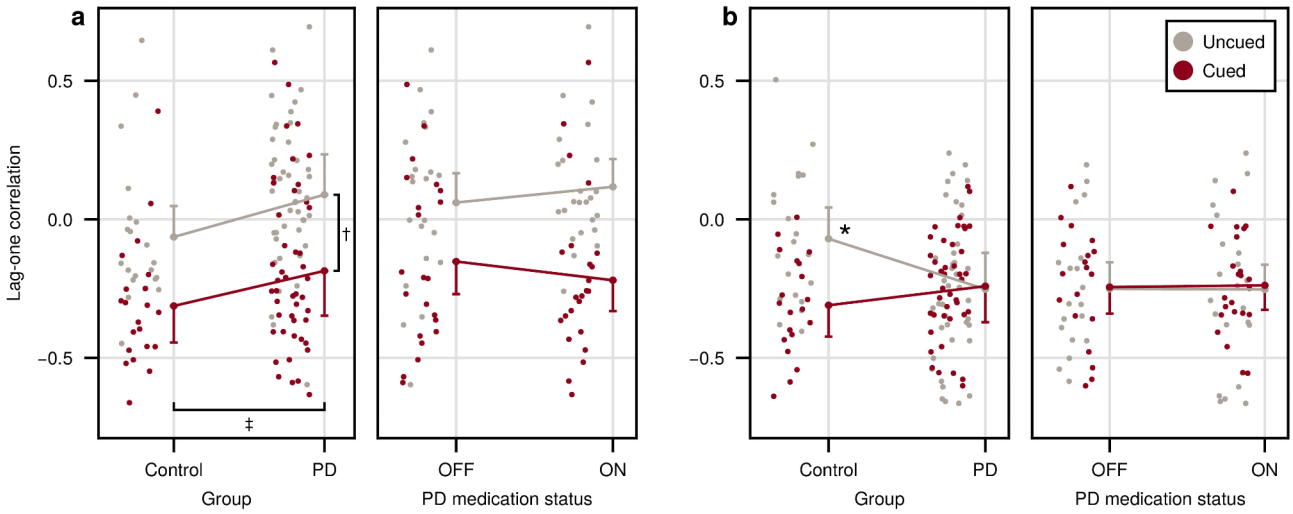

Fig. 3. Lag-one correlation during repetitive reaching (**a**) and stepping in place (**b**). Lag-one correlation measures the dependence of consecutive steps/reaches. † Simple main effect of decreased lag-one correlation when cued for repetitive reaching, −0.27 95% CI [−0.4, −0.2]. ‡ Simple main effect of greater lag-one correlation in PD for repetitive reaching, 0.31 [0.04, 0.6]. * Post-hoc tests confirmed ($p < 0.001$) that controls responded to cueing when stepping in place, while the PD group did not.

Discussion

This study explored the effects of medication and auditory cueing on temporal characteristics of bilateral RRT and SIPT in people with PD. For both tasks, we found decreases in the self-selected fastest sustainable stepping/reaching cadence in the PD group when medicated and decreases in cadence error in both groups when cued; the PD group had a faster self-selected target SIPT cadence. Both groups displayed reduced internal clock variance for the RRT when cued, and the PD group showed increased clock variance ON medication when not cued compared to other conditions (cued and/or unmedicated). Motor delay variance for the RRT decreased in both groups when cued, but for the SIPT, the PD group was unaffected by cueing or medication. Similarly, lag-one correlation was reduced in both groups when cued for the RRT but was unaffected by cueing or medication in the PD group for the SIPT. Our results support the existence of impaired timing in PD, observable at the level

Variable	Effect of PD vs. Controls		Effect of cueing		Effect of ON medication	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Cadence (bpm)	27	[0.2, 50.0]	N/A		13	[−20.0, −5.0]
Cadence error (%)	−6.5	[−8.0, −4.0]	n.s.		n.s.	
PCI (°)	3.7	[1.0, 6.0]	0.057	[−0.4, 0.5]	n.s.	
Clock variance (s^2)	n.s.		n.s.		n.s.	
Motor variance (s^2)	0.00035	[3.0e−5, 0.0007]	7.5e−5	[5.0e−6, 0.0001]	n.s.	
Lag-one correlation*	−0.36	[−0.6, −0.09]	−0.073	[−0.1, −0.02]	n.s.	
MA CoV (%)	n.s.		n.s.		n.s.	
LA CoV (%)	n.s.		n.s.		n.s.	

Table 3. Significant main effects for the SIPT. *Lag-one correlation is unitless.

of multi-joint movements in the upper and lower limbs, but dopaminergic modulation of these timing deficits is minimal.

Prescribed cadence was individually self-selected per session as the fastest sustainable cadence for each task. In the PD group, this cadence was determined while subject to that session's medication condition, ON or OFF. Therefore, this self-selected cadence was experimentally susceptible to any effects of medication. In the PD group, we found similar reductions in cadence in both tasks while ON medication. Due to the standardized order of session medication, we cannot reject the possibility of a learning effect due to the order; however, our results showed no change in cadence between sessions within the control group, for either task. Future research should counterbalance medication order to avoid this confound. In general, medication has null[48] or positive[33,47,49,50] effects on reducing clinically measured bradykinesia (i.e. UPDRS). This was observed in our study in the PD group ON medication, as a significant decrease in a bradykinesia related UPDRS sub-score compared to OFF. Several studies have found that maximum finger tapping cadence is increased by medication[51,52]. Additionally, a small (N = 8) study found no effect of medication on maximal tapping rate[18], but this null finding is less informative because the small sample size limits the statistical power to detect small to moderate effects. Stegemöller et al.[14] tested continuous tapping with incremental cadence increases, and found no effect of medication on the fastest achievable rate, despite significant reductions in UPDRS finger tap impairment with medication. In gait, preferred walking cadence shows no effect of medication[53,54]. In sum, the decreased cadence ON medication is unlikely to be the result of a pharmacologically mediated change in bradykinesia.

The unexpected decrease in cadence ON medication may instead be the result of a change in the internally generated timing or time perception. However, ample evidence links dopamine depletion in mouse and human models (both pharmacological, e.g. haloperidol, and pathological, e.g. PD) to decreases in internal clock speed, with complementary speed increases when dopamine is restored or enhanced[55–57]. Such effects would contradict our results and lead to increased cadence ON medication. Therefore, our results are likely not due to intrinsic changes in the internal clock speed.

The PD group exhibited a faster maximal stepping cadence than the control group, likely the result of shuffling gait, which is common in people with PD[58]. Fast stepping in place is a paradigm often used to trigger freezing of gait in PD[36], and we are not aware of any studies which included a control group we could compare our results to. However, in gait, Almeida et al.[53] found no difference in cadence for (sub-maximal) self-paced gait between PD and controls.

Cadence error was not detectably affected by medication, which is consistent with relative error results from Jones et al.[13], and with other measurements of accuracy for tapping and bimanual oscillation tasks[10,16,23]. In addition, Elsinger et al.[10] found increased error in PD compared to controls during the "continuation" phase (i.e. uncued) of the synchronization-continuation paradigm which was not replicated in our results (i.e. no significant *group* × *cueing* interaction).

When it comes to timing variability in the upper limbs, several studies have found no differences in total variability between ON PD and healthy peers during the continuation phase[16–18]. However, reports on the effects of medication disagree, with evidence for[16] and against[10]. Our results found no effect of medication on total variability (COV) for either side; however, COV was higher than controls on the LA side for the RRT. Although we did not directly compare LA and MA COV, our results do not suggest an increased variability on the "worse" (i.e. MA) side compared to the LA side and compared to controls as reported by O'Boyle et al.[16]. Consistent with previous results[10,13], cueing resulted in decreases in COV, for both groups.

The different behavior of clock and motor variance in our results support the presence of structure within overall timing variance. Our observed increases in clock variance in PD, regardless of medication, has also been previously noted by O'Boyle et al.[16]. Although Ivry and Keele[17] found no effect of medication on clock variance, they noted that their subjects were "unable to walk and showed extreme bradykinesia in arm movements." We also found an interaction between medication and cueing that resulted in higher clock variance when ON medication and uncued; this contradicts previous findings that noted reduced clock variance ON medication[16]. While dopaminergic medication does not uniformly improve all movement characteristics[59], this finding is counter to our expectations based on neuroimaging studies that report normalized activation in various networks following administration of dopaminergic medication[10,60].

Also counter to expectations, motor variance was not larger in PD compared to controls and showed no interaction with medication, as in O'Boyle et al.[16]. The decrease in motor delay variance due to cueing does

not fit with the Wing-Kristofferson model, but the number of negative motor variances when uncued—which should not occur under the model—suggest that other factors are at play (see below). Similarly, the lag-one correlation seemed to be greatly improved when cued, with fewer deviations from the model (values not within 0 to – 1/2) in both groups, but particularly in the PD group. Despite these aberrant observations, the correlations strongly support the presence of impaired timing in PD.

In the SIPT, total variability was not different in PD compared to controls, nor was it affected by cueing or medication in PD. A previous study of rhythmic auditory stimulation (cueing) during gait found no effect of cueing or medication on stride time variability (COV), but COV was increased in PD compared to controls[61]. Furthermore, the *group* × *cueing* interactions in PCI, clock variance, motor variance, and lag-one correlations all show the same behavior: the control group modifies their gait timing in response to cueing, but the PD group does not. Previous studies show that people with PD maintain an ability to adapt gait timing in response to cueing, for cadences at or near participant's preferred cadence[61,62]. Therefore, the lack of a response to cueing in the PD group appears to reflect an impaired ability to apply the external cues to step timing. Such a conclusion is seemingly contradicted by the change in cadence error, where both groups reduced their cadence to better match the target cadence when cued. However, the self-selected maximal stepping rate may be too fast for the PD group to accommodate additional modulation of step timing beyond what is required to maintain dynamic stability; this may be due to the attentional demands of the fast stepping pace approaching the limit of participants' motor repertoire. The slightly reduced cadence when cued may be sufficiently slower to allow the observed adherence to cues.

Some differences between the RRT and SIPT limited direct comparisons between tasks. Movement amplitude was fixed for the RRT due to positioning of the subject relative to the touch target, while the stepping height was not controlled during the SIPT. In addition, the SIPT required subjects to maintain dynamic stability while stepping. A cycling/ergometer is an alternate task that could be performed identically by both arms and legs and be more suitable for comparing upper and lower limb timing behaviors. Future work that focuses on comparing the function of upper vs lower limb tasks could help predict the everyday tasks that would pose the biggest problems in people with PD.

The present work possesses some limitations due to the chosen methods. In particular, the Wing-Kristofferson model is based on assumptions that likely oversimplify the underlying phenomena. Previous studies using this model often record incongruous correlations caused by negative motor variance estimates[16,17,63], which suggest that model assumptions are being violated. Clock drift, which causes bias in the clock and motor variance estimates, is found with increasing likelihood as the number of recorded intervals increases[64]. Ogden and Collier[64] proposed an extension of the Wing-Kristofferson model which reduces bias but increases the standard errors of estimates; therefore, the authors recommend the extended model only when drift is of specific research interest.

Negative motor variance estimates, seen in our results (15 cued and 34 uncued observations for RRT, 4 cued and 17 uncued for SIPT) and in previous studies, can sometimes arise from drift, however they may be a result of sampling error "because the tail of the sampling distribution will be in the negative region even when no drift is present"[63]. Ivry and Keele[17] amended negative motor variances by resetting them to zero, resting on an assumption that motor variances are small[63]. In the context of PD, such an assumption is questionable, and our stepping and reaching tasks have greater opportunity for non-negligible motor variance due to being biomechanically larger and more complex, relative to the typical single joint tapping tasks previously evaluated with the Wing-Kristofferson model.

Furthermore, an implicit assumption of the Wing-Kristofferson model is that motor delays are independent of clock pulses (i.e. movement time cannot be anticipated or adjusted to synchronize the movement extent with the target interval); this is shown by the model's formulation of observed intervals as the sum of internal clock intervals and the motor delay. For tapping tasks, movement time is negligible compared to the inter-response intervals, but the movement time required for our tasks cannot be ignored. Wing[65] found smaller motor variances correlated to larger movements, which may suggest an incorporation of movement time into response timing. Perceptible movement times weaken such an assumption, and developing an alternate model that accounts for this strategy may be appropriate.

Another potentially inappropriate assumption is the sharing of motor variance between sides. Limb dominance can contribute to the presence of different variances by side in healthy (i.e. generally symmetric) populations ([66], Exp. 1). Even more so, previously observed, prominent asymmetric patterns, both during clinical assessment and during gait, in early to moderate PD[4,67] support the possibility of different motor variances on the MA and LA sides. O'Boyle et al.[16] qualitatively observed a trend for an interaction between limb dominance and more affected side in PD (during unilateral tapping). For timing tasks using bilateral end-effectors, an extension of the Wing-Kristofferson model to account for differences in side (e.g. $I_{j,MA} = C_j + D_{j,MA} - D_{j-1,LA}$) is likely warranted to improve model fidelity, but would need additional data (e.g. EMG or separate unilateral timing trials to directly estimate motor variance, etc.) to distinguish motor delay variance between the MA and LA sides. Wing[68] proposed a related extension of their model for the context of simultaneous bilateral repetitive movements, but alternating bilateral movements would require a different formulation.

Conclusion

In this study we investigated the effects of medication and cueing on the temporal characteristics of repetitive reaching and stepping in place in people with PD. People with PD showed a paradoxical decrease in maximal cadence when ON medication. Total timing variability was not significantly different from healthy controls. However, variability decomposed using the Wing-Kristofferson model showed differences between PD and controls, despite evidence that some assumptions by the Wing-Kristofferson model may not be appropriate. In PD, medication interacted with cueing during the reaching task and produced increased clock variance. These

results suggest that overall timing variability may not capture temporal impairments in PD compared to healthy peers. More research is needed to explore more faithful timing models and the effects of medication on timing in PD.

Data availability

The data and software produced to analyze said data in this work are openly available at the Zenodo data repository at https://zenodo.org/records/10685620[38].

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Author contributions

A.H.: Conceptualization, Data Curation, Formal Analysis, Methodology, Resources, Software, Visualization, Writing – Original Draft, Writing – Review & Editing. H.C.: Conceptualization, Data Curation, Funding Acquisition, Investigation, Project Administration, Writing – Review & Editing. J.N.C.: Conceptualization, Funding Acquisition, Project Administration, Resources, Supervision, Writing – Review & Editing. J.N.: Conceptualization, Funding acquisition, Resources, Supervision, Writing – Review & Editing.

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4.3.3. Additional methods

4.3.3.1. Task description

There were two tasks in this study: a stepping in place task (SIPT) and a repetitive reaching task (RRT). The SIPT was developed by Nantel et al. (2011); participants were instructed to step in place. The RRT was developed previously by Lomond and Côté (2010), and was chosen as an upper-limb task, analogous to the SIPT. Participants were given two trials at the beginning of each session to practice performing the task as fast as comfortably and sustainably possible. The faster cadence of the two trials in each task was selected as the target cadence, and participants were instructed to step/reach at that cadence (according to the metronome or the remembered cadence, depending on the experimental condition).

4.3.3.2. Reach and step identification

The goal of this study was to measure participants' continuous timing performance, so two necessary prerequisites were to identify reaches and steps, and to exclude any interruptions in reaching or stepping. In the context of research involving pwPD, freezing episodes are the most likely cause of interruptions in reaching or stepping. Therefore, we used the term "plausible freezing episodes" (PFE) to discuss interruptions, where "plausible" highlights their nature as freezing episodes which have not been confirmed (e.g. using multiple trained observers as in Cantú et al. (2018)). For consistency, we excluded PFE from the data in both tasks (RRT and SIPT) and both groups (controls and pwPD). Although the PD group would be expected to produce the majority of PFEs, this analysis decision created the potential for PFE to be identified in healthy controls, who could not "plausibly" freeze. In such cases, the term PFE is still used for consistency, despite the origins being different and unrelated to freezing in PD (e.g. caused by algorithmic false positive).

Kinematic data was intended to be the initial/primary source of data for step/reach detection. However, a low quality of marker data (caused by a small number of motion capture cameras and non-ideal camera placement/aiming) necessitated the use of additional data signals

(capacitive touch target for the RRT, dual force plates for the SIPT) to accurately detect all steps/reaches. The kinematic data contained a large number of gaps which feasibly be filled with an acceptable accuracy or in a reasonable amount of time. The large number of gaps and cumulative gap length within trials prevented using a single marker (in either task) for identifying steps/reaches.

Steps and reaches were identified automatically using a custom developed algorithm. An algorithm was chosen instead of manual identification to save time and improve reproducibility (Miyakawa, 2020). (While automatic identification is dependent on the sole existing source of raw data—the motion capture data, manual identification would add a new source of irreproducible “raw” data.) The complete codified algorithms for identifying steps/reaches in the SIPT and RRT are available in a Zenodo repository (Hill et al., 2024).

4.3.3.2.1. Stepping in Place: Step identification

Markers from the feet and ankle (LTOE, LMT5, LHEE, and LANK from the marker set; same for the right side) were collectively used for initial step identification. However, due to low marker visibility, force plate data was supplementally used to identify steps as needed. All aforementioned markers were required to be visible for at least half[7] of the trial duration for use in identifying events for any given trial. The sufficiently visible markers were searched for local maxima in the vertical axis with a minimum height of 8 mm[8] above resting height where resting height was calculated as the vertical marker position when the foot is firmly planted (i.e. has negligible velocity) and not loading or unloading. A total of 4 separate maxima could be identified per step if all 4 markers on a side were included and visible. The DBSCAN clustering

[7] Markers which were cumulatively visible for less than half of the trial duration were typically composed of many short segments (10-40 frames at 100 Hz) which were not accurately labelled manually or automatically. Labelling these markers resulted in the inclusion of a non-negligible amount of noisy phantom markers which interfered with future stages of event identification.

[8] The minimum step height of 8 mm was chosen by trial-and-error to balance the inaccuracy of stance height estimates with the smallest step height that would definitely reflect a complete step, in terms of weight unloading.

algorithm was used to form groups of at least 2 maxima that occurred within 150 ms of each other; the cluster center (i.e. average of maxima times) was rounded to the nearest whole frame, and these formed the initial array of identified steps. After removing any maxima used in clusters, any additional individual maxima that occurred within a “long” inter-step interval (defined as one and a half times the median interval between currently identified steps) and ¼ the median interval away from either bounding step were included in the array of identified steps. Finally, any remaining maxima were included in the identified steps array when all (visible) feet markers were within 5.5 cm internally from any edge of the respective side’s force plate and when the loaded force plate was bearing at least 90% body weight while the unloaded force plate was bearing less than 5% body-weight. Identified steps were assessed for false positive double steps and removed. Finally, steps were grouped into full cycles (defined as three consecutive contralateral steps) and any cycling interruptions were excluded as PFE. An example trial with numerous PFE is shown in Figure 3A.

4.3.3.2.2. Repetitive reaching: Reach identification

The capacitive touch-sensitive target provided an unambiguous signal to identify reaching. However, a primary limitation was that the touch target signal could not reveal which side made a given reach. In addition, participants sometimes made complete reaches but missed touching the target (see Figure 3B). Kinematic data was used to supplement these limitations. The touch target signal was used for initial reach identifications, measured as local maxima in the rate of change of the signal. Some participants repeated a reach (on the same side), presumedly to “correct” missed touches or touches perceived as “incomplete.” Double reaches were identified (using all hand adjacent markers: index and finger markers, and lateral and medial wrist markers) and removed.

“Long” inter-reach intervals, defined as greater than 1.5 the median inter-reach interval, were investigated for unobserved reaches (e.g. a reach that did not touch the target, etc.). First, local maxima in the anteroposterior axis of the R/LFIN marker (placed on the index metacarpal)

with a prominence of more than 100 mm which occurred more than ½ the median interval away from either bounding reach were included as identified reaches. Next, for any remaining long inter-reach intervals, a maxima clustering approach was taken. This was similar to the previous SIPT clustering, using all hand-adjacent markers (hand to forearm) visible in more than 25% of the trial. Maxima in the anteroposterior axis with a prominence of at least 100 mm and which occurred more than ½ the median inter-reach interval away from known reaches were grouped into clusters of at least two maxima that were within 100 ms of each other. As with the SIPT, cluster centers were found and rounded to the nearest frame, and any maxima that were part of a cluster were removed from further consideration. Additionally, any remaining maxima which occurred within 150 ms of any clusters were removed from further consideration. Finally, any remaining individual maxima in the hand-adjacent markers were included in the final array of reaches. As with the SIPT, double reaches were removed, which could be false positives or actual “corrected” reaches following a perceived insufficient reach or missed touch. Reaches were grouped into full cycles (defined as three consecutive contralateral steps), and PFE were excluded (see Figure 3C).

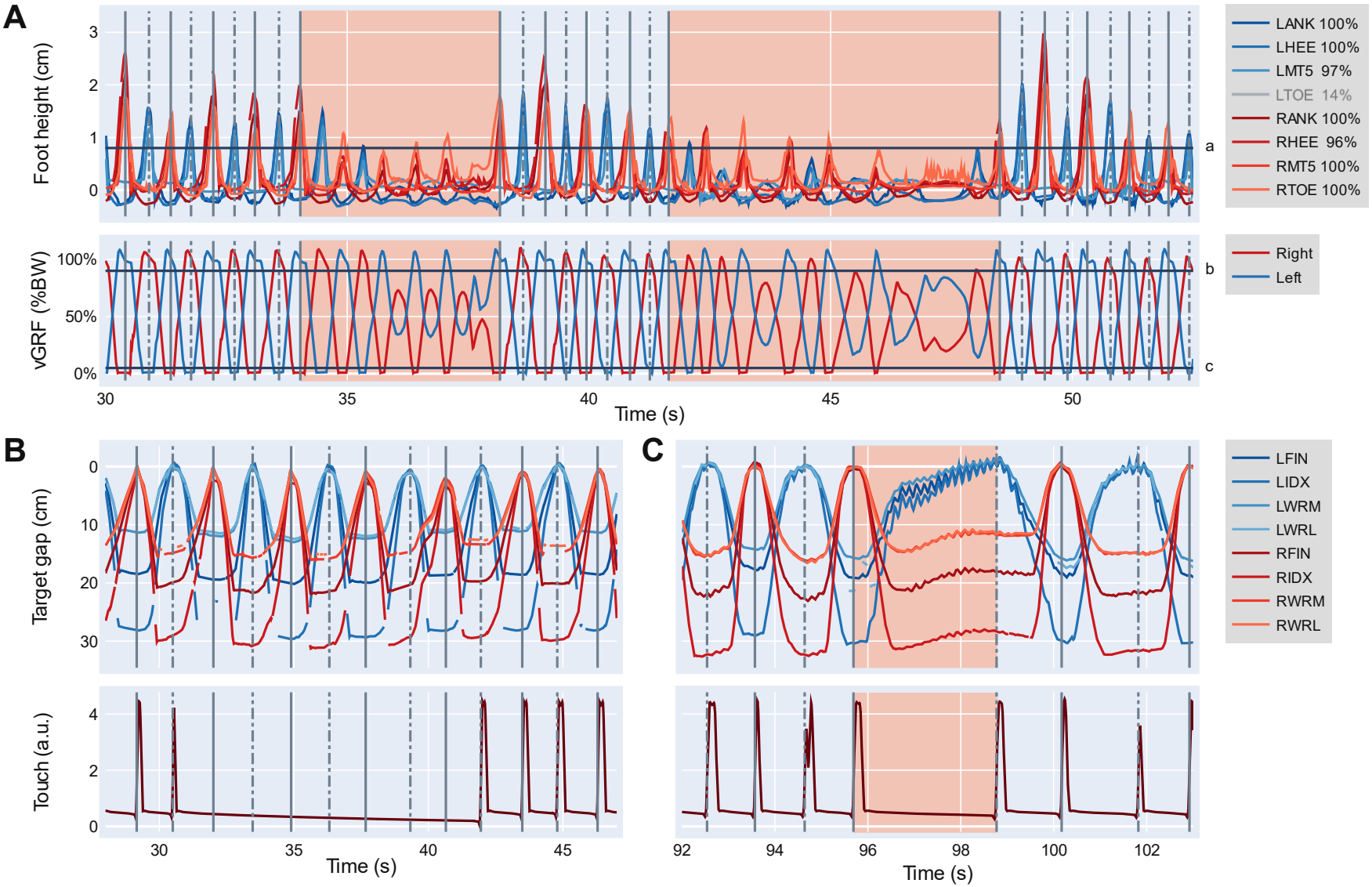

Figure 3 Stepping and reaching identification. *Steps and reaches are depicted by vertical dashed and solid lines for the left and right sides, respectively.* ***Panel* A** *shows two PFE (the pink shaded regions) during a SIP trial, detected by insufficient stepping height (noted by horizontal line* **a** at 0.8 cm*) and/or incomplete weight transfer (90%BW [body weight] upper and 5%BW lower thresholds denoted by horizontal lines* **b** *and* **c***). Percentages after marker labels in the legend describe the cumulative marker presence for that trial; LTOE was not used (or plotted) due to its minimal presence.* ***Panel* B** *shows continuous reaching during an RRT trial with multiple reaches that were detected with marker data because the participant missed the touch sensitive target.* ***Panel* C** *shows an example of a PFE during the RRT. The lower axes in panels* **B** *and* **C** *show the signal from the touch sensitive target.*

4.3.3.3. Statistical methods

Traditional repeated measures ANOVAs are a common approach to statistically testing the effects of experimental manipulations in correlated data (e.g. multiple measurements from the same participant). However, a weakness of repeated measures is an inability to directly handle unbalanced data, where some measurements are missing, which requires row-wise removal (e.g. remove all remaining measurements from a participant for that dependent variable) or using multiple imputation (Baguley, 2012). Another weakness of repeated measures ANOVAs is the inability to model additional known sources of correlated variance in the data (e.g. family members may have similar data, etc.) (Baguley, 2012). Mixed-effects models (also known as multilevel models) are unaffected by either weakness (Cohen et al., 2002; Pinheiro & Bates, 2000). Therefore, mixed-effects models were chosen for the statistical analysis.

A common approach for dealing with outliers is to remove all values more extreme than 1.5 times the interquartile range. However, this comes with the risk of removing values that are consistent with the actual distribution of the underlying data, and this risk is exacerbated in small samples (Baguley, 2012). Simultaneously, outliers in small samples have a more dramatic influence on the results of a statistical model (Cohen et al., 2002, Chapter 10). There is an alternative approach that acknowledges that “extremeness” is not solely appropriate to define an outlier. “Influence” is the quantitative, measurable effect a particular observation has on the model, which can be measured as a change in the model prediction, aggregate change in coefficients, or change in specific coefficient(s); observations with a large influence are problematic because a single or small number of observations can result in flawed conclusions being drawn from incorrect models (Cohen et al., 2002, Chapter 10). Influential observations were identified following the procedure recommended by Cohen et al. (2002, Chapter 10) and removed as outliers.

5. Discussion

Neurodegeneration of the basal ganglia in PD occurs alongside cascading neurodegeneration elsewhere and the development of deficits in coordination, including increased movement asymmetry and timing deficits. The extent and origin of these coordination deficits, whether directly due to dopaminergic neuronal loss or due to cascading neurodegeneration, is unclear. Studies with a focus on movement asymmetry are common within the fields of PD and stroke research. However, limited prior research suggested that existing methods of measuring asymmetry may not be equally well suited to the task, which could lead to reduced research efficiency (Patterson et al., 2010; Sant'Anna et al., 2011). **Article 1** of this thesis demonstrated that several methods are equally sensitive to asymmetry, but some transformations can have negative impacts on achieved power. While movement asymmetry is a directly observable coordination deficit, some coordination deficits (including MA/LA side-specific deficits in coordination) may not be normally observable because of compensation for and adaptation to motor symptoms in pwPD. A dual task can challenge PD gait and provoke coordination deficits which might be normally masked by compensation (Woollacott & Shumway-Cook, 2002). The findings in **Article 2** of this thesis provided support for some side-specific coordination deficits, while other aspects of coordination are similar between sides. Finally, as timing is a core aspect of coordination, pathological timing performance may decrease coordination. Healthy basal ganglia are active during time perception and reproduction, however, pwPD show altered brain activation and mixed evidence suggests the presence of impaired timing (Coull et al., 2011). **Article 3** of this thesis presented evidence in support of specific timing impairments in pwPD when performing repetitive movements, with a minimal effect of dopaminergic medication. The findings of this thesis suggest that methodologically sound measurements of coordination support the presence of deficits in pwPD, including asymmetric impairment, and that dopaminergic neuronal loss may not be directly responsible for impaired timing in PD. These findings suggest alternative

therapies (e.g. non-dopaminergic or timing-focused physical/occupational therapies), may provide benefits separate from any positive effects of dopaminergic medication. However, further investigation is needed to better understand the interaction between timing and coordination deficits.

5.1. Asymmetry in pwPD

Departures from symmetric movements are clinically and potentially diagnostically of interest due to natural tendencies towards temporal and spatial movement symmetry (Haken et al., 1985; Schöner et al., 1990). A prerequisite for detecting asymmetry is a definition of (a)symmetry (Sadeghi et al., 2000). In practice, many authors use a working definition that describes the method of measuring (a)symmetry but fails to explain or justify the conceptualization of (a)symmetry (Sadeghi et al., 2000). Prior to S.A. Alves et al. (2020), no studies had explicitly discussed the conceptual goals of characterizing (a)symmetry, regardless of target movement characteristic. One key epistemological question is apparent from previous studies and reviews: Does “(a)symmetry” exist *de novo* or relative to a reference (i.e. does asymmetry meaningfully exist in an absolute sense, without reference)? (Sadeghi et al., 2000) Despite profound implications for subsequent analysis, this question has only been implicitly answered in previous asymmetry research—(a)symmetry definitions express researcher’s decisions but not reasons—and typically have not been explicitly acknowledged or discussed.

The question of *de novo* existence of (a)symmetry has not been widely discussed in the literature. Sadeghi et al. (2000) noted that authors in a minority of reviewed studies had defined symmetry as the absence of statistically-significant differences between sides. Ignoring this statistically incorrect interpretation of a null result, the charitable converse definition (asymmetry exists when there is a significant difference between sides) lacks a standard reference (a)symmetry, which makes findings of “asymmetry” less generalizable. Using this definition, any sufficiently large sample size will produce a determination of “asymmetry” in any population, regardless of asymmetry magnitude (Cohen, 1988). Similarly, using this definition, any

comparison of asymmetry (e.g. between pathological and healthy control populations, or between experimental conditions) requires testing for interaction effects which can require vastly larger sample sizes to be sufficiently powered, in comparison to the power of main effects; in fact, many studies which test for interaction effects are significantly underpowered (McClelland & Judd, 1993). Nonetheless, the widespread existence of detectable differences between sides for numerous movement characteristics in healthy people (Sadeghi, 2003; Sadeghi et al., 2000), indicates that “asymmetry” should primarily be considered relative to an appropriate “symmetric” reference range of asymmetry (e.g. a typical range of asymmetry from a healthy population). This approach naturally lends itself to choosing symmetry metrics, which provide individual-based measurements of asymmetry, instead of group-level tests for differences between sides. In contrast to the definition of asymmetry as a group-level difference between sides, individual measurement of (a)symmetry allows directly testing for changes/differences in asymmetry (e.g. between groups or experimental conditions) without the need to test for interactions. Although, depending on the study design, some interactions may still need testing. Additionally, although a null (i.e. “symmetry”) cannot be proven, an equivalence test, such as the two one-sided *t*-test approach (Lakens, 2017), may be used to produce a qualified finding of “symmetry”: A significant “equivalent” finding from an equivalence test states that (given the specified α of the test) the magnitude of asymmetry (at a group level) is lower than a “symmetric” reference asymmetry magnitude (regardless of whether the data are significantly different than the “symmetric” numeric value, e.g. zero, depending on the symmetry metric).

Using an individually-based conceptualization of (a)symmetry, the next part of a complete definition of (a)symmetry is the method of measuring asymmetry. Multiple viable asymmetry metrics exist, and despite the numeric incompatibility of these asymmetry metrics, S.A. Alves et al. (2020) showed that several are internally valid and equivalent based on some key metric characteristics. However, alongside methodological validity, an important factor in considering available methods is reproducibility, including the desired statistical power of tests in a study.

Low statistical power results in research waste by increasing the probability of type II error (Ioannidis et al., 2014). Therefore, all other factors being equal, a metric with the highest sensitivity (i.e. metric with the highest probability of distinguishing true differences in asymmetry magnitude) should be preferred. Choosing a more sensitive method is a low-cost way to increase statistical power without affecting the overall study design (e.g. sample size).

Two key findings from **Article 1** are particularly relevant for study design with consideration for power. First, the asymmetry ratio (the ratio between two sides, for a given movement characteristic) magnifies group variability more than other metrics, such that as group variability increases, the asymmetry ratio will exhibit increasingly lower sensitivity (and effect sizes) relative to other evaluated metrics (Hill & Nantel, 2022). Heterogenous progression and presentation of PD symptoms is well-known within PD literature (Jankovic et al., 1990), and this can lead to large group variability. However, accurate *a priori* estimates of group variability can be challenging for novel research (Albers & Lakens, 2018). Therefore, asymmetry metrics other than the ratio will more consistently detect true differences in asymmetry amidst potentially large group variability due to a heterogenous presentation of PD. Secondly, directional asymmetry values (e.g. an asymmetry value which indicates by the sign which side is larger/smaller) should not be transformed with an absolute value, because this reduces the metric sensitivity and effective power (Hill & Nantel, 2022). Appropriate dichotomization of side (e.g. MA/LA instead of left/right, etc.) and/or one-sided statistical tests, when justified, can be used to achieve similar findings without a loss of power. The presence of a bimodal distribution of asymmetry direction, even when using a relevant side dichotomization, may support an alternate dichotomization of sides, or suggest the existence of differently responding subgroups, which is likely worth investigation.

Asymmetric neuromotor deficits in pwPD are responsible for the directly observed asymmetries in movement, such as arm swing (Mirelman et al., 2016; Roggendorf et al., 2012) and step swing time (Yogev et al., 2007). The inherently relative nature of coordination

challenges the detection of any asymmetric coordination deficits. However, some neuromotor deficits may be more readily observed when challenged, such as when posture is perturbed (Boonstra et al., 2014) or during a dual task (Plotnik et al., 2009; Rochester et al., 2014). In **Article 2**, the DTC in the MA and LA sides were compared; any differences could indicate the presence of asymmetric neuromotor deficits between sides. The comparison of DTC by side (using a paired *t*-test) is identical to testing for a change in asymmetry due to dual-tasking, when using the "bilateral difference" asymmetry metric, recommended in **Article 1**[9].

From the perspective of asymmetry, the changes in shoulder and hip range of motion due to dual-tasking are not fully coherent: the LA shoulder swing reduced, but arm swing asymmetry did not change; while neither hip swing changed, yet hip swing asymmetry was different (Hill & Nantel, 2024). However, in general these changes appear to be consistent with previous findings that pwPD exhibit losses in automaticity for some aspects of gait, including those related to coordination (Plotnik et al., 2007; Yogev-Seligmann et al., 2013; Rochester et al., 2014; Penko et al., 2018); as well, the changes suggest that the LA side adapts to neuromotor deficits and challenging novel tasks, while adaptation on the MA side is not detected (Boonstra et al., 2014). Furthermore, although multiple equivalence tests in article 2 were inconclusive, the nature of equivalence tests reduces the opportunity for incorrect interpretation ("non-significant null-hypothesis tests are evidence for no effect") by adding an explicit (and tested) threshold for what is functionally considered "no effect" (Lakens, 2017).

Many pathological movement characteristics in PD evolve as the disease progresses, and a general expectation of "worsening" characteristics is often justified. This expectation could be applied to the focus of **Article 2**—unilateral variables related to coordination and the presence of between-side differences in coordination automaticity. However, several aspects of **Article 2**

[9] $\left(MA_{dual} - MA_{single}\right) - \left(LA_{dual} - LA_{single}\right) \equiv \left(MA_{dual} - LA_{dual}\right) - \left(MA_{single} - LA_{single}\right)$, where the left side of the equivalence statement is the actual expression of the tests in article 2, and the right side of the equivalence statement is the effective expression to test for a difference in asymmetry due to a dual-task using the "bilateral difference" asymmetry metric

limit attempts to extrapolate results to more severe PD. First, heterogenous presentation of PD is a well-recognized complication in PD research [cite], and the sample in **Article 2** was fairly homogenous, with a group UPDRS score variability of 5.3 (Hill & Nantel, 2024), which weakens the generalizability (i.e. usefulness in extrapolating to different demographics, such as more severe PD) of **Article 2**. Second, some movement characteristics (particularly arm swing ROM and asymmetry) from the results in **Article 2** were atypically preserved, compared to previous studies on similarly affected (in terms of UPDRS scores) PD (Isaias et al., 2012; Mirelman et al., 2016; Roggendorf et al., 2012; Sterling et al., 2015); this provides further evidence that the **Article 2** results may not generalize well. For example, there is some evidence that arm swing ROM and asymmetry evolves with PD progression, where more severe PD has lower arm swing asymmetry due to bilateral ROM reducing to similarly small levels; this behavior contradicts a simplistic view of "movement characteristics get 'worse' with disease progression" (Roggendorf et al., 2012). In contrast, measuring intra- and inter-limb coordination in PD using CRP has been done so rarely that no inference about a relation to PD severity can be supported. A larger sample size would facilitate statistically modeling the effects of PD severity (e.g. UPDRS scores) as a covariate, and/or adding PD subtype as a factor, and this would enable a greater understanding of the ways in which severity and disease presentation effect inter- and intra-limb coordination deficits in PD.

5.2. Timing and coordination in pwPD

The contributions of timing deficits to general coordination deficits in pwPD is not well understood. **Article 2** and **Article 3** of this thesis investigated different perspectives of potential timing deficits with direct and indirect effects on coordination performance. In **Article 2**, cycle-average variability in continuous timing (relative phase) in major proximal joint (hips and shoulders) pairs was measured. This form of timing variability is interpreted as a direct indicator of coordination stability, as increases often predict changes in coordination modes (Haken et al., 1985). The absence of any significant differences in this metric suggests that any potential loss

of automaticity in inter- and intra-limb coordination for mild–to–moderate pwPD is likely not large.

Although **Article 3** was not specifically concerned with attention, Iansek et al. (1995) observed that “it is not easy to separate the requirement for faster speed in movement from the attentional requirements needed in attaining that speed”. The self-selected maximal reaching and stepping cadences likely required significant attention to produce and maintain. Such attentional demands may be greater than previously studied finger-tapping tasks (e.g. due to increased coordinative complexity) and may have affected the findings. A few studies have found worse scores of attention in pwPD OFF medication using multiple cognitive tests of attention (Lange et al., 1992; Lord et al., 2011). However, the sole significant effect of dopaminergic medication from **Article 3** (increased repetitive-reaching clock variance when uncued and ON medication) could not plausibly be interpreted as primarily the result of a (positive) change in attentional performance. There is one similar finding of medication inducing increased variability (in stride time) when internally cued (although not a temporally focused cue) (Rochester et al., 2011). However, this is not supported by results from other studies, where instructions for increased internal focus improved timing characteristics in ON medication pwPD (Baker et al., 2008; Cunnington et al., 1995). More research is needed to confirm and understand how dopaminergic medication and an increased internal focus on movement interact to produce increased temporal variability.

In **Article 3**, the minimal effects of dopaminergic medication on timing in pwPD suggest that timing deficits may not be the direct result of neurodegeneration in the basal ganglia, but instead reflect increased compensation in other parts of the distributed network that participates in explicit timing, including the SMA. The majority of previous research on timing in pwPD has not found any effects of dopaminergic medication on timing deficits (Elsinger et al., 2003; Jahanshahi et al., 2010; Spencer & Ivry, 2005), despite neuroimaging demonstrating normalized basal ganglia activation after administration of medication (Elsinger et al., 2003; Jahanshahi et

al., 2010). There are a few key differences in protocol of **Article 3** compared to previous observations of effects of dopaminergic medication on timing in pwPD: target cadence, movement, and trial length. Previous studies have primarily used finger tapping at moderate cadences for relatively short trial durations, often with roughly 30 “taps” to be analyzed (Elsinger et al., 2003; Jones et al., 2011; Michely et al., 2012; O’Boyle et al., 1996). Therefore, the findings in **Article 3** extend previous research by demonstrating that a minimal role of dopaminergic medication in modulating timing deficits in pwPD can be observed more generally, in larger, more complex, and prolonged movement tasks.

Under the implicit vs. explicit timing framework proposed by Coull and Nobre (2008), the key distinction of explicit timing is that participants are required to “provide an overt estimate of duration.” Continuous relative phase could reflect changes in either implicit or explicit timing, depending on the task/instructions. However, typical gait (as in **Article 2**) does not have instructions to maintain an explicit cadence, and any consistency in step/stride timing is an emergent effect of higher-level movement goals (e.g. maintaining a consistent gait speed, or at an even higher level, producing continuous progress towards an intended location). Therefore, continuous relative phase in **Article 2** likely reflected (a lack of) changes in implicit timing under dual-task conditions. In contrast, **Article 3** primarily involved explicit timing due to the explicit instructions to follow/maintain a specified cadence. Data limitations prevented the measurement of CRP which could have provided additional insight into continuous timing characteristics in an explicit timing context. While the protocol in **Article 3** ensured that predominantly explicit timing was being used, the larger movements also allow for the activity of implicit “motor” timing. Coull and Nobre (2008) acknowledge that many interval timing tasks (e.g. finger tapping) likely include a mix of explicit and implicit timing from perceptual motor timing, and this is more likely in the physically larger and (relatively) slower movements in **Article 3**. A similar mix of explicit and implicit timing may be at work in the work of Fernandez del Olmo and colleagues (2006; 2005), who found reduced finger tapping variability after a 4–week physical training program

that paired several gait exercises with rhythmic auditory cues, but did not specifically train finger tapping. In sum, explicit timing deficits in pwPD are likely not directly the result of dopaminergic neurodegeneration, but some research suggests that timing focused therapies can alleviate these deficits.

5.3. Kinematic modeling error

The process of inverse kinematics optimizes a model pose to minimize error between virtual and experimental marker positions (Delp et al., 2007; Lu & O'Connor, 1999). Before performing inverse kinematics, a virtual biomechanical model must be scaled, and virtual markers must be placed ("registered") on the model (Delp et al., 2007). Inaccuracies in these two earlier steps can lead to large differences in final joint angle estimates, on the order of 10s of degrees (Dunne et al., 2021; Uchida & Seth, 2022). When kinematic modeling error is considered, the results of **Article 2**, which found differences of 1-2° in sagittal ROM and peak flexion between task or side, may be debated. However, there are two factors which may lessen the potential for these differences to be the result of kinematic modeling error: all comparisons were within-subjects and from a single experimental session (i.e. same model). In combination, this may lead to the modeling error cancelling/balancing by being equally present in both experimental conditions. It is unclear how and to what extent the results of Uchida and Seth (2022) apply to within-subjects comparisons during a single motion capture session, where the model scale and marker registration are consistent among experimental conditions. Because of the prevalence of within-subjects experiments, a replication/extension of Uchida and Seth (2022) looking at within-subjects comparisons (i.e. perform the uncertainty analysis and measure the resulting intra-session variability on common kinematic and kinetic outcomes) would provide important insight into the reliability of small within-subjects differences.

5.4. Future work

A logical extension of **Article 1** is a comparison of continuous asymmetry metrics. Previous reviews have noted the existence of multiple continuous asymmetry metrics appropriate for

comparison (Sadeghi et al., 2000; Viteckova et al., 2018). Continuous asymmetry metrics are capable of detecting transient and intracycle changes in asymmetry (similar to the benefits of CRP vs discrete relative phase noted by Krasovsky and Levin (Krasovsky & Levin, 2010)), so an exploration of the benefits and disadvantages of continuous asymmetry metrics would be a valuable addition to the literature.

The small sample size, mild PD characteristics, and lack of a healthy control group were fundamental limitations of **Article 2**. Collecting a larger sample would have several benefits beyond the obvious increase in statistical power. First, a larger sample would reduce the impact of kinematic modeling error, as recommended by Uchida and Seth (2022). In addition, a larger sample (possibly with an added focus on recruiting participants with a wider range of PD progression) would enable the use of more complex statistical tests and/or models, such as modeling the effects of PD progression, or testing for differences in subgroups (e.g. between right and left affected PD (Munhoz et al., 2013; Poletti et al., 2013), between freezers and non-freezers (Jacobs et al., 2014), or between PD subtypes (van Rooden et al., 2011)). In particular, studies show that arm swing ROM asymmetry varies with progression of PD, and the largely preserved arm swing ROM and minimal asymmetry in the PD cohort from **Article 2** is contrary to previous studies (Lewek et al., 2010; Mirelman et al., 2016; Roggendorf et al., 2012).

The limitations of the Wing-Kristofferson model were extensively discussed in **Article 3**, along with next steps, including developing a more appropriate timing model in the context of asymmetric PD. Such a model would theoretically be more sensitive to central timing deficits in PD, which would be beneficial to future investigations of the effects of dopaminergic medication on timing in PD. Furthermore, a correlation between the progressive neurodegeneration and worsening central timing deficits in PD may plausibly exist. Preliminary exploration of the data in **Article 3** did not appear to support such a link, but the relatively small sample size and limited range of UPDRS scores across participants were not sufficient for a publishable investigation.

A particularly interesting continuation of **Article 3** is to use a cycling ergometer as the motor task, for both the upper and lower limbs. The RRT and SIPT were not directly comparable for numerous reasons, and maintaining dynamic stability during the SIPT is one key factor that may have contributed to (untested) observed task differences. The cycling movement using ergometer would result in identical movements of the end-effectors, while maintaining a similar neuromotor coordination complexity. The greater coordination complexity in these tasks, compared to finger tapping, is important in the context of PD because there is strong evidence for both timing deficits as well as motor deficits which will contribute to general timing variability, but finger tapping is a simple and small enough movement that motor variability magnitude may not be large enough to detect with any sensitivity.

While removing outliers can improve replicability by removing aberrant, extreme observations (with the potential to affect study outcomes and lead to flawed conclusions), removing outliers may also introduce bias to a study. Two methods of replications could verify the findings of **Article 3**, with respect to bias introduced by the chosen approach for identifying and handling outliers. First, the openly available code and raw data (Hill et al., 2024) enables anyone to perform a secondary analysis using a different approach for identification and treatment of outliers. Second, a protocol replication with a larger sample size would lessen the potential influence of outliers on study outcomes. One additional factor that may have contributed to the outliers observed in **Article 3** is the suitability of the Wing-Kristofferson model in the context of PD. As discussed, multiple observations provided evidence that model assumptions were being violated, which may have contributed to the extremity of some outliers. Development of a better timing model may also reduce the number and extremity of outliers in timing data.

6. Conclusion

The purpose of this thesis was to better understand the nature and extents of coordination deficits in pwPD by examining the effects of dual tasking and medication on aspects of coordination in pwPD. In the pursuit of this, several methods of measuring asymmetry—which is a prominent coordination deficit in PD—were compared to determine which method is most suitable for future research and studies. It was found that several methods were similarly sensitive to asymmetry, but a simple bilateral difference (e.g. left – right, MA – LA) is the most sensitive. Healthy adults can perform well-learned movements automatically, without close attention, but coordination deficits in pwPD can lead to a loss of automaticity. This thesis found that interlimb coordination in pwPD is mostly unchanged when walking during a dual task, which suggests that interlimb coordination is preserved in mild-to-moderate PD. However, the third part of this thesis confirmed that pwPD exhibit deficits in timing, which may contribute to or reflect the presence of coordination deficits. PwPD showed disturbed timing of sequential movements (lag-one correlation) compared to healthy controls, where reach correlation was significantly greater than controls—indicating worse timing, despite a significant reduction from external cues, but step correlation was not affected by external cues, in contrast to healthy controls. The only effect of dopaminergic medication (increased central timekeeper variability ON medication without external cues) was counter to expectations based on previous neuroimaging findings of normalized basal ganglia activity with medication. This could suggest that alternate (e.g. non-dopaminergic or timing-focused physical/occupational therapies) therapies are needed to treat timing deficits in PD. However, more research is needed to understand if this was a statistical artifact, or if other factors are contributing.

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