Differentiating Gait Behaviors between Early-Stage Dementia with Lewy Bodies and Parkinson's Disease

by

Karen Dawn Angela Mathias

A thesis

presented to the University of Waterloo

in fulfillment of the

thesis requirement for the degree of

Master of Science

in

Kinesiology and Health Sciences

Waterloo, Ontario, Canada, 2022

Author’s Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Dementia with Lewy bodies (DLB) and Parkinson's disease (PD) can be difficult to differentially diagnose, given the overlap in clinical and pathological features. Evidence suggests gait may be a sensitive and selective marker of neurodegeneration. The complexity of the behavior combined with the multilevel neural circuity required for effective gait provides an opportunity to assess how pathological overlap with these neural networks can result in distinct gait changes between DLB and PD. Given both PD and DLB patients have impaired basal ganglia function, research postulates that a compensatory shift to greater cortical control is employed to maintain safe walking. Therefore, it is theorized that a cognitively demanding task while walking (dual tasking) may unmask and amplify subtle differences in walking impairments between PD and DLB patients. Evidence shows that PDD patients have greater swing and stance time asymmetry compared to patients with DLB during self-paced walking. However, no studies to date have assessed gait profiles during single-task walking between individuals with early-stage PD and DLB or whether dual tasking may exacerbate subtle walking differences between these two Lewy body disorders. Thus, this thesis aimed to (i) comprehensively characterize gait in Early PD and Early DLB, and evaluate whether there are differences in discrete gait characteristics between Early PD and Early DLB patients during normal walking, (ii) assess the sensitivity and specificity of specific gait characteristics in accurately discriminating between individuals with Early PD and Early DLB and (iii) investigate whether increasing cognitive load by modifying task complexity (i.e., serial 1 vs. serial 7s dual-task walking) impacts gait behaviors between Early PD and Early DLB patients.

Forty-six Lewy Body disorder patients (26 PD, 20 DLB) that were within five years since diagnosis ('early' stage) as well as 16 healthy older adults walked across a 6-meter pressure sensor walkway under three conditions, (i) normal self-paced walking, (ii) walking while subtracting 1s from 100 and (iii) walking while subtracting 7s from 100. To determine whether walking differences existed between Early PD and Early DLB patients during normal walking, 16 spatiotemporal gait measures were evaluated during self-paced gait and compared between groups. Results showed during self-paced gait, Early DLB had significantly worse gait performance in some features of pace (velocity, $p=0.008$; step length, $p=0.042$) and rhythm (stance time, $p=0.015$) compared to Early PD patients. An assessment of outcome measure accuracy revealed step time (AUC=0.709), stance time (AUC=0.739) and step velocity variability (AUC = 0.719) were able to discriminate Early DLB

patients from Early PD patients with moderate accuracy. To assess whether increasing cognitive load unmasked and/or exacerbated gait differences between the two Lewy body disorders, 16 spatiotemporal gait metrics were measured across the serial 1s and serial 7s dual-task conditions between the Early PD and Early DLB groups. The study found increasing cognitive load during dual-task walking (serial 1s vs. serial 7s) did not expose or intensify any gait differences between Early PD and Early DLB. However, a significant main effect of condition was seen for step velocity variability ($F(1,38) = 4.684$, $p = 0.037$) whereby step velocity variability was greater during the serial 7s dual task compared to the serial 1s task regardless of disease group. In closing, this study found a normal walking assessment revealed several differences in gait behaviors between Early DLB and Early PD, some of which had a moderate ability to discriminate between the groups. This study aids in understanding unique gait profiles at the early stages of the disease which is critical if gait is ever to be used as a tool for predicting disease trajectory in at-risk individuals.

Acknowledgements

I would sincerely like to thank my supervisor Dr. Kaylena Ehgoetz Martens and committee members Dr. Sean Meehan and Dr. Karen Van Ooteghem for their invaluable feedback and expertise. I would also like to express my deepest gratitude to the research team at the University of Sydney's Brain and Mind Centre particularly Dr. Simon Lewis, Dr. Elie Matar and Dr. Joseph Phillips. This thesis would not have been possible without their collaboration and support.

I would also like to extend a special thank you to the study participants from the University of Sydney. Words cannot express my gratitude for their time and willingness to participate in this research study. It has been an absolute privilege to work with the data provided by these individuals and I am forever grateful for their contributions to research.

Many thanks to the members of the Neurocognition and Mobility, SCiLL and SINAPs labs for their friendship, support and doses of laughter throughout this journey.

Finally, I would like to thank my family. I could not have undertaken this journey without your infinite love and support. Thank you from the bottom of my heart for your endless encouragement and strength throughout this process.

Table of Contents

List of Figures

List of Tables

Chapter 1
Introduction

Lewy body (LB) disease is an umbrella term referring to a group of pathologically related neurodegenerative disorders including Parkinson's disease (PD) and dementia with Lewy bodies (DLB) (Spillantini et al., 1998). A hallmark pathological feature of LB disorders (PD and DLB) is the presence of Lewy bodies (Spillantini et al., 1998). Lewy bodies are intraneuronal inclusions predominately composed of abnormal α-synuclein protein aggregates (Spillantini et al., 1998). Dissociating between subdivisions of LB disorders particularly, PD and DLB can be challenging given common Lewy body pathology which results in overlapping clinical features (Lippa et al., 2007). However, differentially diagnosing between PD and DLB is critical due to the stark contrast in disease trajectory. Individuals who develop PD symptoms around 60 years old may live between 10 and 20+ years after being diagnosed (Golbe & Leyton, 2018; Ishihara et al., 2007). Yet, those with DLB typically have a median survival rate of fewer than five years (Larsson et al., 2018). Furthermore, by the time an individual is diagnosed substantial neurodegeneration has already occurred limiting therapeutic success (Cheng et al., 2010; McKeith, 2004). Thus, early diagnostic markers are needed for the development of effective neuroprotective treatments capable of slowing or stopping disease progression.

Evidence suggests distinct alterations in walking behaviors may parallel the pathological progression of separate neurodegenerative processes (Lord, Galna, & Rochester, 2013; Morris et al., 2016; Wilson et al., 2019). Hence, gait (i.e., walking behavior) may be a potential early diagnostic marker for neurodegeneration. Although more work is needed to fully comprehend the diagnostic capacity of gait for detecting early pathology, studies demonstrate the promise of this research area. For example, evidence shows newly diagnosed unmedicated (de novo) PD patients present with reduced speed, shorter strides, slower swing time and increased swing time asymmetry between the left and right limbs compared to age-matched healthy controls (Baltadjieva et al., 2006). Another study found early PD patients (<36 months since diagnosis) on medication relative to age-matched controls walked slower, had shorter strides and increased stride time variability (Rochester et al., 2012). Research evaluating walking differences between controls, Alzheimer's disease (AD), and DLB participants found people with dementia have reduced velocity, stride length and an increased percentage of time spent in double support compared to healthy older adults (Merory et al., 2007).

Taken together, these studies demonstrate the potential for walking to reflect neuropathological changes in the brain.

The potential diagnostic ability of gait alterations is further exemplified by work differentiating gait behaviors between PD with dementia (PDD), DLB and AD patients (Mc Ardle et al., 2020). This study found PDD patients had greater step-to-step spatial and temporal variability as well as asymmetry between stance times of the left and right limbs compared to those with AD (Mc Ardle et al., 2020). Conversely, DLB patients compared to AD had more variability in the length and velocity of their steps (Mc Ardle et al., 2020). Distinct differences in walking asymmetry were also observed between PDD and DLB patients where individuals with PDD had greater asymmetry in swing and stance times than those with DLB (Mc Ardle et al., 2020). This work provides evidence for the presence of unique walking impairments between PD and DLB patients at the advanced disease stages highlighting the potential specificity of gait in dissociating between neurodegenerative disorders. However, pathological progression at the later disease stages is more extensive than at the early stages therefore walking alternations at the advanced disease stage cannot necessarily be inferred at the early stages of the disease. Furthermore, individuals with PDD present with cognitive decline that is sufficiently severe to interfere with daily activities (Jellinger & Korczyn, 2018). A growing body of research suggest certain features of gait overlap with aspects of cognition, hence characteristics of gait influenced by cognition, for PDD patients may not necessarily reflect those observed in early PD patients (Morris et al., 2016). Thus, the current study sought to address this research gap by characterizing and differentiating walking behaviors between PD and DLB patients at the early stages of the disease to determine if unique signatures of gait exist between the two Lewy body disorders early on in disease course. This understanding of walking behaviors in Early PD and Early DLB is critical if gait is ever to be used as a marker for neurodegeneration.

Chapter 2
Literature Review

2.1 Early Clinical Features of PD and DLB

2.1.1 Motor Features

The clinical distinction between Parkinson's disease and dementia with Lewy bodies can be challenging given the overlap in motor and non-motor symptoms (Gomperts, 2016; Jellinger & Korczyn, 2018). Parkinsonism, a general term used to depict a group of neurological disorders defined by movement impairments like stiffness, tremors, etc., is a shared key motor feature of both PD and DLB patients (McKeith et al., 2017; *Parkinson's Disease vs. Parkinsonism*, 2022). However, early on in disease course the severity and laterality of parkinsonian signs differ slightly between the two Lewy body disorders. PD is a movement disorder primarily characterized by three cardinal motor features: bradykinesia (slowness of movement), rigidity and tremor at rest (Postuma et al., 2015). A clinical diagnosis of PD is contingent on the combination of limb bradykinesia and at least one other cardinal motor sign (Postuma et al., 2015). According to the 2015 Movement Disorders Society (MDS) diagnostic criteria, bilateral symmetric motor signs early on in disease course are thought to be a "red flag" against a diagnosis of PD. Hence, unilateral or asymmetric motor features are often used to support a diagnosis of PD (Postuma et al., 2015). In contrast, parkinsonism in individuals with DLB is indicated by the presence of at least one cardinal motor symptom which is often akinetic-rigid without the classical rest tremor (Geser et al., 2005; McKeith et al., 2017). Contrary to PD patients, motor signs in individuals with DLB are typically expressed bilaterally (Geser et al., 2005; McKeith et al., 2017). Postural instability, a feature of parkinsonism is characteristically seen in DLB patients at the early stages of the disease, while PD patients tend to show deficits in postural stability at the later disease stages (McKeith et al., 2017; Postuma et al., 2015). However, those Early PD patients who do exhibit the postural instability and gait disorder (PIGD) subtype are likely to have greater motor and cognitive decline compared to those without (Burn et al., 2006). Taken together, both PD and DLB patients exhibit parkinsonian signs. However, subtle differences in motor symptom severity and symmetry may help dissociate the two Lewy body disorders.

Given the overlap in parkinsonian motor features, it is not surprising that gait and balance disturbances are frequent causes of impairment for patients with PD and DLB early on in disease

course. Work shows 75% of DLB patients and 43% of PD patients have a parkinsonian gait disorder (short shuffling steps) (Allan et al., 2005). Early-stage PD patients have slower and shorter steps than healthy older adults (Galna et al., 2015). Research also shows individuals with PD compared to healthy controls have increased asymmetry between the left and right limbs, decreased arm swing amplitude, increased gait variability (stride-to-stride fluctuations) and reduced automaticity (Galna et al., 2013; Mirelman et al., 2016; Pistacchi et al., 2017; Yogev et al., 2005). In contrast, DLB patients relative to controls have reduced velocity, shorter strides and increased time spent in double limb support (Merory et al., 2007). Yet, little work has been done to compare walking patterns between PD and DLB patients at the early stages of the disease, highlighting an area of research for future consideration. Overall, shared clinical motor features between PD and DLB such as parkinsonism and gait and balance disturbances underscore the challenge associated with distinguishing between the disorders. Whilst there are subtle differences in motor symptom severity and symmetry between PD and DLB patients, further research is needed to objectively quantify and dissociate these clinically observed differences. The use of objective quantitative measures rather than subjective visual examinations may improve diagnostic accuracy between Lewy body disorders.

2.1.2 Non-Motor Features

A differential diagnosis between PD and DLB is further complicated by the myriad of overlapping non-motor features. Individuals with PD and DLB at the early stages of disease can experience psychiatric dysfunction such as depression, anxiety and hallucinations (McKeith et al., 2017; Postuma et al., 2015). PD and DLB patients may also suffer from sleep abnormalities including excessive daytime sleepiness and symptoms of Rapid Eye Movement (REM) sleep behavior disorder (RBD) (McKeith et al., 2017; Postuma et al., 2015). RBD is a sleep condition characterized by a history of dream enactment and muscle atonia (temporary paralysis of the limbs) during REM sleep (St Louis & Boeve, 2017). Additionally, autonomic dysfunction (i.e., constipation, dizziness when standing after laying/sitting down and frequent daytime urinary urgency) is a common clinical feature of PD and DLB patients (McKeith et al., 2017; Postuma et al., 2015). Likewise, PD and DLB patients have overlapping cognitive features, for example, they share impairments in executive functioning, attention and visuospatial skills (Aarsland, 2016; Getz & Levin, 2017; McKeith et al., 2017). However, the temporal onset of cognitive impairment is a key distinguishing feature between the two Lewy body disorders. The current approach to differentiating PD from DLB is done in part by the temporal onset of parkinsonism versus cognitive decline (Lippa et al., 2007; McKeith et al., 2017;

Postuma et al., 2015). Early PD patients often demonstrate a period of pure motor symptoms whilst cognitive decline presents earlier in DLB (Lippa et al., 2007; McKeith et al., 2017; Postuma et al., 2015). DLB patients at the time of diagnosis typically experience cognitive alterations and visual hallucinations while developing parkinsonian motor features (McKeith et al., 2017). In contrast, a clinical diagnosis of PD is dependent upon the presentation of cardinal motor symptoms (i.e., slowed movements, tremors at rest, rigidity) with impairments in cognition typically occurring later in disease course (Postuma et al., 2015). Although, this distinction in conjunction with medical history is helpful in elucidating a diagnosis it is qualitative in nature, highlighting once again the need for objective quantitative diagnostic markers for differentiating between PD and DLB patients.

In summary, substantial overlap in motor and non-motor symptoms exists between PD and DLB patients making a differential diagnosis challenging. This shared symptomology is thought to reflect the pathological overlap observed between the two LB disease subgroups (Braak et al., 2003, 2006; Jellinger & Korczyn, 2018). Since, clinical feature development is theorized to parallel the pathological progression of a neurodegenerative disease, subtle differences among the overlap in features may demonstrate degeneration of specific circuitry in the brain (Braak et al., 2003, 2006; Jellinger & Korczyn, 2018). Thus, the next section will describe the overarching pathophysiology of LB disease. It will underscore the relationship between pathological progression and clinical symptom development and aid in understanding how differences in symptoms between PD and DLB patients may relate to differences in pathophysiology.

2.2 General Pathophysiology Model of Lewy Body Disease

The gradual evolution of LB disease symptoms is thought to parallel the spread of Lewy body pathology throughout the brain (Braak et al., 2003, 2006). Braak and colleagues proposed a six-stage pathological staging model describing the temporal development of LB pathology. They postulated α-synuclein aggregates ascend rostrally from the brainstem to regions of the cortex over time as shown in Figure 1 (Braak et al., 2003, 2006). At the earliest stages of the disease (Braak stage 1) LB pathology is restricted to the medullary dorsal motor nucleus of the vagus nerve (DMV) and anterior olfactory nucleus in the olfactory bulb (Braak et al., 2003, 2006). The DMV contains parasympathetic motor neurons that project to the periphery and innervate viscera of the thorax and abdomen (Jiang & Zsombok, 2014). Neurons within the DMV play a key role in modulating autonomic functions suggesting a relationship between α-synuclein aggregation in the DMV and symptomatic autonomic

dysfunction in LB disorder patients (Braak et al., 2003, 2006; Jiang & Zsombok, 2014; Mussa & Verberne, 2013). Similarly, LB pathology in the olfactory bulb is thought to deteriorate an individual's sense of smell (Braak et al., 2003, 2006).

As LB disease progresses pathology spreads to the upper brainstem nuclei (Braak stage 2) including the caudal raphe nuclei, gigantocellular reticular nucleus and the locus coeruleus (LC) in the pons (Braak et al., 2003, 2006). The degeneration of these brainstem nuclei particularly the LC and magnocellular reticular formation has been implicated in RBD, an early symptom of both PD and DLB (Boeve et al., 2007). Braak stages 3 and 4 involve pathology infiltrating structures in the midbrain and basal forebrain important for movement such as the substantia nigra pars compacta (SNc), pedunculopontine nucleus (PPN) and central nuclei of the amygdala (CeA) (Braak et al., 2003, 2006). The SNc is a dopamine-rich component of the basal ganglia (Lanciego et al., 2012). The basal ganglia is a group of subcortical nuclei consisting of the striatum (caudate nucleus, nucleus accumbens and putamen), globus pallidus externus (GPe) and internus (GPi), the subthalamic nucleus (STN), substantia nigra pars reticulata (SNr) and the SNc (Lanciego et al., 2012). The basal ganglia is primarily responsible for motor control and also plays role in motor learning (Lanciego et al., 2012). Thus, dysfunction of the basal ganglia is often associated with increased disturbances in gait and development of parkinsonian motor signs in patients with LB disease (French & Muthusamy, 2018; Pahapill & Lozano, 2000; Takakusaki, 2017). The PPN and CeA are highly connected with the basal ganglia and brainstem hence pathological changes in these regions are theorized to worsen motor symptom progression in LB disease (French & Muthusamy, 2018; Pahapill & Lozano, 2000; Takakusaki, 2017).

During the final stages of LB disease progression (Braak stage 5 and 6) pathology is thought to have extended to cortical regions of the brain such as the frontal, temporal, and parietal cortices (Braak et al., 2003, 2006). Dysfunction at the level of the neocortex in LB disease patients is associated with impairments in cognition such as reduced executive functioning, visuospatial skills, and attention; as well as the presence of neuropsychiatric symptoms including visual hallucinations and emotional dysregulation (Braak et al., 2003, 2006; Kao et al., 2009).

The model posited by Braak and colleagues demonstrates the relationship between pathological progression and clinical symptom development in LB diseases and emphasizes the pathological overlap between LB disease subgroups (PD versus DLB). However, a key pathological

difference between early-stage PD and DLB patients lies in the distribution of Lewy bodies across the brain (Berman & Miller-Patterson, 2019; Lippa et al., 2007). Early in disease course PD patients have Lewy body inclusions surrounding brainstem and limbic regions representative of Braak stages 2 and 3 (Berman & Miller-Patterson, 2019; Braak et al., 2003, 2006; Lippa et al., 2007). Whilst Early DLB patients have more widespread inclusions extending to the neocortex typical of pathology seen at Braak stages 5 and 6 (Berman & Miller-Patterson, 2019; Braak et al., 2003, 2006; Lippa et al., 2007). Thus, the greater cognitive impairments observed in DLB patients compared to PD patients is thought to reflect this pathological variance (Lippa et al., 2007).

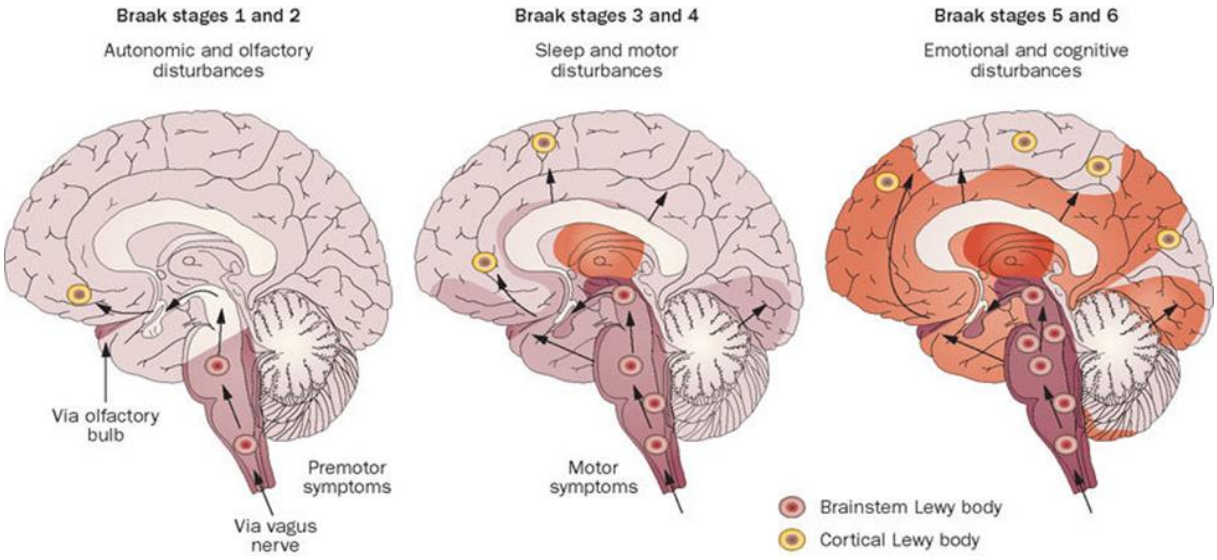


Figure 1. Braak staging model schematic showing the systematic progression of Lewy body pathology from the brainstem to the subcortex researching cortical brain regions. The red shaded regions represent the pathological pattern at a specific Braak stage (Doty, 2012).

The Braak staging scheme has garnered wide acceptance among the research community (Dickson et al., 2010). Some evidence has shown that the spread of LB pathology is consistent with the Braak staging scheme (Dickson et al., 2010; Jellinger, 2003). However, it is important to be critical of this pathological model given the profound impact it can have on how researchers address early diagnosis and development of biomarkers. A major limitation of the Braak scheme is the exclusion of DLB patients during development (Braak et al., 2003, 2006). Given the overlap in clinical and pathological features between PD and DLB, the exclusion of DLB cases limits the generalizability of the model to all LB diseases (Lippa et al., 2007). For example,

immunocytochemical analysis of 76 brains containing Lewy bodies from the Medical Research Council Cognitive Function and Aging Study (MRC CFAS) revealed 51% of cases conformed with the Braak staging scheme while 17% displayed pathology in the cortex but not the brainstem and 29 % had Lewy body pathology restricted to the amygdala (Zaccai et al., 2008). Their study underscores how caudal to rostral ascension of LB pathology from the brainstem to the cortex may not fully explain LB pathogenesis (Zaccai et al., 2008). Recent work suggests factors beyond the brain connectome influence LB distribution across the brain (Surmeier et al., 2017). Surmeier and colleagues propose LB pathology is propagated by cell-or-region autonomous factors. They theorized neurons vulnerable to LB pathology share common functional features that increase LB susceptibility (Surmeier et al., 2017). Characteristics of neurons vulnerable to LB pathology include neurons with highly branched axons, slow, rhythmic action potentials, elevated intracellular calcium ion levels and increased mitochondrial oxidative stress and damage (Surmeier et al., 2017). This combination of features can be found in SNc dopaminergic (DA) neurons (Surmeier et al., 2017). The reduction of SNc DA neurons is a key pathological feature of PD and DLB (O'Brien et al., 2004). Imaging work using dopamine transporter single photon emission computed tomography (DAT SPECT) scans shows in both PD and DLB, there is a decrease in striatal dopamine (Berman & Miller-Patterson, 2019). Therefore, providing evidence for the consideration of selectively vulnerable neurons in LB pathogenesis. Further work is required to better understand how Lewy body susceptible neurons drive pathological progression and how selective changes in behaviors reflect this pattern of progression. However, Surmeier et al., 2017 theorize that LB pathogenesis may be an evolution of Braak's model where LB pathological spread is restricted to a subset of selectively vulnerable neurons. Overall, Braak's model supports how the advancement of LB disease symptoms parallels LB pathological progression. It offers an understanding of how particular behaviors reflect specific neuropathological processes. While there are limitations to Braak's model, research assessing factors beyond the brain connectome may clarify why anatomical exceptions, and in turn behavioral differences occur between PD and DLB patients. An understanding of LB disease pathogenesis lays the foundation for mapping the pathological differences that may explain the behavioral distinctions observed between PD and DLB patients.

2.3 Mapping Clinical to Pathophysiological Differences Between PD and DLB

2.3.1 Pathophysiology of Cognitive Impairment Manifestation

The clinical and pathological overlap between PD and DLB makes them difficult to dissociate diagnostically. However, differences in cognitive and motor features such as the severity of cognitive decline and gait disturbances may correspond to specific pathological alternations (Jellinger & Korczyn, 2018; McKeith et al., 2017; Postuma et al., 2015). An understanding of how selective behaviors reflect pathological differences provides insight into potential diagnostic markers. As previously discussed, during the early stages of the disease the temporal onset of cognitive dysfunction versus parkinsonism is a key clinical difference between PD and DLB patients (McKeith et al., 2017; Postuma et al., 2015). Early-stage PD patients often have a period of pure motor symptom expression disease thought to reflect pathological changes in the brainstem and subcortical brain regions (Braak et al., 2003, 2006; Postuma et al., 2015). Conversely, Early DLB patients, display greater cognitive dysfunction prior to or concurrently with parkinsonian motor signs (McKeith et al., 2017). According to Braak's model, symptoms in Early DLB patients represent a pathologically advanced phenotype of LB disease where LB pathology is distributed more diffusely across the brain affecting the brainstem, subcortical and cortical brain regions (Braak et al., 2003, 2006). Braak's model suggests motor symptoms appear prior to the development of cognitive impairments (Braak et al., 2003, 2006). However, this notion does not necessarily align with the clinical manifestation of DLB symptoms where cognitive impairments may appear before parkinsonian motor signs (McKeith et al., 2017). The Unified Staging System for Lewy Body Disorders (USSLB), an alternative model of LB pathogenesis, aimed to address this discrepancy (Beach et al., 2009). Stage I in the USSLB, as shown in Figure 2, is defined by Lewy body pathology localized to the olfactory bulb (Beach et al., 2009). Dysfunction of the olfactory bulb results in a loss of smell which is a common early non-motor symptom of PD and DLB (Beach et al., 2009; McKeith et al., 2017; Postuma et al., 2015). On rare occasions, the olfactory bulb may initially not be involved in disease pathogenesis (Beach et al., 2009). Therefore, Stage I is not required for staging classification (Beach et al., 2009). An individual may be assigned a higher stage without the presence of olfactory blub pathology (Beach et al., 2009).

From the olfactory bulb, LB pathology is thought to diverge into two pathways: brainstem predominate (Stage IIa) and limbic predominate (Stage IIb) (Beach et al., 2009). The brainstem

contains nuclei highly interconnected with the nigrostriatal system (Lanciego et al., 2012). The loss of dopaminergic cells due to degeneration of the nigrostriatal system is likely associated with parkinsonian motor signs (Molano et al., 2010; Takakusaki, 2017). Hence, research suggests Stage IIa is an early pathological stage of PD (Adler et al., 2019; Beach et al., 2009). In contrast, the limbic system is intimately connected to cortical regions like the prefrontal cortex and is associated with cholinergic projections from the basal forebrain (Rajmohan & Mohandas, 2007). Cognitive impairment may possibly be related to cholinergic reductions due to limbic system/basal forebrain/neocortical degeneration (Molano et al., 2010). Thus, Stage IIb is theorized to represent an early pathological stage of DLB (Adler et al., 2019; Beach et al., 2009). Collectively, Stage II may signify an early stage of Lewy body disease where different pathways of pathological progression reflect unique disease trajectories (Adler et al., 2019; Beach et al., 2009).

The two paths converge in Stage III of the USSLB where pathology is observed in the brainstem and limbic regions (Beach et al., 2009). LB pathology in the brainstem and limbic regions is theorized to represent a variety of motor and non-motor symptoms (i.e., parkinsonism, cognitive decline, automatic dysfunction) (Adler et al., 2019; Beach et al., 2009; McKeith et al., 2017; Postuma et al., 2015). In the final stage, Neocortical Stage IV, LB pathology has extended to cortical regions such as the temporal, frontal and parietal cortices (Beach et al., 2009). Cortical dysfunction is associated with cognitive impairments such as executive functioning, visuospatial skills and attention as well as psychiatric symptoms (Kao et al., 2009). Overall, the USSLB provides a biological framework for the broad range of motor and non-motor clinical features observed in all LB diseases (Beach et al., 2009). In contrast to Braak's model, the USSLB highlights a biological difference to explain why cognitive features may appear prior to parkinsonism in DLB patients. Regardless, both models demonstrate selective behaviors that may reflect specific pathological changes in the brain.

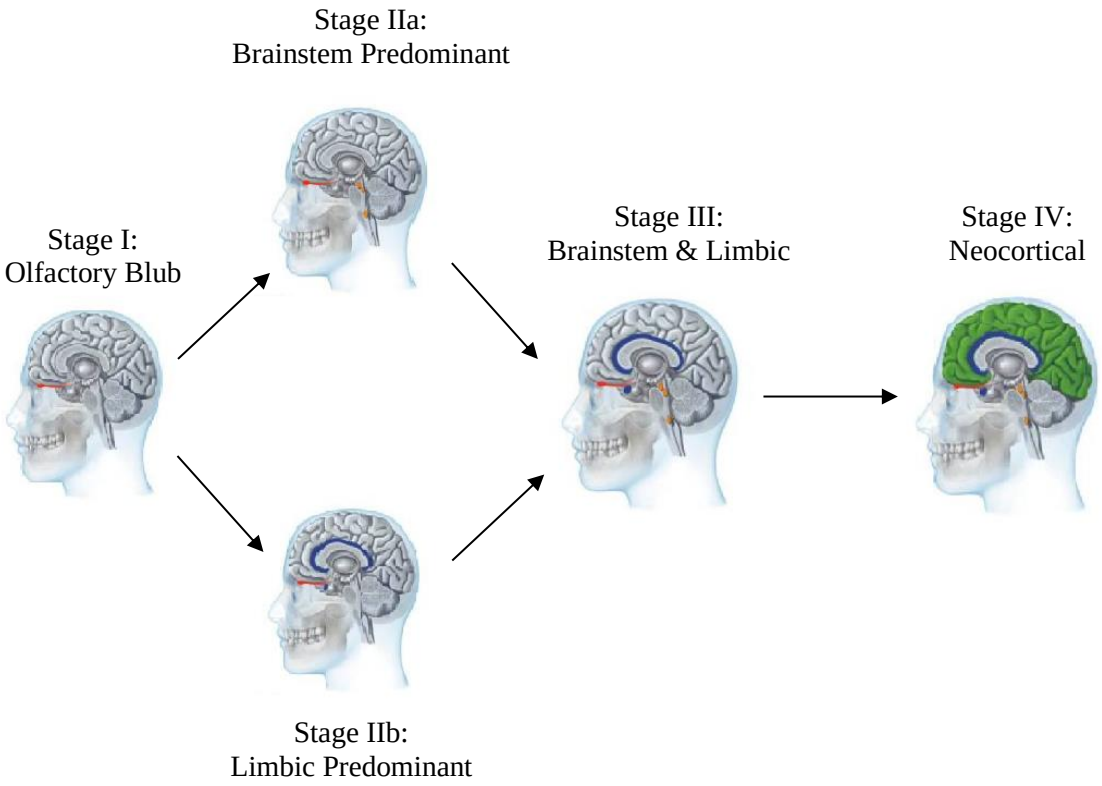


Figure 2. Unified Staging System for Lewy Body Disorders schematic showing how the Stage IIa progression pathway may be consistent with Early PD while the Stage IIb pathway may correspond to Early DLB pathological progression. Red represents pathology in the olfactory bulb and tract; orange represents pathology in the brainstem nuclei-substantia nigra, the dorsal motor nucleus of the vagus, and locus coeruleus; blue represents pathology in the limbic regions-amygdala and cingulate cortex; the green region represents pathology in the neocortex (Adler et al., 2019; Beach et al., 2009).

2.3.2 Pathophysiology of Clinical Motor Features

As previously discussed, Early PD and Early DLB patients exhibit motor deficits namely parkinsonism and gait disturbances (McKeith et al., 2017; Postuma et al., 2015). While both Lewy body disorders have clinical motor manifestations, PD and DLB patients show differences in motor symmetry, the pattern of parkinsonian features (akinetic-rigid versus tremor dominate), postural instability and gait disturbances (Burn et al., 2006; McKeith et al., 2017; Postuma et al., 2015). The variance in motor symptom expression may perhaps indicate disease-specific neuropathological changes.

The unilateral manifestation of motor symptoms or motor asymmetry is often utilized by clinicians to help facilitate a diagnosis of PD (Postuma et al., 2015). Interestingly, DLB patients often demonstrate bilateral or symmetric motor symptoms (Gomperts, 2016). Although the underlying mechanisms for motor lateralization remain unclear, some suggest interhemispheric asymmetries in dopamine levels play a role (Haaxma et al., 2010; Tucker & Williamson, 1984). Evidence shows individuals with PD have selective degeneration of nigrostriatal dopaminergic cells demonstrated by asymmetric reductions in dopaminergic uptake in the putamen compared to DLB patients and controls (Walker et al., 2004). However, no significant differences in putamen asymmetry were observed between DLB and control groups (Walker et al., 2004). Furthermore, the caudate-to-putamen volume ratio was greater in the PD group compared to the DLB and control groups; however, did not significantly differ between DLB and control participants (Walker et al., 2004). Walker et al., 2004 demonstrate DLB patients have a more uniform decrease in dopamine uptake while the pattern of striatal dopaminergic dysfunction is more asymmetric in PD patients. Evidence in PD patients shows unilateral motor features are related to contralateral nigrostriatal degeneration (Haaxma et al., 2010; Wang et al., 2015). Yet, little work has been done to understand the relationship between bilateral motor signs and lateralization of nigrostriatal degeneration in DLB patients. Further work is needed to better understand the relationship between motor symmetry and neural circuitry between PD and DLB patients. Nonetheless, the pattern of striatal dopaminergic dysfunction may potentially explain the variations in motor symmetry between the two LB diseases.

Another clinical difference between PD and DLB is the form of cardinal motor features expressed. Early DLB patients typically demonstrate akinetic-rigid motor signs without the classical rest tremor (Geser et al., 2005; McKeith et al., 2017). Conversely, a study assessing 418 PD patients found ~88% of PD patients had at least one type of tremor (i.e., rest tremor, postural tremor, action tremor) of which rest tremor was the most common (~69%) (Gupta & Kuo, 2018). A resting tremor is defined as a tremor that occurs when a part of the body is not voluntarily activated or is at rest (Deuschl et al., 1998). Rest tremor amplitude is moderate with a medium frequency of 4-6 hertz (Deuschl et al., 1998). Evidence suggests the pathophysiology of rest tremors differs from that of bradykinesia and rigidity (Pirker, 2003). It is important to note that while bradykinesia refers to the slowness of a movement and akinesia is the lack/reduction of movement, both are characterized by an inability to perform voluntary movements (Berardelli et al., 2001). As such, for this discussion, the pathophysiology of bradykinesia will also apply to that of akinesia. It is well-established that

nigrostriatal dopamine depletion is a feature of both PD and DLB (McKeith et al., 2017; Postuma et al., 2015; Walker et al., 2004). This reduction in dopamine impacts cortico-striatal circuitry which is related to bradykinesia and rigidity symptoms but not tremor at rest (Pirker, 2003). Rest tremor is thought to result from a pathological interaction between the basal ganglia and the cerebello-thalamic-cortical circuit (Helmich et al., 2011). Anatomical evidence using voxel-based morphometry (VBM), a magnetic resonance imaging (MRI) technique, found cerebellar gray matter reductions in the right quadrangular lobe and declive of the cerebellum in PD patients with rest tremor compared to those without (Benninger et al., 2009). Physiological evidence using fluorodeoxyglucose (FDG)-positron emission tomography (PET) observed that PD patients with tremors had increased network activity comprised of the thalamus, pons and premotor cortex (Antonini et al., 1998). Both studies demonstrate the involvement of the cerebello-thalamic-cortical circuit in the pathogenesis of resting tremors. Imaging work investigating the pathophysiology of bradykinesia supports the notion of cortico-striatal involvement by demonstrating decreased activity of the supplementary motor cortex (SMA) and cortical motor regions with increased activation of the lateral premotor area (Berardelli et al., 2001). The reduction in SMA and decreased cortical activity is thought to be associated with deficits in movement preparation resulting in prolonged reactions and slower movements (Berardelli et al., 2001). In contrast, greater premotor region activity may be related to compensatory processes used to improve performance with the use of external cues to guide movements (Berardelli et al., 2001). Similarly, rigidity or stiffness associated with an increased muscular tone may manifest in response to impaired cortico-striatal circuitry (Baradaran et al., 2013; Magrinelli et al., 2016). Research suggests abnormalities in long-latency reflexes related to deficits in basal ganglia function and decreased SMA activity result in the hyperexcitable of the motor cortex, clinically manifesting as rigidity (Baradaran et al., 2013). Long-latency reflexes are burst of muscle activity that occurs 50-100ms after a stretch is applied to a muscle (Baradaran et al., 2013). They can be thought of as muscle activation that happens after spinal reflexes but before a voluntary reaction (Baradaran et al., 2013). Evidence shows individuals with PD have increased long-latency reflexes and show a decreased connection from the putamen to SMA associated with increased clinical rigidity severity (Baradaran et al., 2013; Magrinelli et al., 2016). Although more work is needed to understand the pathophysiology of rigidity, its mechanistic overlap with bradykinesia but not rest tremor underscores how selective behaviors may reflect specific impairments in neural circuitry. The expression of cardinal motor features in DLB patients is often akinetic-rigid without rest tremor which may reflect

impairments in cortico-striatal circuitry. In contrast, Early PD patients often have tremors which may parallel dysfunction of the cerebello-thalamic-cortical circuit. Thus, highlighting a potential difference in impaired neural connectivity that may be reflected in behavioral variations between the two Lewy body disorders.

Postural instability is difficulty balancing due to impairments in postural reflexes (Kim et al., 2012). Early DLB patients often have deficits in posture while early PD patients tend to express postural changes as the disease worsens (McKeith et al., 2017; Postuma et al., 2015). PDD and DLB patients also show differences in walking asymmetry (Mc Ardle et al., 2020). Nonetheless, postural balance control and gait are complex motions requiring the coordination of sensory and motor systems to formulate, modify and implement movements needed to maintain postural stability and safe effective walking (Horak et al., 1992; Kim et al., 2012; Takakusaki, 2017). To compensate for dopaminergic loss, research suggest other neurotransmitter systems such as the cholinergic system are employed to cortically control posture and gait (Bohnen et al., 2018). Evidence in support shows PD patients with preserved cortical cholinergic function displayed a normal average gait speed regardless of dopaminergic deficits (Bohnen et al., 2013). Their work suggests the cholinergic system plays an adaptive role during early-stage dopaminergic loss; when cholinergic system dysfunction occurs compensatory strategies will diminish and manifest as slow gait with greater cognitive decline (Bohnen et al., 2013). This work demonstrates circuitry beyond the nigrostriatal pathway is implicated in disease and may be reflected by motor behavior alterations. The multilevel circuity involved in gait and postural control speaks to the complexity of these motor tasks. To better understand this concept the next section will discuss the physiological complexity of walking. Knowledge of the underlying neural intricacy related to gait will help bring an appreciation as to why gait may be a sensitive and selective marker for neuropathological changes in the brain.

2.4 General Physiological Model of Gait and Posture Control

Safe and effective gait requires the integration of sensory, cognitive and motor resources as shown in Figure 3 (Takakusaki, 2017). External stimuli elicit several sensory signals (visual, vestibular, auditory, somatosensory and visceral) needed for various processes in the central nervous system (Takakusaki, 2017). Signals are processed by the cerebral cortex and limbic system to provide cognitive and emotional references respectively to produce voluntary or emotional movement behaviors (Takakusaki, 2017). Information from the cerebral cortex and limbic regions flows

downstream toward structures like the basal ganglia, brainstem and spinal cord to generate postural and motor adjustments (Takakusaki, 2017). Equally some information may require higher cortical processing for navigation of unfamiliar environments (Takakusaki, 2017). The cerebellum, used for motor coordination regulates automatic and cognitive information (Takakusaki, 2017). This hindbrain structure plays a central role in movement control via thalamocortical projections to the cortex and brainstem (Takakusaki, 2017). Takakusaki's (2017) model of gait and posture control demonstrates the multilevel circuitry involved in motor control. Impairments in particular circuits may correspond to selective alterations in gait behavior (Peterson & Horak, 2016; Takakusaki, 2017).

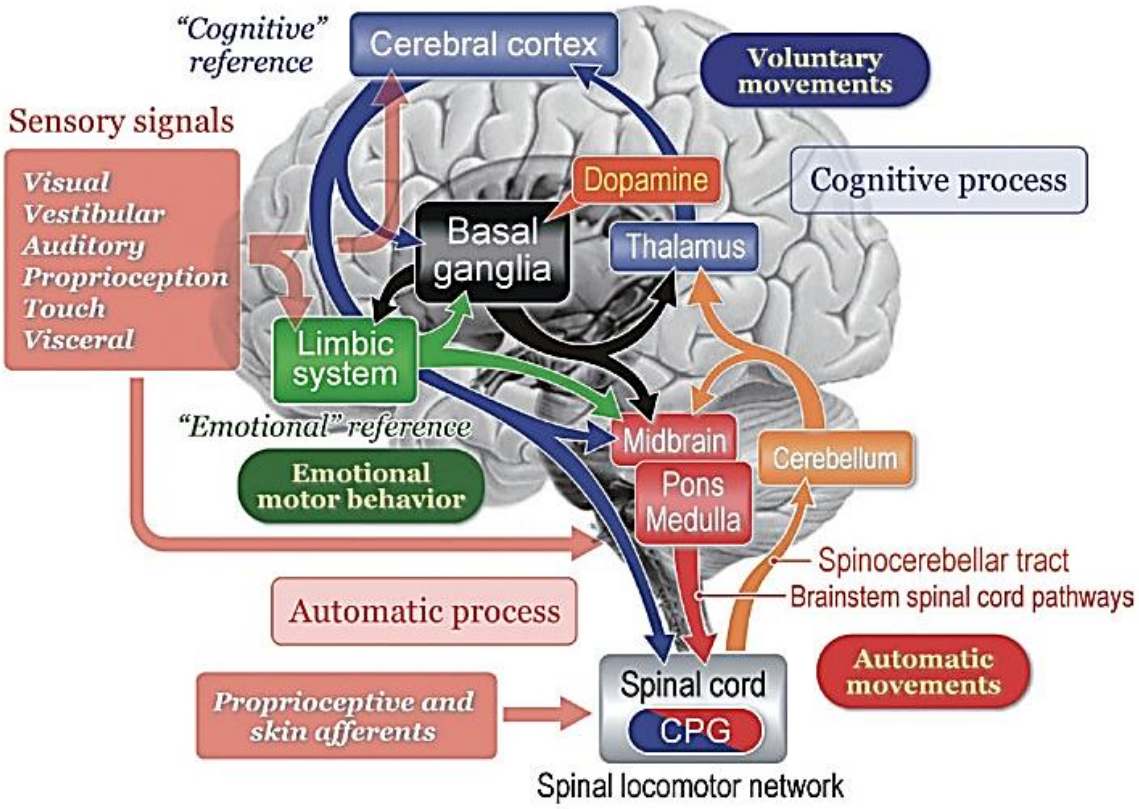


Figure 3. Schematic model of neurophysiological mechanisms involved in gait and posture control. The schematic highlights the complex multilevel circuitry involved in gait and posture control. Sensory and proprioceptive signals provide cognitive and emotional references to the cerebral cortex and limbic system to propagate voluntary or emotional motor movements. Postural control is facilitated by the brainstem and spinal cord regions (Takakusaki, 2017).

2.5 Gait as a Marker for Neurodegeneration

2.5.1 Conceptual Models of Gait

The neural mechanisms underlying gait are quite complex (Takakusaki, 2017). Hence, comprehensive conceptual models of gait have been described to help represent and measure the intricate neural circuitry involved in walking (Hollman et al., 2011; Lord, Galna, Verghese, et al., 2013; Verghese et al., 2007). An early model of gait, generated using factor analysis proposed eight gait outcome measures that could be grouped into three independent domains: pace, rhythm and variability (Verghese et al., 2007). Pace refers to how fast or slow an individual walks; rhythm is a temporal measure of gait reflecting timing and cadence; variability indicates step-to-step fluctuations in gait (Verghese et al., 2007). Their model showed how independent gait factors are associated with specific cognitive functions; the rhythm domain was related to memory decline while the pace domain was associated with executive functioning in individuals who went on to develop dementia (Verghese et al., 2007). However, the model proposed by Verghese et al., 2007 selected only few aspects but not all potential aspects of gait analysis (Hollman et al., 2011; Lord, Galna, Verghese, et al., 2013).

Hollman and colleagues (2011) addressed this limitation in their model by including 23 gait parameters in their investigation regarding walking behaviors in older adults. They conducted a factor analysis on 23 walking outcome measures to produce a five-factor model of gait (Hollman et al., 2011). Gait outcome measures were categorized into five walking domains: rhythm, phases, variability, pace and base of support (Hollman et al., 2011). The phase factor was comprised of temporophasic divisions of the gait cycle such as the percentage of the gait cycle spent in swing, stance, single support and double support (Hollman et al., 2011). The base of support domain encompassed step width and step width variability (Hollman et al., 2011). Hollman and colleagues (2011) demonstrated additional aspects of gait complexity not previously considered. However, the model was developed in older adults and therefore requires validation in clinical populations.

Lord and colleagues remedied this discrepancy with their model of gait developed in older adults and validated in PD patients (Lord, Galna, & Rochester, 2013; Lord, Galna, Verghese, et al., 2013) They used principal components analysis and factor analysis on 16 gait outcome measures to generate five gait domains: pace, rhythm, variability, asymmetry, and postural control as shown in Figure 4 (Lord, Galna, Verghese, et al., 2013). Asymmetry refers to the difference between left and

right-sided gait metrics; posture is characterized by elements that help an individual maintain an upright position while walking (Lord, Galna, Verghese, et al., 2013). The model developed by Lord and colleagues captures a greater breadth of the spatiotemporal intricacies of gait than the model proposed by Verghese et al., 2007. In contrast to the Hollman et al., 2011 model, the framework proposed by Lord and colleagues can be used for both healthy older adults and PD populations. While Hollman et al., 2011 used 23 gait metrics as opposed to the 16 variables, the reduced number of variables included in the analysis does not detract from the extent of gait complexity captured. For example, single and double support times were not included in Lord's model since they were captured by swing time and stance time (Lord, Galna, Verghese, et al., 2013). Furthermore, compared to Hollman's model, gait metrics representing asymmetry, a key clinical feature of PD, were included better capturing gait behaviors in PD populations (Lord, Galna, Verghese, et al., 2013; Postuma et al., 2015). The development of conceptual gait frameworks helps represent and objectively measure the neural complexity of walking. Together, knowledge of the complex multilevel circuity underlying gait combined with a comprehensive assessment of walking may generate unique walking profiles that may reflect specific neurodegenerative processes underway in the brain. Hence, the next section will discuss the relationship between walking neural circuitry and gait domains. It will do this by integrating the framework proposed by Lord and colleagues with an understanding of how impairments in gait may reflect specific neuropathology.

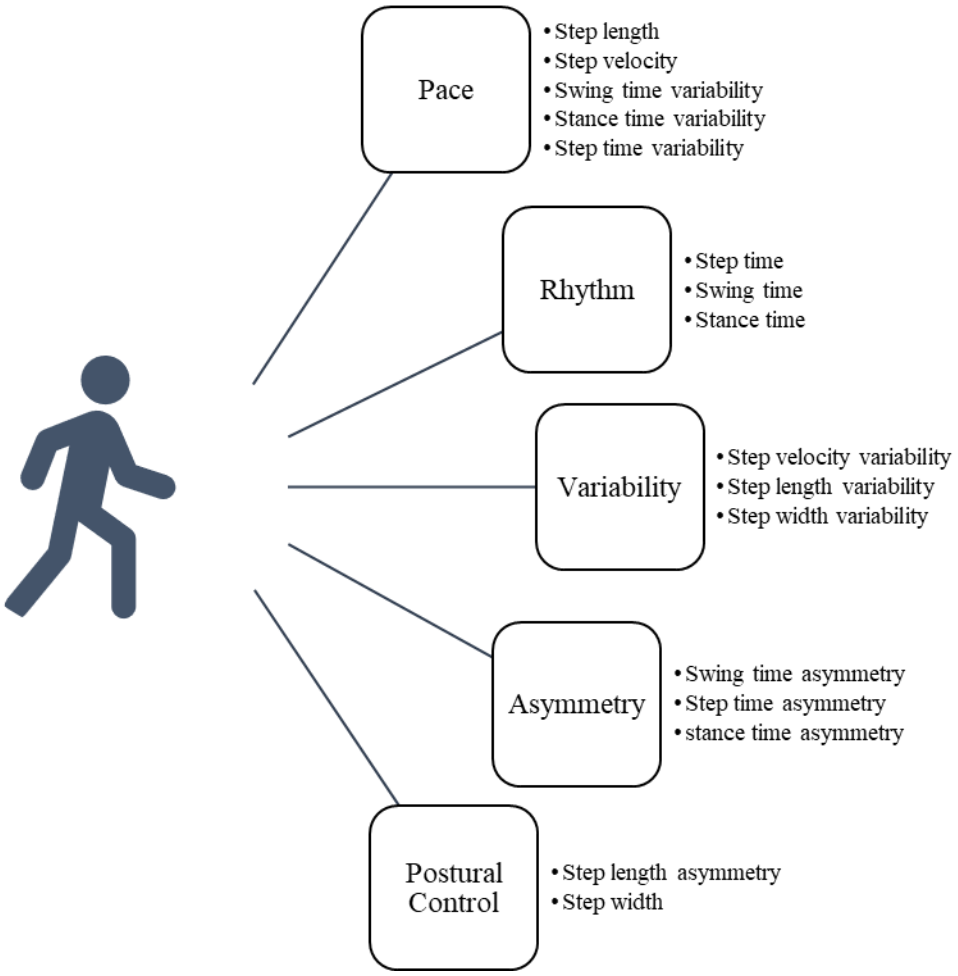


Figure 4. Model of gait behaviors proposed by Lord and colleagues (2013). Gait is subdivided into independent domains: pace, rhythm, variability, asymmetry, and postural control and further broken down into discrete walking characteristics (Lord, Galna, Verghese, et al., 2013).

2.5.2 Relationship between Gait Neural Circuitry and Domains of Walking

Research postulates distinct neural substrates may parallel specific elements of walking (Lord, Galna, Verghese, et al., 2013; Morris et al., 2016; Peterson & Horak, 2016; Wilson et al., 2019). A structured review in older adults found within the pace domain, studies consistently showed an association between reduced gait velocity and decreased gray matter volume in a broad range of neural structures (i.e., frontal cortex, basal ganglia, hippocampal and cerebellar areas) (Wilson et al., 2019). This suggests gait velocity, a feature of pace, may correspond to global neural circuitry (Wilson et al., 2019). Step length, a spatial gait feature within the pace domain has also been related

to gray matter volume in several brain regions including hippocampal, prefrontal, parietal, supplementary motor, sensorimotor, occipital, and limbic areas (Wilson et al., 2019). However, not all brain areas related to gait velocity also showed a relationship with step length suggesting the specificity of step length to more cortical regions (Wilson et al., 2019). The neural correlates of other pace domain characteristics namely, step time variability, step swing time variability and step stance time variability remain unclear (Wilson et al., 2019). Evidence shows an acetylcholinesterase inhibitor decreases step time variability in PD patients; revealing cholinergic involvement may play a role in step-to-step variations (Henderson et al., 2016).

Temporal measures such as step time, swing time and stance time are elements within the rhythm domain (Lord, Galna, Verghese, et al., 2013). Studies assessing white matter lesions related to elements of rhythm have shown mixed findings (Wilson et al., 2019). Two studies observed no relationship between white matter lesions and cadence (De Laat et al., 2011; Nadkarni et al., 2009) while one study found that increased overall white matter lesions, as well as brainstem-specific white matter lesions, were associated with greater double support time (Rosano et al., 2005). Although imaging evidence remains unclear, the physiological gait schema suggests brainstem nuclei (i.e., PPN) and spinal circuitry are involved in generating rhythm and locomotion patterns (Takakusaki, 2017). However, in response to neuropathological changes related to aging and/or disease, features of rhythm may require higher level control (Morris et al., 2016). Evidence for this concept comes from a study in middle-aged and elderly adults demonstrating an association between gait rhythm and information processing speed (Verlinden et al., 2014). Processing speed is a cognitive process that refers to the amount of time needed to respond to and process information in the surrounding environment (Horning & Davis, 2012). Research shows that reduced processing speed in PD patients is associated with decreased dopaminergic uptake in the thalamus, anterior cingulate gyrus and caudate nucleus (Jokinen et al., 2013). Therefore, dopaminergic deficits within neural networks connecting the striatum and prefrontal cortex like the frontostriatal circuit may be involved in reduced information processing speed and in turn impairments in gait rhythm (Jokinen et al., 2013; Morris et al., 2016; Verlinden et al., 2014).

Gait variability is quantified by step-to-step fluctuations in step velocity, step length and step width (Lord, Galna, Verghese, et al., 2013). An increase in gait variability is thought to result from a compensatory shift from automatic movements to more voluntary control (Peterson & Horak, 2016). Automatic movements rely on subcortical brain regions whilst voluntary control requires increased

attention and cortical involvement (Peterson & Horak, 2016). Hence, in LB disease groups where dysfunction of basal ganglia and brainstem pathways are present, a compensatory shift to higher-level cortical control may result in greater gait variability (Peterson & Horak, 2016). Evidence supports this theory by showing an association with increased gait variability and decreased global cognition in PD patients (Lord et al., 2014) and reduced executive functioning in older adults (Verlinden et al., 2014). Research also demonstrates an association between cortical acetylcholinesterase and attentional and executive functions (Bohnen et al., 2005). Thus, speculatively aspects of gait variability may be mediated by the cortical cholinergic network. A study in PD patients supports this notion by showing greater gait variability is associated with greater atrophy of the Nucleus Basalis of Meynert, a key cortical cholinergic network node (Wilkins et al., 2020). Taken together, gait variability may involve non-dopaminergic circuitry at the subcortical and cortical levels of the brain (Peterson & Horak, 2016; Wilkins et al., 2020).

As previously mentioned, asymmetry may be a result of asymmetric basal ganglia output (Takakusaki, 2017). Limited neuroimaging work has assessed the relationship between gait asymmetry and specific neural correlates (Wilson et al., 2019); however, no associations between gait asymmetry and elements of cognition have been reported, suggesting higher level cortical brain regions may not be involved (Morris et al., 2016).

Finally, the postural control domain is thought to correspond to cholinergic structures like the PPN (Peterson & Horak, 2016; Takakusaki, 2017). The PPN is highly interconnected to cortical and subcortical brain regions which suggests multilevel circuitry is involved in postural control (Takakusaki, 2017). Research in support of this cortical involvement shows, step width, a metric of postural control, is associated with decreased gray matter volume in the inferior partial cortex (Wilson et al., 2019). Further research is needed to better understand the neural correlates associated with the domains of walking. However, the complex neural circuitry spanning the brainstem, subcortical and cortical regions of the brain in conjunction with a comprehensive assessment of walking may offer an opportunity to assess how pathological overlap with these neural networks might result in distinct gait changes as demonstrated in Figure 5.

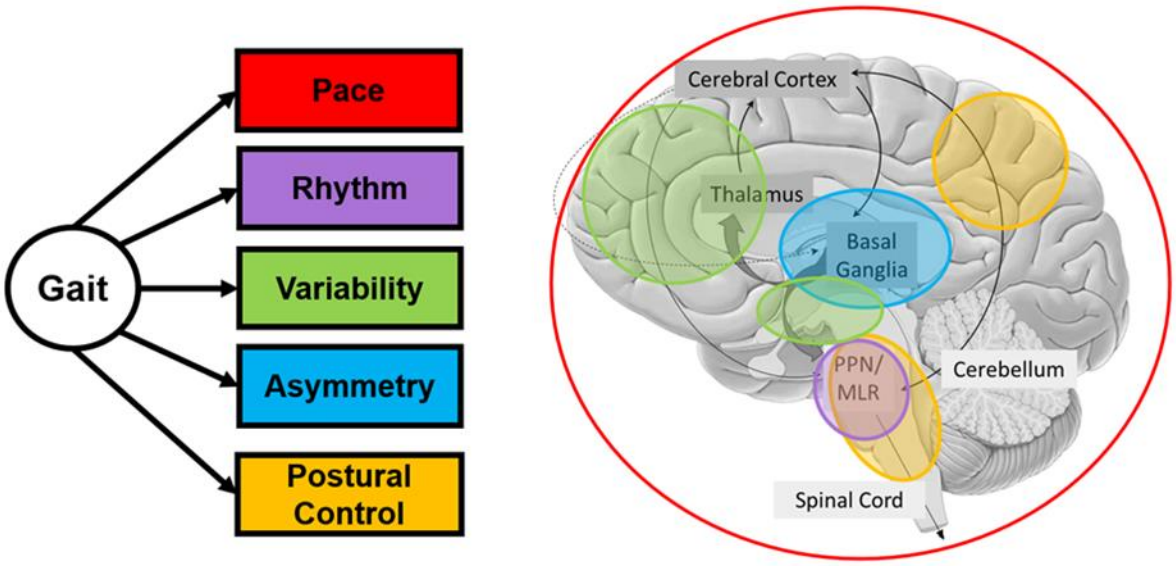


Figure 5. Adapted framework for the neural control of gait, mapping domains of gait to regions of the brain which may be implicated in disease (Lord, Galna, Verghese, et al., 2013; Peterson & Horak, 2016; Takakusaki, 2017; Wilson et al., 2019).

2.6 Gait Behaviors in PD and DLB

The relationship between domains of gait and distinct neural circuitry provides an opportunity to assess how specific pathological changes may be reflected as unique walking signatures. However, to capture this relationship, one must first understand the gait behaviors associated with clinical populations like those with PD and DLB. Gait behaviors in PD have been described to a greater extent in the literature compared to walking behaviors in observed in DLB (Galna et al., 2013; Merory et al., 2007; Mirelman et al., 2016; Pistacchi et al., 2017; Yogev et al., 2005). For example, PD patients compared to healthy controls have increased asymmetry between the left and right limbs, decreased arm swing amplitude, increased gait variability (stride-to-stride fluctuations) and reduced automaticity (Galna et al., 2013; Merory et al., 2007; Mirelman et al., 2016; Pistacchi et al., 2017). Conversely, DLB patients relative to controls have decreased velocity, shorter strides and greater impairments in rhythm (increased time spent in double limb support) (Merory et al., 2007). While alterations in gait are apparent when comparing LB disorders to healthy aging, little work has been done to evaluate gait differences between PD and DLB groups. One study evaluating gait and balance using the Tinetti gait and balance assessment found dementia groups including those

with DLB had worse gait and balance scores than PD and AD patients (Allan et al., 2005). However, the Tinetti assessment uses a Likert-type scale (i.e., the score is either 0,1, or 2), showing reduced specificity in dissociating between disorders (Mancini & Horak, 2010).

Evidence objectively quantifying gait demonstrates individuals with LB dementia (DLB and PD with dementia) had slower speed, reduced stride length and an increased percentage of time spent in the stance phase compared to PD patients without dementia (Fritz et al., 2016). However, only five gait characteristics (i.e., velocity, stride length, the percentage in swing, swing time, the percentage in stance, and the percentage in double support) representative of the pace and rhythm domains were evaluated (Fritz et al., 2016). Overlooking potentially meaningful measures such as variability, asymmetry and postural control (Fritz et al., 2016; Lord, Galna, Verghese, et al., 2013).

To date, only one study has comprehensively compared walking behaviors between PDD and DLB (Mc Ardle et al., 2020). Gait behaviors were quantified using an accelerometer-based wearable sensor as well as an instrumented walkway for reference (Mc Ardle et al., 2020). Individuals with PDP, DLB and AD at the *advanced disease stages* performed six 10 meter walks at a comfortable pace (Mc Ardle et al., 2020). The study demonstrated that while using a wearable sensor, PDD patients compared to DLB at the advanced disease stages showed increased stance time asymmetry and swing time asymmetry (Mc Ardle et al., 2020). Furthermore, this study highlighted these features of asymmetry quantified using a wearable sensor were able to discriminate advanced DLB from PDD with moderate accuracy (swing time asymmetry [AUC=0.755], stance time asymmetry [AUC=0.758] (Mc Ardle et al., 2020). PDD compared to AD had greater step time variability, swing time variability, stance time variability, step velocity variability and stance time asymmetry (Mc Ardle et al., 2020). Conversely, advanced DLB compared to AD showed greater deficits in step velocity variability and step length variability (Mc Ardle et al., 2020). It is interesting to note that results from the instrumented walkway varied from those observed using the wearable sensor showing a lack of coherence within subjects between the two quantitative measures (Mc Ardle et al., 2020). Hence, further research is needed to better understand the tools used to quantify gait behaviors within these clinical populations. Overall, gait differences were shown between PDD and DLB patients (Mc Ardle et al., 2020). However, gait impairments at the advanced stage cannot necessarily be assumed at the early stages given the broader distribution in pathology and level of neurodegeneration (Braak et al., 2003, 2006). Thus, it remains largely unknown how early PD gait behaviors compare to those of early DLB patients. However, this understanding is critical if gait is ever to be used as a marker for

predicting disease trajectory in those at high risk of developing LB disease. Given the relationship between gait domains and selective neural circuitry, a comprehensive evaluation of walking may be a sensitive and selective diagnostic marker in dissociating between the two LB disease groups. Furthermore, the ability to detect differences at the earlier disease stage can be enhanced by employing a more challenging walking paradigm beyond normal forward walking (Peterson & Horak, 2016). A more cognitively demanding walking task may help to reveal previously masked walking disturbances (Peterson & Horak, 2016).

2.7 Unmasking Gait Disturbances Using Dual Tasking

Research suggests patients with dopaminergic depletion, a common LB disease feature, have greater deficits in automaticity and thus shift their stepping behavior to be more voluntary (Peterson & Horak, 2016). This compensatory shift from automatic to more voluntary gait control is hypothesized to represent an adaptive neural response to pathological changes in the brain (Peterson & Horak, 2016; Takakusaki, 2017). Therefore, during a common motor task like normal forward walking some gait disturbances may be masked due to higher-order cognitive resources compensating for deficits in automaticity (Peterson & Horak, 2016). However, walking while performing a secondary task or dual tasking, may help to unmask gait disturbances by disrupting cortical control (Peterson & Horak, 2016). Evidence has demonstrated during simple walking reductions in stride time variability and swing time variability were greater in PD patients compared to healthy controls (Yogev et al., 2005). However, dual tasking revealed increased swing time variability in PD patients but not healthy controls (Yogev et al., 2005). PD patients also made significantly more mistakes than controls during the subtracting 7s dual-task condition (Yogev et al., 2005). This increase in variability during the dual-task condition suggests individuals who rely on more cognitive resources to effectively walk, like those with DLB, may show greater variability. While little work has evaluated dual-tasking effects in DLB, research in cognitively impaired populations like individuals with mild cognitive impairment (MCI) show increased stride time variability specifically under dual-task conditions, supporting this hypothesis (Montero-Odasso et al., 2012).

The capacity-sharing model of dual-task performance assumes attentional resources are limited, therefore attention must be divided when individuals are performing two simultaneous tasks (Tombu & Jolicoeur, 2003). The way attention is divided depends on the complexity of the task, the more challenging the dual task the greater decrements in performance for one or both tasks (O'Shea

et al., 2002; Tombu & Jolicoeur, 2003). Therefore, dual-task walking paradigms of increasing complexity provide an opportunity to exacerbate subtle gait deficits potentially masked due to cortical influences on gait (Kelly et al., 2012).

Research comparing two dual tasks of varying complexity on gait variability in individuals with mild cognitive impairment (MCI) compared to controls, offers evidence for this theory (Montero-Odasso et al., 2012). This study demonstrated that increasing cognitive load during dual tasking significantly increased gait variability and reduced gait velocity in those with MCI compared to those without (Montero-Odasso et al., 2012). Interestingly, the effect of increased dual-task complexity was greater for gait variability than the effect of increased dual-task complexity on gait velocity (Montero-Odasso et al., 2012). This suggests selective neural circuitry related to gait variability may be more profoundly impacted by competing attentional tasks. Additionally, their work showed that a difficult cognitive task with high cortical demand, such as subtracting 7s from 100 would have a greater detrimental effect on gait when compared to the less challenging dual task (Montero-Odasso et al., 2012). The greater deterioration in gait performance may reflect dysfunctional neural circuitry previously masked. Therefore, dual-task walking may draw out disease-specific gait changes as dual task complexity increases. However, to the best of our knowledge, no study to date has examined how increasing dual-task walking complexity (increase in cognitive load) impacts walking behaviors between PD and DLB patients at the early stages of the disease.

Chapter 3: Current Study

3.1 Rationale

The neuropathological and clinical feature overlap between PD and DLB makes them difficult to differentiate (Lippa et al., 2007; McKeith et al., 2017; Postuma et al., 2015). Yet, a differential diagnosis between PD and DLB is important given the striking difference in the disease trajectory and consequently, in treatment. PD patients may live more than 20 years after diagnosis (Golbe & Leyton, 2018; Ishihara et al., 2007) while DLB patients have a median survival rate of fewer than five years (Larsson et al., 2018). In addition, current practice means that by the time an individual has been diagnosed considerable neurodegeneration has already taken place limiting the success of therapeutic interventions (Cheng et al., 2010; McKeith, 2004). Hence, early diagnostic markers are critical for the development of neuroprotective therapies that aid in modifying disease course. A growing body of work suggests gait may be a sensitive and selective diagnostic marker for neurodegeneration (Lord, Galna, Verghese, et al., 2013; Morris et al., 2016; Wilson et al., 2019). Gait or walking is a complex motor task, underpinned by intricate multilevel neural circuitry (Lord, Galna, Verghese, et al., 2013; Takakusaki, 2017). This multilevel circuity combined with a comprehensive assessment of walking may generate unique walking profiles that may parallel specific neurodegenerative processes underway in the brain. Yet only one study to date has comprehensively evaluated gait differences in PD and DLB patients and this study only examined advanced disease stages where both clinical groups demonstrated cognitive decline that interfered with daily functioning (Mc Ardle et al., 2020). They found PDD patients had significantly greater stance time asymmetry and swing time asymmetry than DLB patients (Mc Ardle et al., 2020). This work demonstrates the presence of unique walking impairments between PDD and DLB at the advanced stages of the disease, emphasizing the potential specificity of gait in dissociating between neurodegenerative disorders. However, gait at the advanced disease stages cannot necessarily be inferred to that at the early stages given pathological progression at the advanced disease stages is more diffuse (Braak et al., 2003, 2006). Furthermore, patients with reduced automaticity due to impaired brainstem and subcortical circuity, as is the case for individuals with PD and DLB, are theorized to employ more cortical control to maintain safe and effective walking (Peterson & Horak, 2016). Therefore, employing a cognitively challenging gait paradigm such as walking while performing a secondary cognitive task may unmask cortically controlled gait disturbances and

exacerbate subtle gait differences (Montero-Odasso et al., 2012) even in early stage disease. However, little work has evaluated dual-task performance between early PD and early DLB patients. Thus, the current study sought to address these research gaps by characterizing and distinguishing walking behaviors between early PD and early DLB patients during normal and dual-task walking conditions, to determine if unique signatures of gait exist between the two groups and if increased cognitive load can unmask and/or amplify subtle gait disturbances. This understanding of unique walking behaviors between early PD and early DLB is critical if gait is ever to be used as a marker for neurodegeneration.

3.2 Objectives and Hypotheses

The current study aimed to evaluate whether PD patients display a unique signature of gait deficits compared to DLB patients at the early stages of the disease. Thus, the main objectives were as follows:

Objective 1: To comprehensively characterize and evaluate differences in walking between Early PD and Early DLB patients during normal self-paced walking by examining sixteen gait outcome measures representative of five independent domains: pace, rhythm, variability, asymmetry and postural control.

Hypothesis 1: The clinical expression of cognitive impairments (i.e., progressive cognitive decline, fluctuating cognition, recurrent visual hallucinations) is a key diagnostic feature for DLB (McKeith et al., 2017) while motor deficits are a crucial symptom of PD diagnosis (Postuma et al., 2015). Furthermore, Early DLB patients have more widespread α-synuclein pathology spanning the brainstem to the neocortex while Early PD patients have pathology localized to the brainstem and midbrain regions (Jellinger & Korczyn, 2018; Lippa et al., 2007). Past work suggests gait features within the domains of pace, variability and postural control reflect more cortically controlled aspects of walking (Lord, Galna, Verghese, et al., 2013). While rhythm is a “rudimentary” element of gait controlled by brainstem and spinal cord networks (Lord, Galna, & Rochester, 2013; Lord, Galna, Verghese, et al., 2013), it may become more cortically mediated in response to pathological changes in the brain (Lord, Galna, & Rochester, 2013; Lord, Galna, Verghese, et al., 2013). Thus, it was hypothesized that Early DLB patients will have worse features of pace (reduced velocity and step length as well as increased step time coefficient of variation (CV), step swing time CV and step stance

time CV), rhythm (increased step time, swing time and stance time, variability (increased step velocity CV, step length CV and step width CV) and postural control (increased step width and step length asymmetry) compared to Early PD patients. Given the diagnostic criteria for PD emphasizes the presentation of unilateral motor deficits (Postuma et al., 2015), Early PD patients were hypothesized to have greater gait asymmetry (i.e., more asymmetric step time, swing time and stance time) than those with Early DLB.

Objective 2: To examine the sensitivity and specificity of particular gait characteristics in discriminating Early DLB patients from Early PD patients during normal walking.

Hypothesis 2: Past work assessing the discriminatory ability of gait in dissociating advanced DLB from PDD shows pace (i.e., step velocity, step length and step time standard deviation (SD)) has low accuracy; variability particularly swing time SD had moderate accuracy; rhythm (i.e., step time, stance time and swing time) have low accuracy; asymmetry (i.e., swing time asymmetry and stance time asymmetry) has moderate accuracy; postural control (i.e., step length asymmetry) has low accuracy (Mc Ardle et al., 2020). Thus, it was hypothesized that gait characteristics related to gait variability (i.e., step velocity CV, step length CV and step width CV) and asymmetry (i.e., step time asymmetry, swing time asymmetry and stance time asymmetry) will have moderate accuracy in discriminating Early DLB from Early PD. In contrast, elements of pace (i.e., velocity, step length, step time CV, step swing time CV, step stance time CV), rhythm (i.e., step time, swing time and stance time) and postural control (i.e., step width and step length asymmetry) will have low accuracy.

Objective 3: To evaluate whether increasing cognitive complexity (serial 1s versus serial 7s) during dual tasking influences gait performance differently between Early PD and Early DLB patients.

Hypothesis 3: Based on past work (Kelly et al., 2012; Montero-Odasso et al., 2012; Yogev et al., 2005), it was hypothesized that increased task complexity will exacerbate differences in gait impairments between Early PD and Early DLB patients. More specifically, Early DLB patients will have worse gait performance in features related to pace (reduced velocity and step length as well as increased step time coefficient of variation (CV), step swing time CV and step stance time CV), rhythm (increased step time, swing time and stance time,

variability (increased step velocity CV, step length CV and step width CV) and postural control (increased step width and step length asymmetry) than Early PD patients during the serial 7s task compared to the serial 1s dual task. In contrast, Early PD compared to Early DLB patients will have greater deficits in gait asymmetry (i.e., more asymmetric step time, swing time and stance time) during the serial 7s dual task than during the serial 1s dual task. Evidence of this dual task effect is demonstrated when PD patients had significantly greater gait asymmetry during dual tasking as compared to normal walking while dual tasking did not affect gait asymmetry in healthy controls (Yogev et al., 2007).

3.3 Methods

3.3.1 Participants

A total of 62 participants (16 healthy controls, 26 Early PD patients and 20 Early DLB patients) were recruited from the ForeFront Parkinson's Disease Research Clinic at the Brain and Mind Centre in Sydney, Australia. The healthy control recruited were often spouses and controls from the ForeFront Parkinson's Disease Research Clinic controls database. All participants provided informed consent and this study was approved by the Human Research Ethics Committees at the University of Sydney and the University of Waterloo. The University of Waterloo Human Research Ethics Committee approval permitted secondary data analysis of the baseline data collected at the University of Sydney in 2017. A neurologist clinically assessed all participants to confirm the diagnosis. PD patients were diagnosed based on the Movement Disorder Society diagnostic criteria (Postuma et al., 2015). DLB patients were diagnosed using the fourth consensus diagnostic criteria by McKeith et al., 2017. PD and DLB patients were classified as "Early" if they were within five years since diagnosis. The healthy control group consisted of adults between the ages of 52-87 years of age and were screened for underlying conditions such as musculoskeletal disorders and circadian or sleep disorders. Healthy controls were recruited if they were able to function independently, showed no cognitive impairment (Montreal Cognitive Assessment (MoCA) $\geq$ 25), had no diagnosis of dementia, PD or DLB. Participants were excluded if they had any co-existing neurological conditions (i.e., vascular parkinsonism) or movement disorders outside of PD and DLB. Participants also were excluded if they presented with a mood disorder and/or a severe mental illness (i.e., bipolar disorder, anxiety disorders, major depressive disorder, schizophrenia).

3.3.2 Clinical Assessment

All participants completed the Hospital Anxiety and Depression Scale (HADS-A, HADS-D) to evaluate affective disturbance. All patients were administered the Movement Disorder Society Unified Parkinson's Disease Rating Scale section III (MDS-UPDRS III) which assessed motor symptom severity (Goetz et al., 2008). A comprehensive neuropsychological battery was conducted to evaluate cognitive impairments in all participants. Neuropsychological tests included the MoCA (to measure global cognition), forward and backward digit span test (attention and working memory), Wechsler Memory Scale III (logical memory), Trail Making Tests A and B (processing speed and attention), Stroop tasks (executive function), verbal fluency with letters and animals (executive function), clock drawing task (visuospatial) and the Boston naming test (language) (Goldman et al., 2015). Patients were tested while on their normal medications with 26 Early PD patients on either levodopa or dopamine agonist medication and 19 Early DLB patients on cholinesterase inhibitors of which 7 Early DLB patients were also taking dopaminergic medications.

This study was part of a larger project called, “Predicting pre-clinical Parkinson’s Disease and other synucleinopathies in patients with idiopathic Rapid Eye Movement Sleep Behavior Disorder.” The aim of this larger project was to comparatively and comprehensively map cognitive, neurobiological, behavioral and motor markers of Lewy body disease (which includes, Parkinson's disease, dementia with Lewy bodies and Multiple System Atrophy) relative to healthy controls to predict disease trajectory across the various synucleinopathy subgroups in high-risk individuals like those with isolated Rapid Eye Movement Behavior Disorder. An ongoing longitudinal data collection is being conducted at the University of Sydney to follow and track motor and non-motor changes in isolated Rapid Eye Movement Behavior Disorder patients to see which disease they develop

3.3.3 Gait Protocol

Participants completed a 10 meter walk across a 6.1m x 0.61m Zeno pressure sensor walkway (ProtoKinetics, Havertown, PA; 120 Hz). Individuals initiated their walk from a mark 1.5m before the instrumented walkway and terminated their walk 1.5m after the sensor carpet. All participants walked once under three different conditions (i) normal self-paced walking, (ii) self-paced walking while counting backward from 100 by 1s, and (iii) self-paced walking while subtracting 7s from 100. Participants were given no instructions regarding task prioritization when completing the dual-task walking conditions.

Gait analyses were performed using the PKMAS software package (v.509C3, ProtoKinetics, Havertown, PA). Sixteen gait outcome metrics representing five independent domains of walking were measured: pace (velocity [cm/s], step length [cm], step time coefficient of variation (CV) [%],swing time CV [%], stance time CV [%]), rhythm (step time [s], swing time [s], stance time [s]), variability (step velocity CV [%], step length CV [%], step width CV [%]), asymmetry (i.e., the absolute difference between left and right steps) (step time asymmetry [s], swing time asymmetry [s], stance time asymmetry [s]), and postural control (step width [cm], step length asymmetry [cm]). These measures were obtained from a gait model framework proposed by Lord et al., (2013) developed in older adults and validated in PD patients. Given the paucity of research in this field, this model of gait was selected to allow for findings to be comprehensively reported and facilitate comparisons to past work in PD and DLB groups.

3.3.4 Statistical Analysis

Given, the overall objective of this thesis, Early PD and DLB were directly compared. A 2x2 Chi-squared contingency test was used to evaluate differences in sex between Early PD and Early DLB patients and a two-tailed independent samples t-test (or Mann-Whitney U tests when normality and/or homogeneity of variance were violated) was used to evaluate differences in demographic and neuropsychological performance between Early PD and Early DLB when $P \leq 0.05$. It is noteworthy that while healthy controls were collected as part of this cross-sectional study they were not included as a comparison group in the current statistical analysis since the goal of the study was to characterize differences in walking between Early PD and Early DLB. Rather, the healthy control data were used to standardize the differences in gait between the two clinical groups (see methods below?) to aid in interpretations (see Fig 6).

To comprehensively characterize and evaluate differences in walking between Early PD and Early DLB patients during normal self-paced walking (Aim 1), sixteen parametric one-way between-groups analysis of covariance (ANCOVA) tests were used to control for differences in age while testing for group differences between Early PD and Early DLB during normal walking. In addition to reviewing normality and homogeneity of variance using Shapiro-Wilks and Levene's tests, violation of the homogeneity of regression slopes was evaluated by inspection of the interaction between the covariate age and group for each gait characteristic per condition. A Quade nonparametric ANCOVA test was utilized when the assumptions for the parametric ANCOVA were violated. Given this study

is the first of its kind to evaluate gait signatures between Early PD and Early DLB patients, a threshold of $P \leq 0.05$ was applied.

To examine the sensitivity and specificity of particular gait characteristics in discriminating Early DLB patients from Early PD patients during normal walking (Aim 2), Receiver Operating Characteristics (ROC) curves and the computed area under the curve (AUC) determined the accuracy of selected gait metrics in discriminating Early DLB patients from Early PD patients. Based on previous work (Mc Ardle et al., 2020) an AUC of 0.5–0.7 indicated low accuracy, 0.7–0.9 moderate accuracy and 0.9–1 high accuracy. Gait characteristics were selected if they showed a significant difference ($P < 0.05$) between Early PD and Early DLB as determined in Aim 1.

Finally, to evaluate whether increasing cognitive complexity during dual tasking influences gait performance differently between Early PD and Early DLB (Aim 3), patients a two-way mixed repeated measures ANCOVA was used to evaluate whether increasing task complexity (serial 1s vs. serial 7s) differentially impacted walking performance (sixteen gait outcome measures) between the two groups. The between-subjects factor was group (i.e. Early PD and Early DLB) and the within-subjects factor was condition (serial 1s [low cognitive load] and serial 7s [high cognitive load]). Given 25% (5/20) of Early DLB patients were unable to complete the subtract 7s dual-task condition a sub-analysis was performed looking at differences between Early PD and Early DLB during serial 1s dual tasking. The dual-task walking sub-analysis consisted of sixteen parametric one-way between groups ANCOVAs tests with age as the covariate to control for differences in age while testing for group differences between Early PD and Early DLB during serial 1s dual-task walking. In addition to reviewing normality and homogeneity of variance, violation of the homogeneity of regression slopes was evaluated by inspection of the interaction between the covariate age and group for each gait characteristic per condition. A Quade nonparametric ANCOVA test was utilized when the assumptions for the parametric ANCOVA were violated. This study is the first study of its kind hence a threshold of $P \leq 0.05$ was applied.

Chapter 4: Results

4.1 Participant Demographics and Clinical Performance

Demographic differences are illustrated in Table 1. A total of 62 participants were assessed. Age significantly differed between the groups ($F_{2,59} = 5.7$, $p = 0.005$, $\eta^2 = 0.162$). Tukey's HSD Post Hoc test revealed Early DLB patients were significantly older than Early PD ($p = 0.004$) but there no differences were observed between HC and Early PD patients ($p=0.599$) or Early DLB (0.108). Sex differed between the groups (X^2 [2, N=62] = 6.7, $p = 0.035$). A 2x2 Chi-squared contingency test showed no differences between HC and Early PD (X^2 [1, N=42] = 0.008, $p = 0.927$). However, a significant difference in the ratio of females to males was seen between Early DLB and both HC (X^2 (1, N=36) = 5.4, $p = 0.020$) and Early PD (X^2 (1, N=46) = 5.8, $p = 0.016$). Global cognition (total MoCA score) significantly differed between the groups (H[2]=35.4, $p<0.001$); particularly, as expected, Early DLB had significantly worse cognition than both HC ($U[N_{Hc}=16, N_{DLB}=19] = 9.5$, $z= -4.7$, $p<0.001$) and Early PD ($U[N_{PD}=26, N_{DLB}=19] = 11.5$, $z = -5.4$, $p<0.001$) but no differences were seen between HC and PD ($U[N_{Hc}=16, N_{PD}=26] = 174.5$, $z = -0.9$, $p=0.378$). Anxiety symptom severity measured using the HADS-A differed between the groups (H[2]=7.9, $p=0.018$). Early DLB had a significantly greater total HADS-A score than HC ($U[N_{Hc}=15, N_{DLB}=19] = 65.5$, $z = -2.7$, $p=0.006$); no significant differences were observed between Early PD and Early DLB ($U[N_{PD}=22, N_{DLB}=19] = 136.0$, $z = -1.9$, $p=0.055$) or between HC and Early PD ($U[N_{HC}=15, N_{PD}=22] = 128.5$, $z = -1.1$, $p=0.262$). Depressive symptoms measured using the HADS-D significantly differed between the groups (H[2]=14.4, $p<0.001$]; Early DLB had a significantly greater total HADS-D score than HC ($U[N_{Hc}=15, N_{DLB}=19] = 42.0$, $z = -3.5$, $p<0.001$] and Early PD ($U[N_{PD}=22, N_{DLB}=19] = 108.0$, $z = -2.7$, $p=0.08$] while no differences were observed between HC and Early PD patients ($U[N_{HC}=15, N_{PD}=22] = 114.5$, $z = -1.6$, $p= 0.112$). Early PD and Early DLB were matched in Hoehn and Yahr disease stage ($U[N_{DLB}=19, N_{PD}=26] = 210.0$, $z = -0.96$, $p=0.337$) and disease duration ($U[N_{DLB}=20, N_{PD}=26] = 193.0$, $z = -1.5$, $p=0.132$). Early DLB had greater motor symptom severity (higher MDS-UPDRS III score) ($t_{44} = -2.9$, $p=0.006$), RBD clinical symptom severity (higher RBD-SQ total score) ($U[N_{DLB}=20, N_{PD}=26] = 142.5$, $z = -2.6$, $p=0.009$] and lower daily dopamine (or equivalent) dosage levels ($U[N_{DLB}=20, N_{PD}=26] = 124.5$, $z = -3.1$, $p=0.002$] than Early PD.

Table 1. Participant demographics and clinical scores

Outcomes	HC	Early PD	Early DLB
N	16	26	20
Age (years)	67.6 (9.3)	64.9 (9.9) [D]	73.8 (6.9) [P]
Sex	7F; 9M [D]	11F; 15M [D]	2F; 18M [C, P]
MoCA (max. 30)	27.8 (2.0) [D]	28.3 (1.8) [D]	17.8 (6.6) [C, P]
Hoehn & Yahr (1-5)	-	1.5 (0.5)	1.6 (0.8)
Disease Duration (years)	-	2.7 (1.6)	2.0 (1.5)
MDS-UPDRS III (max. 56)	-	23.5 (11.2) [D]	34.2 (14.0) [P]
HADS-A (max. 21)	2.8 (2.0) [D]	4.1 (3.0)	6.8 (4.7) [C]
HADS-D (max. 21)	2.0 (2.2) [D]	3.6 (3.2) [D]	7.4 (4.7) [C, P]
RBD-SQ Total (max. 13)	-	3.7 (3.2) [D]	6.5 (3.7) [P]
DDE (mg)	-	347.6 (299.6) [D]	116.9 (219.3) [P]

Data is represented as a mean (standard deviation). C= different to HC, P = different to Early PD and D= different to Early DLB when $P \leq 0.05$.

Abbreviations: F, female; M, male; HC, healthy controls; PD, Parkinson's disease; DLB, dementia with Lewy bodies; MoCA, Montreal Cognitive Assessment; MDS-UPDRS III, Movement Disorder Society-Unified Parkinson's disease Rating Scale part III; HADS-A, Hospital Anxiety and Depression Scale part A; HADS-D, Hospital Anxiety and Depression Scale part D; RBD-SQ, REM Sleep Behavior Disorder - Screening Questionnaire; DDE, Daily Dopamine Equivalent.

Group differences in neuropsychological performance are displayed in Table 2. Healthy controls and Early PD were cognitively matched across all neuropsychological tests. Early DLB compared to healthy controls had significantly worse performance in verbal fluency letters (p = 0.002), verbal fluency animals (p <0.001), TMT-A (p <0.001), TMT-B (p =0.007), Stroop 1 (p <0.001), Stroop 2 (p <0.001), Stroop 3 (p = 0.003), Stroop 4 (p = 0.003), total digit span score (p <0.001), logical memory I (p <0.001), logical memory II (p <0.001), clocking drawing task (p

<0.001) and Boston naming task (p = 0.007). Similarly, Early DLB compared to Early PD had greater impairments in cognitive performance for verbal fluency letters (p = 0.005), verbal fluency animals (p <0.001), TMT-A (p <0.001), TMT-B (p <0.030), Stroop 1 (p <0.001), Stroop 2 (p <0.001), Stroop 3 (p <0.001), Stroop 4 (p = 0.002), total digit span score (p <0.001), logical memory I (p <0.001), logical memory II (p <0.001), clocking drawing task (p <0.001), Boston naming task (p = 0.012).

Table 2. Neuropsychological performance

Outcomes	HC	Early PD	Early DLB	Differences between all groups	
				F/H	P
Verbal fluency letters, z score	0.55 (0.75) D	0.29 (1.07) D	-0.72 (0.97) C, P	7.75	0.001
Verbal fluency animals, z score	0.48 (0.93) D	1.00 (3.71) D	-1.25 (1.12) C, P	17.9	<0.001
Trail Making Test A, z score	0.53 (0.89) D	0.14 (0.85) D	-3.53 (4.39) C, P	19.4	<0.001
Trail Making Test B, z score	0.40 (0.78) D	0.13 (0.77) D	-0.78 (0.63) C, P	5.2	0.010
Stroop 1[a]	9.93 (3.71) D	9.92 (2.21) D	3.94 (2.98) C, P	26.6	<0.001
Stroop 2[a]	10.93 (3.31) D	10.54 (2.37) D	5.53 (3.66) C, P	22.6	<0.001
Stroop 3[a]	11.07 (3.61) D	11.23 (2.78) D	5.11 (3.79) C, P	12.9	0.002
Stroop 4[a]	11.67 (3.22) D	11.27 (3.44) D	6.00 (4.03) C, P	11.4	0.003
Digit span total [a]	12.47 (2.61) D	12.85 (2.46) D	8.89 (2.74) C, P	13.7	<0.001

Logical Memory I [a]	10.87 (3.34) [D]	12.36 (6.97 [D]	4.60 (3.23) [C, P]	26.9	<0.001
Logical Memory II [a]	11.47 (2.33) [D]	12.31 (4.34) [D]	6.11 (3.38) [C, P]	24.9	<0.001
Clock Drawing, z score	0.07 (0.81) [D]	-0.09 (1.32) [D]	-6.39 (7.32) [C, P]	21.6	<0.001
Boston naming total	14.00 (1.20) [D]	13.76 (1.16) [D]	11.53 (3.08) [C, P]	9.4	0.009

Data is represented as a mean (standard deviation). C= different to HC, P = different to Early PD and D= different to Early DLB when $P \leq 0.05$.

Abbreviations: HC, healthy controls; PD, Parkinson's disease; DLB, dementia with Lewy bodies; a, age scaled score.

4.2 Gait Performance

4.2.1 Gait behaviors between Early PD and Early DLB during self-paced gait

Walking behavior between Early PD and Early DLB during normal self-paced walking is shown in Table 3 and Figure 5.

Table 3. Gait differences between Early PD and Early DLB during normal walking

Gait Outcome	**Early PD**	**Early DLB**	**Differences between the groups**		
			F	**P**	**Partial-η2**
Pace					
Velocity (cm/s)	127.88 (22.61)	102.72 (14.50)	7.645	**0.008**	0.151
Step Length (cm)	70.07 (8.93)	61.18 (6.84)	4.377	**0.042**	0.093
Step Time CV (%)	3.08 (1.39)	3.81 (1.83)	0.083	0.775	0.017
Step Swing Time CV (%)	3.83 (1.52)	5.04 (2.52)	1.420	0.240	0.032
Step Stance Time CV (%)	2.88 (0.86)	4.04 (1.89)	2.124	0.152	0.078

Rhythm					
Step Time (s)	0.55 (0.06)	0.60 (0.06)	3.951	0.053	0.084
Swing Time (s)	0.41 (0.04)	0.42 (0.04)	0.454	0.504	0.010
Stance Time (s)	0.70 (0.08)	0.79 (0.09)	6.427	**0.015**	0.130
Variability					
Step Velocity CV (%)	2.53 (1.03)	3.68 (1.62)	3.630	0.063	0.116
Step Length CV (%)	3.40 (1.74)	3.97 (0.16)	0.502	0.482	0.003
Step Width CV (%)	38.37 (57.82)	31.90 (24.77)	1.012	0.320	0.010
Asymmetry					
Step Time Asymmetry (s)	0.016 (0.015)	0.019 (0.014)	0.274	0.603	0.012
Swing Time Asymmetry (s)	0.014 (0.012)	0.013 (0.010)	0.097	0.757	0.009
Stance Time Asymmetry (s)	0.015 (0.012)	0.018 (0.011)	0.030	0.863	<0.001
Postural Control					
Step Width (cm)	4.99 (3.90)	7.38 (3.23)	3.205	0.080	0.069
Step Length Asymmetry (cm)	2.66 (1.85)	2.24 (1.74)	0.950	0.335	0.038

Data is represented as a mean (standard deviation). Bolded P-Values indicate a significant difference between the groups when $P \leq 0.05$.

Abbreviations: HC, healthy controls; PD, Parkinson's disease; DLB, dementia with Lewy bodies; CV, coefficient of variation.

Normal self-paced walking demonstrated differences between Early PD and Early DLB patients for domains of pace and rhythm. Individuals with Early DLB had significantly reduced velocity ($F(1,43) = 7.645$, $p = 0.008$, partial-$\eta 2 = 0.151$) and step length ($F(1,44) = 4.410$, $p = 0.042$, partial-$\eta 2 = 0.093$) compared to Early PD patients. Early DLB patients also had significantly longer stance time ($F(1,43) = 6.427$, $p = 0.015$, partial-$\eta 2 = 0.130$) compared to Early PD patients. A

marginal albeit not significant difference was observed for step time (F (1,43) = 3.951, p = 0.053, partial-η2 =0.084), step velocity CV (F (1,44) = 3.630, p = 0.063, partial-η2=0.116) and step width (F (1,43) = 3.205, p = 0.080, partial-η2 =0.069) between Early PD and Early DLB. No significant differences between the two LB disease groups were observed for features of asymmetry as shown in Table 3. When a Bonferroni adjusted p≤0.003 was employed no differences in walking behaviors persisted between the groups. Gait behaviors between Early PD and Early DLB (standardized to mean performance of healthy control participants) are illustrated in Figure 6.

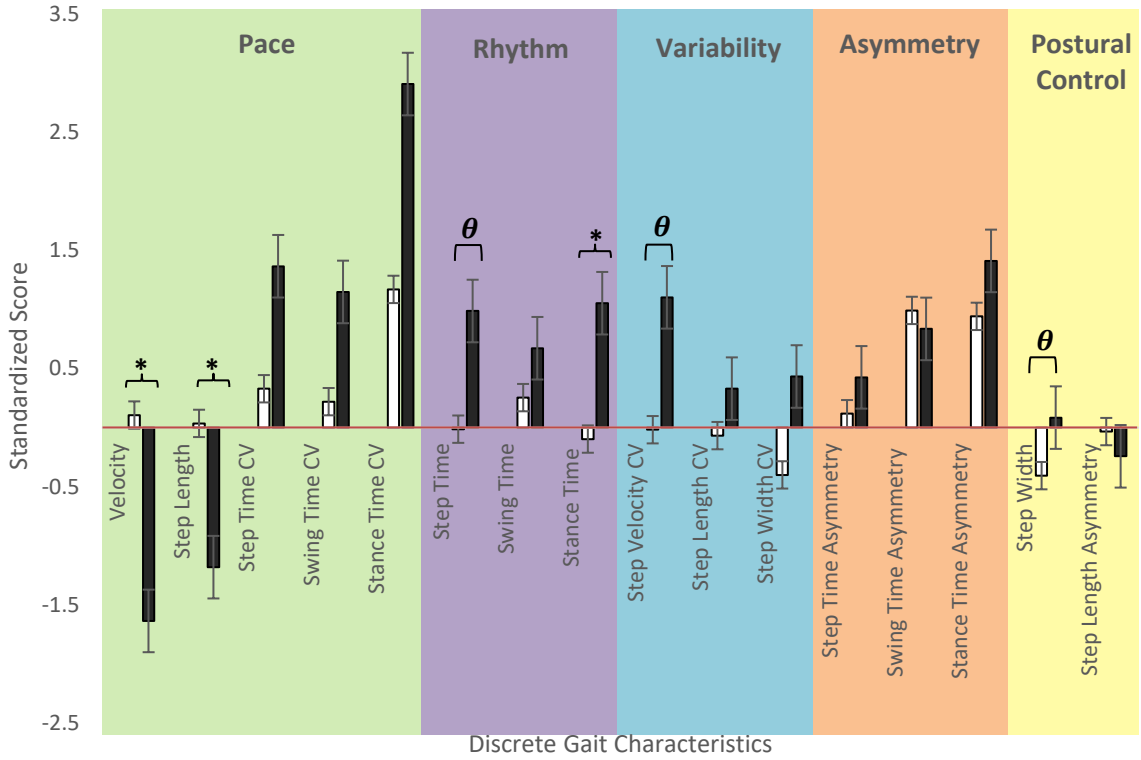
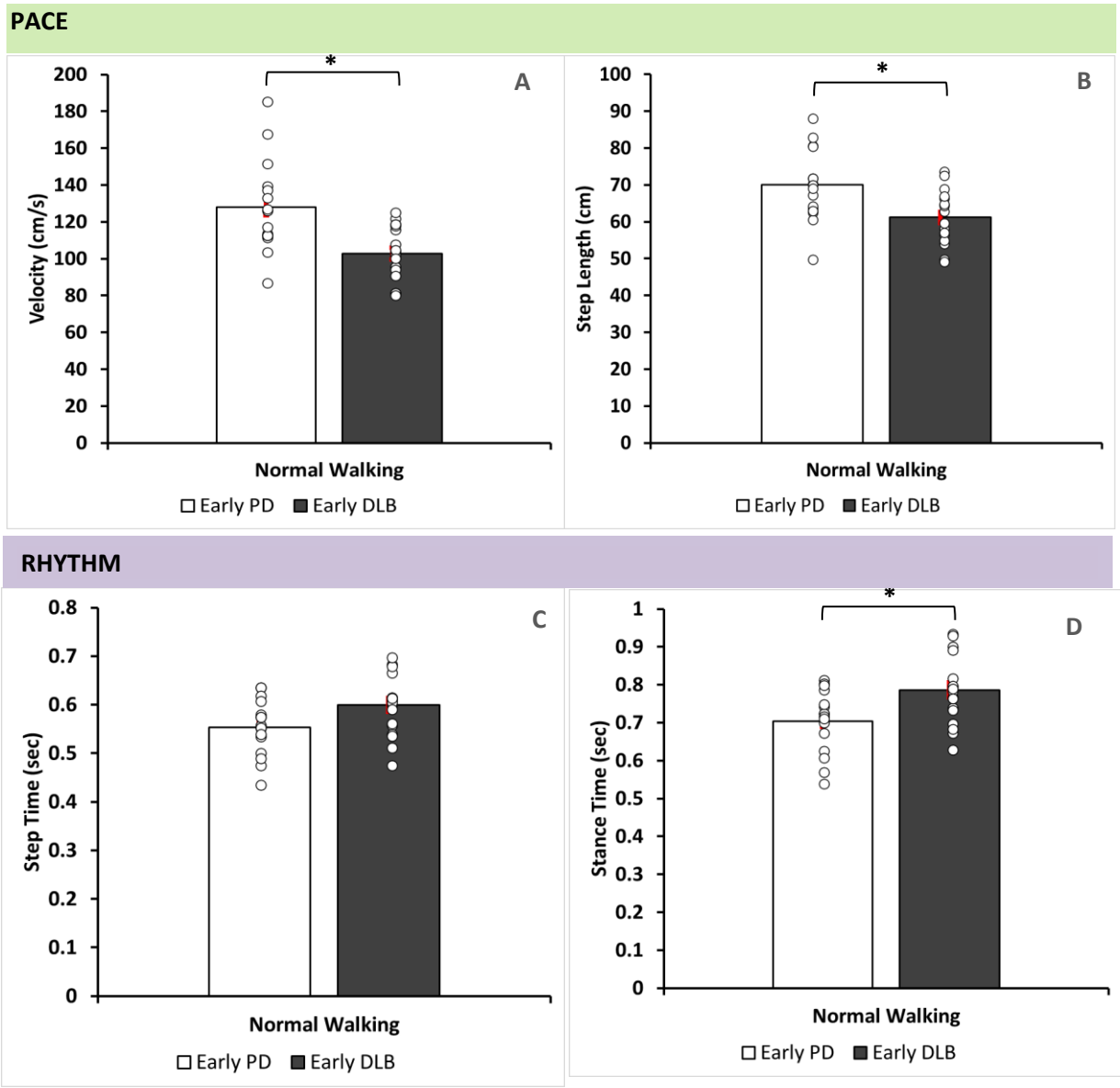


Figure 6. Walking behaviors between Early PD and Early DLB standardized to healthy controls during normal self-paced walking. The solid red line at zero represents healthy older adults. The white bars represent Early PD, and the dark gray bars represent Early DLB. A positive standard deviation from zero indicates gait performance for a disease group was greater relative to controls. A negative standard deviation from zero indicates gait performance for a disease group was reduced relative to controls. * = difference between Early PD and Early

DLB when P ≤ 0.05, θ = trend to significance as defined by a difference between Early PD and Early DLB when 0.090 < P > 0.05.

Abbreviations: PD, Parkinson's disease; DLB, dementia with Lewy bodies; CV, coefficient of variation.



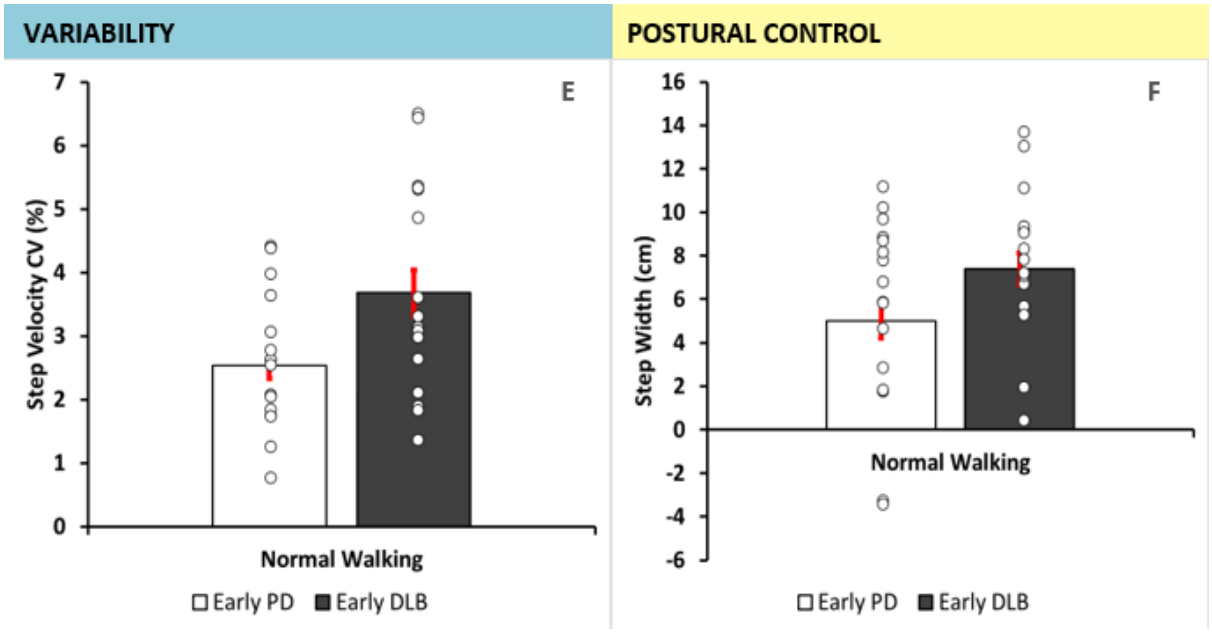


Figure 7. Walking behaviors for Early PD (white bar) and Early DLB (grey bar) with individualized data points (white dots) to show the spread of the data for selected gait measures determined by values that reached or approached significance in Aim 1 including velocity (A), step length (B), step time (C), stance time (D), step velocity CV (E), and step width (F) during normal walking. * = difference between Early PD and Early DLB when P ≤ 0.05.

Abbreviations: PD, Parkinson's disease; DLB, dementia with Lewy bodies; CV, coefficient of variation.

4.2.2 Discriminatory ability of gait during normal walking in Early PD and Early DLB

The top walking metrics of interest included velocity, step length, step time, stance time, step velocity CV and step width as shown in Table 4. Velocity (area under the curve (AUC) =0.175) and step length (AUC =0.219) were very poor in discriminating Early DLB from Early PD with their associated ROC curves showing greater sensitivity than specificity. Conversely, step time (AUC =0.709), stance time (AUC =0.739), and step velocity CV (AUC =0.719) showed moderate accuracy in discriminating Early DLB from Early PD, while step width (AUC =0.671) showed low accuracy (Figure 7).

Table 4. Area under the curve values for gait outcomes measured during normal walking between Early DLB and Early PD patients

	Early DLB (n=20) vs Early PD (n=26)			
	Area	95 % Confidence Interval		p-value
		Lower Bound	Upper Bound	
Velocity (cm/s)	0.175	0.057	0.293	**<0.001**
Step length (cm)	0.219	0.086	0.353	**0.001**
Step time (sec)	0.709	0.556	0.861	**0.016**
Stance time (sec)	0.739	0.596	0.883	**0.006**
Step velocity CV (%)	0.719	0.567	0.872	**0.012**
Step width (cm)	0.671	0.515	0.828	**0.049**

Bolded P-values indicate a statistically significant difference when $P \leq .0.05$. Accuracy values were interpretated as: 0.5 = test due to chance, 0.5-0.7 = low accuracy, 0.7-0.9 = moderate accuracy, 0.9-1 high accuracy (Mc Ardle et al., 2020).

Abbreviations: PD, Parkinson's disease; DLB, dementia with Lewy bodies; CV, coefficient of variation

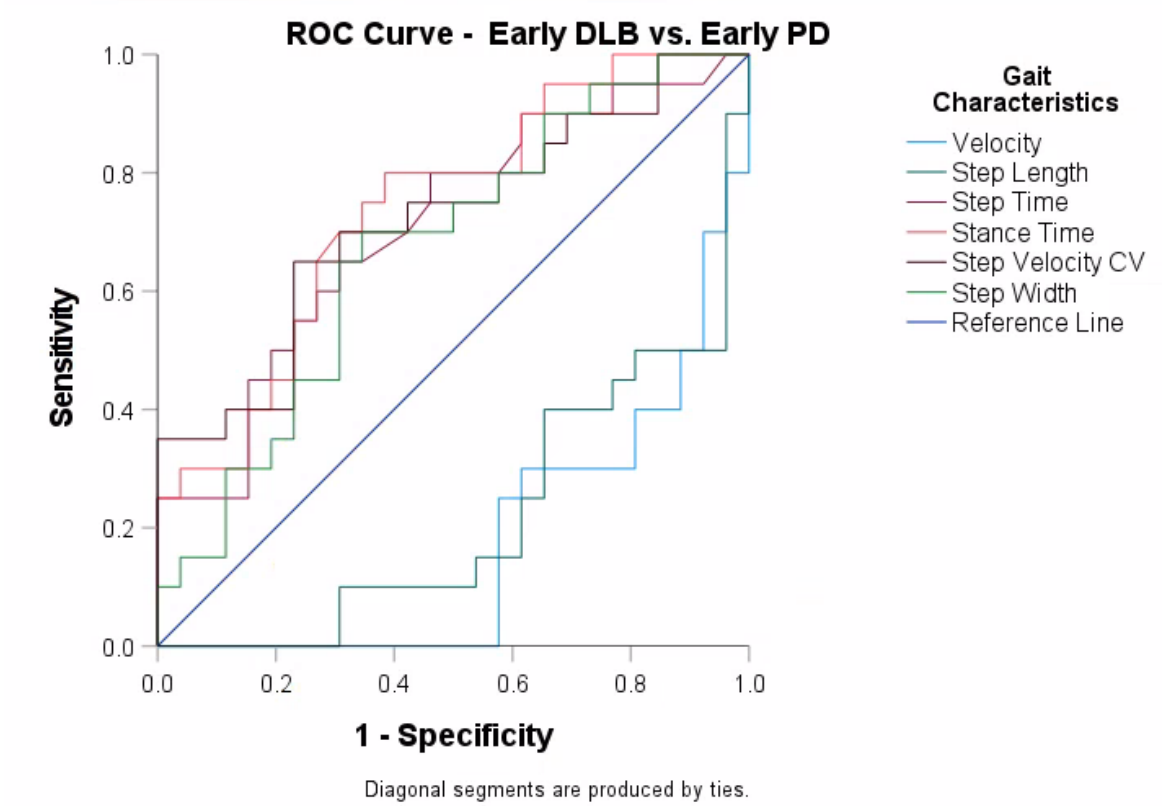


Figure 8. ROC curves for selected gait characteristics discriminating Early DLB from Early PD during normal walking. The dark blue straight 45-degree diagonal line (reference line) indicates an AUC = 0.50. The greater the AUC, the better a gait characteristic can discriminate between the two Lewy Body disease groups

Abbreviations: PD, Parkinson's disease; DLB, dementia with Lewy bodies; CV, coefficient of variation; AUC, area under the curve; ROC, receiver-operating characteristic.

4.2.3 Impact of increasing task complexity on walking behavior

A summary of gait performance during dual task gait conditions between the groups is shown in Table 5. It is important to note that 25% (5/20) of DLB patients were not able to complete the serial 7s dual task. As task complexity increased from serial 1s to serial 7s no differences in gait behaviors between the groups were observed as demonstrated in Table 6. However, a significant main effect of condition was seen for step velocity variability ($F(1,38) = 4.684$, $p = 0.037$) where regardless of

disease group step velocity variability was greater during the serial 7s dual task compared to the serial 1s task.

Table 5. Summary of gait performance between Early PD and Early DLB during serial 1s and serial 7s

	Serial 1s		Serial 7s	
Gait Outcome	**Early PD**	**Early DLB**	**Early PD**	**Early DLB**
Pace				
Velocity (cm/s)	131.56 (23.03)	107.88 (22.78)	114.21 (27.54)	93.44 (25.89)
Step Length (cm)	72.78 (8.98)	64.10 (9.15)	68.22 (11.36)	62.29 (10.38)
Step Time CV (%)	3.77 (1.64)	4.15 (1.31)	4.94 (3.87)	6.43 (4.21)
Step Swing Time CV (%)	4.33 (2.03)	5.13 (1.61)	6.45 (6.20)	8.40 (5.76)
Step Stance Time CV (%)	3.01 (1.21)	4.11 (1.76)	4.27 (2.90)	6.70 (4.75)
Rhythm				
Step Time (sec)	0.56 (0.08)	0.61 (0.09)	0.62 (0.13)	0.71 (0.22)
Swing Time (sec)	0.416 (0.05)	0.427 (0.06)	0.45 (0.07)	0.48 (0.14)
Stance Time (sec)	0.714 (0.11)	0.791 (0.11)	0.80 (0.19)	0.95 (0.32)
Variability				
Step Velocity CV (%)	3.17 (1.58)	4.14 (1.45)	4.59 (4.90)	5.63 (3.14)
Step Length CV (%)	3.23 (1.22)	4.72 (1.61)	5.31 (6.29)	5.56 (2.36)
Step Width CV (%)	22.83 (44.54)	31.78 (17.78)	16.00 (59.07)	34.77 (19.69)
Asymmetry				
Step Time Asymmetry (sec)	0.018 (0.01)	0.021 (0.02)	0.024 (0.02)	0.034 (0.02)
Swing Time Asymmetry (sec)	0.012 (0.01)	0.016 (0.01)	0.019 (0.02)	0.040 (0.05)
Stance Time Asymmetry (sec)	0.013 (0.01)	0.019 (0.02)	0.019 (0.02)	0.040 (0.05)
Postural Control				

Step Width (cm)	5.60 (4.39)	7.39 (3.56)	6.04 (4.10)	8.20 (2.53)
Step Length Asymmetry (cm)	2.30 (1.76)	2.64 (1.78)	3.11 (2.42)	2.67 (1.58)

Data is represented as a mean (standard deviation).

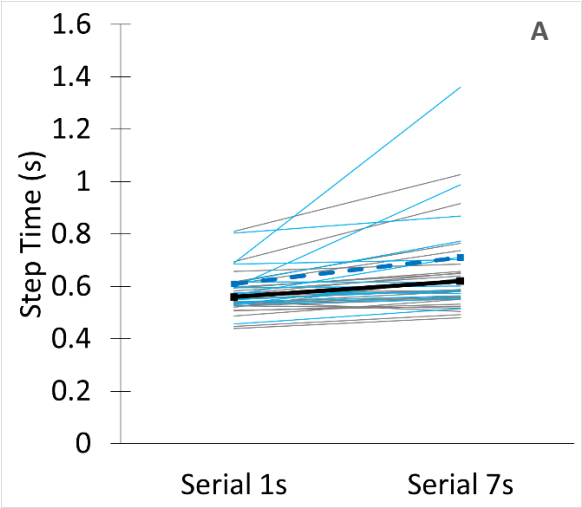
Abbreviations: PD, Parkinson's disease; DLB, dementia with Lewy bodies; CV, coefficient of variation.

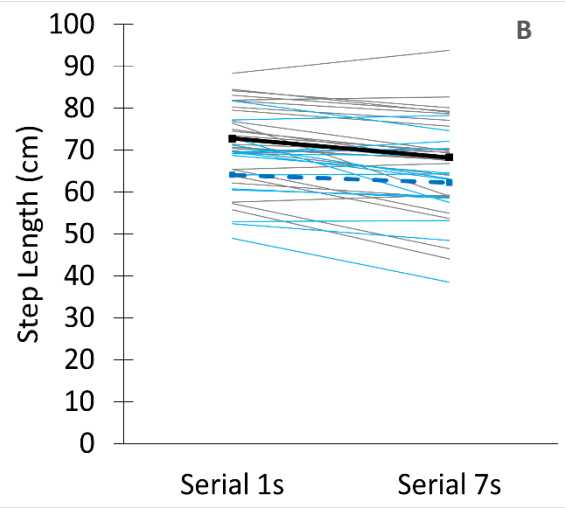
Table 6. Gait performance for Early PD and Early DLB when dual task complexity increases

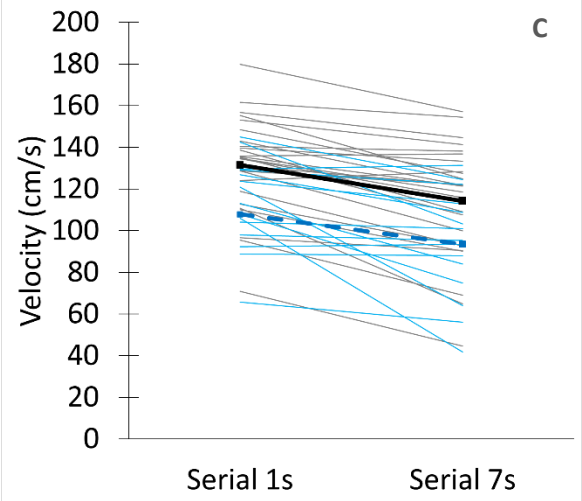
Gait Characteristic	Main Effect/ Interaction	F	P	Partial-η2
Velocity	Group	1.022	0.318	0.026
	Condition	0.072	0.789	0.002
	Group x Condition	0.028	0.868	0.001
Step Length	Group	0.373	0.545	0.01
	Condition	3.02	0.09	0.074
	Group x Condition	2.616	0.114	0.064
Step Time CV	Group	0.023	0.879	0.001
	Condition	2.82	0.101	0.069
	Group x Condition	<0.001	0.983	<0.001
Swing Time CV	Group	0.031	0.861	0.001
	Condition	2.805	0.102	0.069
	Group x Condition	0.072	0.79	0.002
Stance Time CV	Group	1.56	0.219	0.039
	Condition	2.158	0.15	0.054
	Group x Condition	0.255	0.617	0.007
Step Time	Group	0.448	0.507	0.012
	Condition	0.076	0.785	0.002
	Group x Condition	0.929	0.341	0.024
Swing Time	Group	0.029	0.865	0.001
	Condition	0.017	0.896	<0.001
	Group x Condition	1.528	0.224	0.039
Stance Time	Group	0.859	0.36	0.022
	Condition	0.201	0.656	0.005

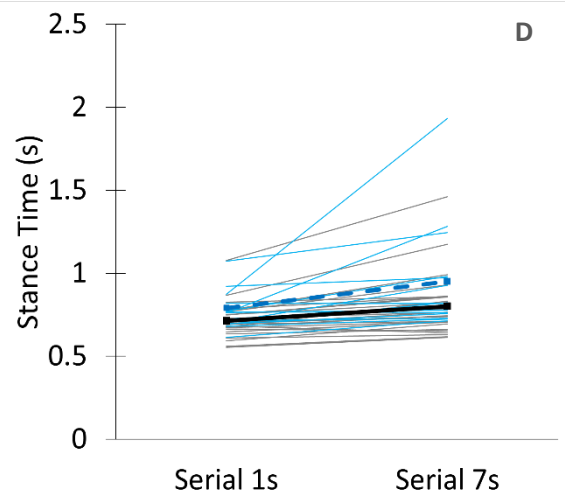
	Group x Condition	0.846	0.364	0.022
Step Velocity CV	Group	0.025	0.876	0.001
	Condition	4.684	0.037	0.11
	Group x Condition	1.292	0.263	0.033
Step Length CV	Group	0.381	0.541	0.01
	Condition	3.25	0.079	0.079
	Group x Condition	1.85	0.182	0.046
Step Width CV	Group	0.266	0.609	0.007
	Condition	2.014	0.164	0.05
	Group x Condition	0.014	0.906	<0.001
Step Time Asymmetry (sec)	Group	0.441	0.511	0.011
	Condition	0.366	0.549	0.01
	Group x Condition	0.811	0.373	0.021
Swing Time Asymmetry (sec)	Group	2.035	0.162	0.051
	Condition	0.048	0.828	0.001
	Group x Condition	3.448	0.071	0.083
Stance Time Asymmetry (sec)	Group	1.899	0.176	0.048
	Condition	1.401	0.244	0.036
	Group x Condition	1.075	0.306	0.028
Step Width (cm)	Group	2.393	0.13	0.059
	Condition	1.048	0.312	0.027
	Group x Condition	0.265	0.61	0.007
Step Length Asymmetry (cm)	Group	0.623	0.435	0.016
	Condition	1.147	0.291	0.029
	Group x Condition	1.509	0.227	0.038

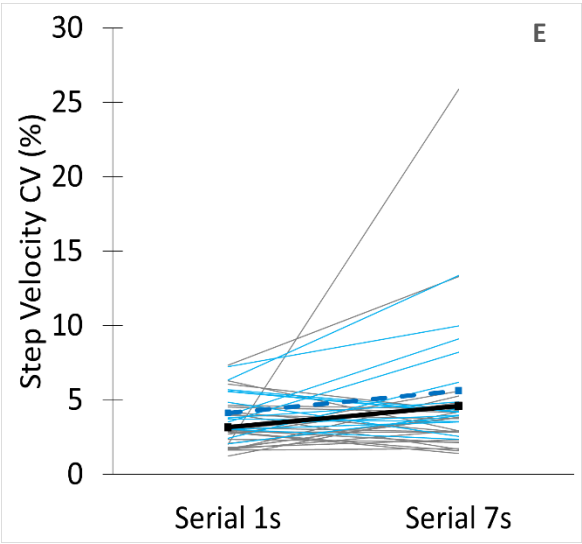
Abbreviations: Parkinson’s disease; DLB, dementia with Lewy bodies; CV, coefficient of variation.

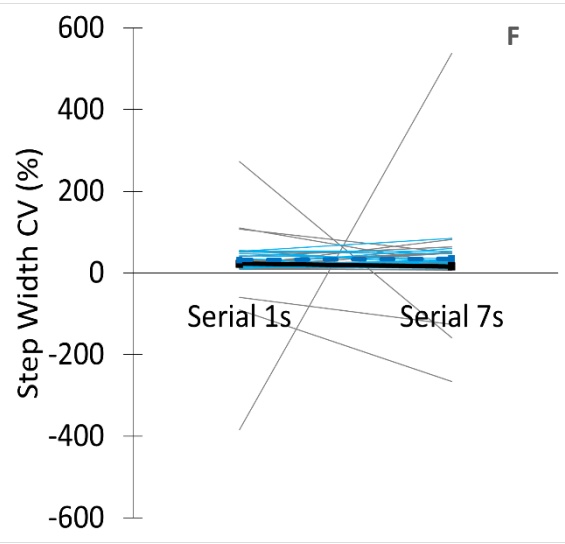

A
Step Time (s)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Serial 1s
Serial 7s


B
Step Length (cm)
100
90
80
70
60
50
40
30
20
10
0
Serial 1s
Serial 7s


C
Velocity (cm/s)
200
180
160
140
120
100
80
60
40
20
0
Serial 1s
Serial 7s


D
Stance Time (s)
2.5
2
1.5
1
0.5
0
Serial 1s
Serial 7s


E
Step Velocity CV (%)
30
25
20
15
10
5
0
Serial 1s
Serial 7s


F
Step Width CV (%)
600
400
200
0
-200
-400
-600
Serial 1s
Serial 7s

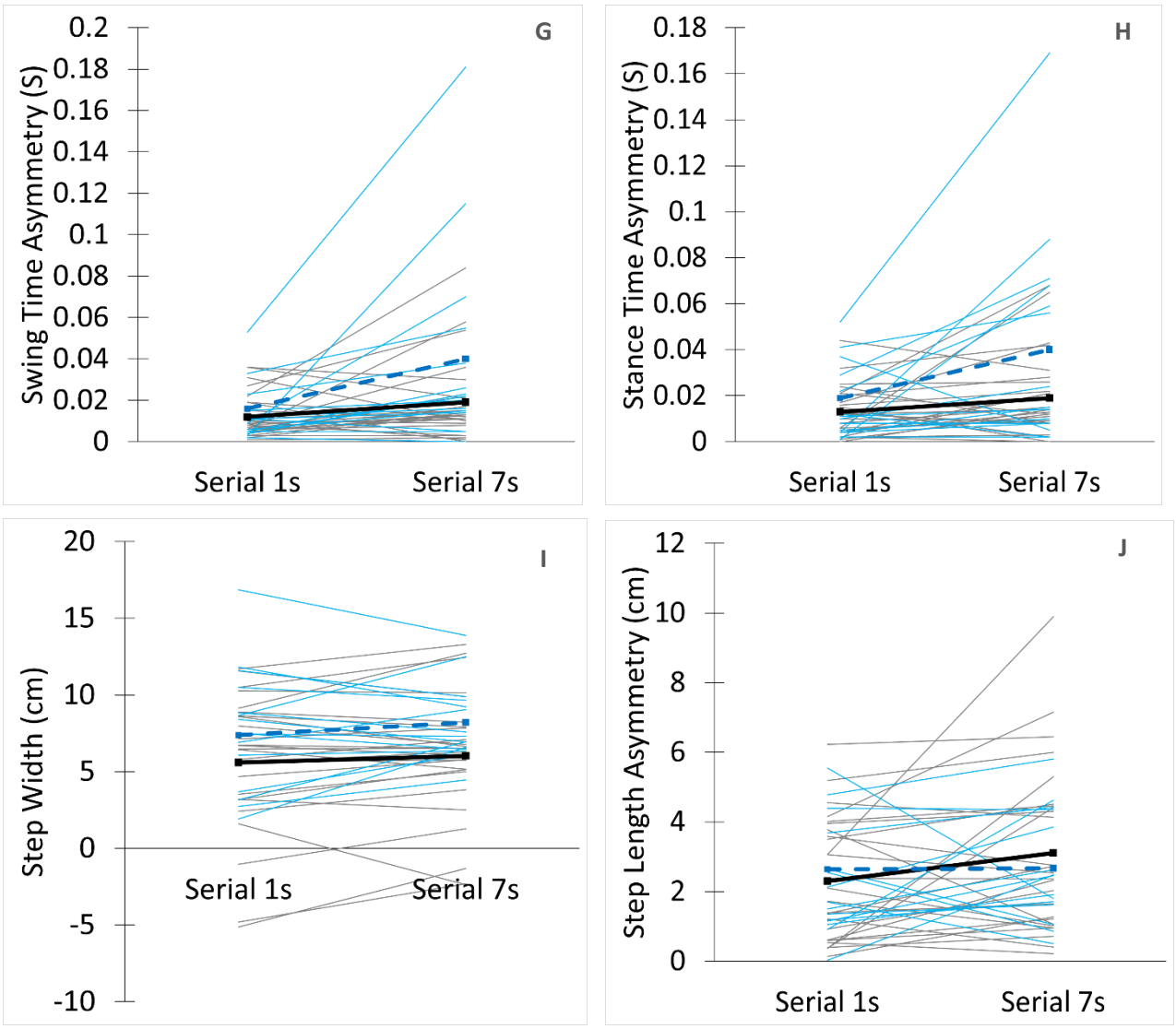


Figure 9. Walking behaviors for Early PD (black solid line) and Early DLB (dark blue dotted line) groups for (A) velocity, (B) step length, (C) step time, (D) stance time, (E) step velocity CV, (F) step width CV, (G) swing time asymmetry, (H) stance time asymmetry, (I) step width and (J) step length asymmetry across dual task walking conditions. The light thin gray line represents gait performance from serial 1s to serial 7s for each Early PD patient. The thin blue line represents gait performance from serial 1s to serial 7s for each Early DLB patient.

Abbreviations: Parkinson's disease; DLB, dementia with Lewy bodies; CV, coefficient of variation.

4.2.4 Sub-analysis of walking differences between Early PD and Early DLB during serial 1s

The serial 7s dual task may have been too challenging for many DLB patients (25% (5/20) Early DLB patients were unable to complete the serial 7s walking condition) thus potentially leading to a floor effect. Therefore, a sub-analysis was performed to compare gait differences between the groups since all participants could complete the serial 1s dual task. The purpose of this sub-analysis was to investigate if serial 1s dual tasking was able to unmask any additional gait differences not previously observed during normal walking. Our results show that Early DLB compared to Early PD during the subtract 1s dual-task condition had significantly greater stance time CV ($F(1,43) = 4.218$, $p = 0.046$, partial-$\eta^2 = 0.089$) and step length CV ($F(1,43) = 6.522$, $p = 0.014$, partial-$\eta^2 = 0.132$) as shown in Figure 8. A marginal but not significant difference was observed for velocity ($F(1,43) = 4.048$, $p = 0.051$, partial-$\eta^2 = 0.086$) and step length ($F(1,43) = 3.475$, $p = 0.069$, partial-$\eta^2 = 0.075$). No significant differences were seen between the groups during the serial 1s task for step time CV ($F(1,43) = 0.241$, $p = 0.626$, partial-$\eta^2 = 0.006$), swing time CV ($F(1,43) = 1.131$ $p = 0.293$, partial-$\eta^2 = 0.026$), step time ($F(1,43) = 0.901$, $p = 0.348$, partial-$\eta^2 = 0.021$), swing time ($F(1,43) = 1.7e\text{-}5$, $p = 0.0997$, partial-$\eta^2 = 1.7e\text{-}5$), stance time ($F(1,43) = 1.972$, $p = 0.167$, partial-$\eta^2 = 0.044$), step velocity CV ($F(1,43) = 2.913$, $p = 0.095$, partial-$\eta^2 = 0.063$), step width CV ($F(1,43) = 0.403$, $p = 0.529$, partial-$\eta^2 = 0.009$), step time asymmetry ($F(1,43) = 0.603$, $p = 0.442$, partial-$\eta^2 = 0.014$), swing time asymmetry ($F(1,43) = 0.851$, $p = 0.361$, partial-$\eta^2 = 0.019$), stance time asymmetry ($F(1,44) = 0.98$, $p = 0.328$, partial-$\eta^2 < 0.001$), step width ($F(1,43) = 2.124$ $p = 0.152$, partial-$\eta^2 = 0.047$) or step length asymmetry ($F(1,43) = 0.34$, $p = 0.563$, partial-$\eta^2 = 0.008$).

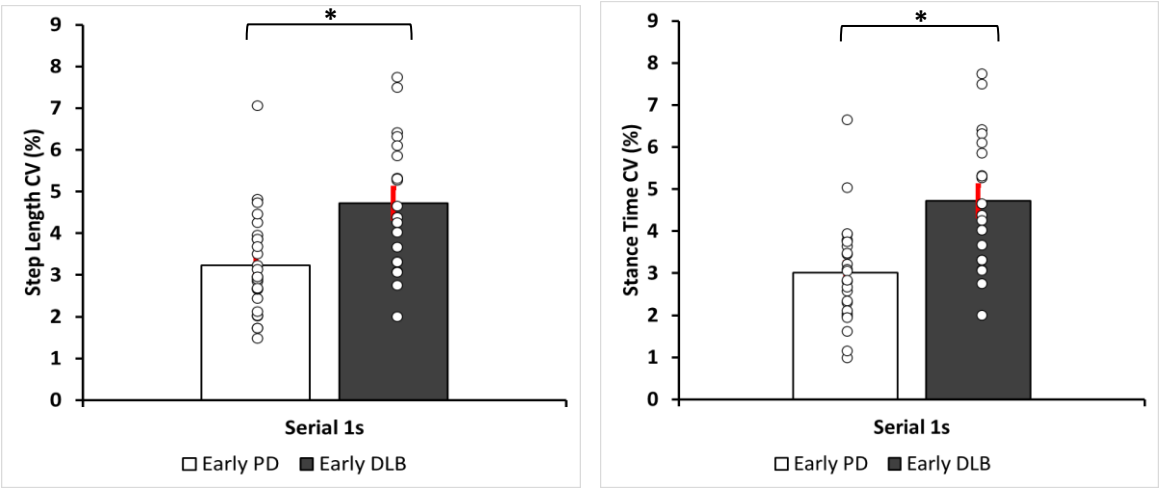


Figure 10. Stance time CV and step length CV between Early PD (white bar) and Early DLB (grey bar) with individualized data points (white dots) to show the spread of the data during the serial 1s dual task condition. * = difference between Early PD and Early DLB when P ≤ 0.05.

Abbreviations: Parkinson's disease; DLB, dementia with Lewy bodies; CV, coefficient of variation.

Chapter 5: Discussion

5.1.1 Summary

This study aimed to investigate whether signatures of walking existed between Early PD and Early DLB patients under single and dual-task gait conditions. By comprehensively examining gait behaviors, this study revealed the presence of gait differences between PD and DLB patients at the early stages of the disease. This finding suggests alterations in gait behaviors may be a differential marker between Lewy body disorder phenotypes. Early DLB compared to Early PD patients demonstrated significantly worse gait impairments in features of pace (decreased velocity and step length) and rhythm (greater stance time) during normal walking. During normal walking when comparing between groups a moderate partial eta-squared ($\eta 2$) effect size was observed for step length, step stance time CV, step time, stance time, step velocity CV and step width. A large partial eta-squared ($\eta 2$) effect size was seen for velocity when comparing between PD and DLB during normal walking. These finding likely reflects the more widespread neocortical distribution of α-synuclein pathology postulated in Early DLB patients compared to Early PD patients (Lippa et al., 2007). Furthermore, aspects of rhythm (step time and stance time) and variability (step velocity CV) could discriminate between early-stage PD and DLB patients with moderate accuracy. Thus, suggesting elements of gait potentially mediated by higher-level neural circuitry may be able to capture disease-specific pathological changes occurring in the brain.

Contrary to the behaviors hypothesized, no substantial differences in gait were observed between the PD and DLB patients as dual-task complexity increased. It is important to note that 25% (5/20) of Early DLB patients could not perform the serial 7s dual-task condition which may have reduced statistical power and increased the likelihood of a type II error. Nonetheless, this study demonstrated regardless of clinical group that in response to a more challenging dual task (serial 7s) participants had significantly greater step velocity variability. This result is in line with previous work that suggests increased cognitive load while walking has a greater effect on spatiotemporal stride-to-stride regulation in clinical populations like those with mild cognitive impairment (Montero-Odasso et al., 2012).

Overall, our results suggest unique signatures of walking exist between PD and DLB patients at the early stages of the disease. This understanding of early unique gait signatures is critical when considering the potential diagnostic and predictive utility of gait in dissociating between Lewy body

disorders and predicting disease trajectory in those at high risk of developing the disease like those with idiopathic RBD.

5.1.2 Gait differences between Early PD and Early DLB during normal walking

The current study found Early DLB patients had significantly worse gait performance in domains of pace (reduced velocity and step length) and rhythm (increased stance time) compared to Early PD patients. These results support past work showing Lewy body dementia patients (including PDD and DLB) had slower speeds, shorter stride lengths and spent a greater amount of time in the stance phases of gait compared to individuals with PD (earlier disease stage of PDD) (Fritz et al., 2016). Imaging evidence in older adults suggests decreased gait velocity is associated with reduced gray matter volume in the frontal cortex, occipital cortex, basal ganglia, hippocampal and cerebellar regions (Wilson et al., 2019). Likewise, reduced step length is associated with decreased gray matter volumes of the prefrontal, parietal, occipital and limbic regions (De Laat et al., 2011; Rosano et al., 2008). The overlap between gray matter regions associated with gait velocity and step length (elements of the pace domain) indicates both characteristics may use similar neural mechanisms involving global brain features influenced by cortical control (Wilson et al., 2019). Therefore, greater impairments in velocity and step length for Early DLB patients compared to Early PD patients may reflect the more widespread distribution of α-synuclein pathology within the cortex theorized for DLB patients (Lippa et al., 2007).

Early DLB compared to Early PD patients also demonstrated longer stance and step times (rhythm domain). However, it is important to note step time approached but did not reach statistical significance but showed a moderate partial eta-squared (η2) effect size. Rhythm is thought to be a "rudimentary" element of gait controlled by brainstem and spinal cord networks (Lord, Galna, Verghese, et al., 2013; Takakusaki, 2017). Early evidence of neural mechanisms implicated in gait rhythmicity comes from research in decerebrate cats showing neural networks in the spinal cord, referred to as central pattern generators (CPGs) are critical in generating rhythmic movements of locomotion (Grillner & Wallén, 1985). Supraspinal involvement via the mesencephalic locomotor region (MLR) and PPN are thought to influence spinal CPGs to produce movement patterns in mammals (MacKay-Lyons, 2002; Takakusaki, 2017). These brainstem areas have projections to various cortical and subcortical brain regions which may allow for greater higher-level control if required (Simon J.G. Lewis & Shine, 2016; MacKay-Lyons, 2002). Evidence in support of this

compensatory shift to greater cortical control is demonstrated by an association between rhythm and executive functioning found in PD patients with the PIGD subtype (Lord et al., 2014). PET imaging work in PD patients also demonstrates PPN modulation via deep brain stimulation is associated with increased regional cerebral blood flow in the cerebellum, thalamus, medial sensorimotor cortex and supplementary motor area (Ballanger et al., 2009). Additionally, research reveals that reduced processing speeds in PD patients are associated with decreased dopaminergic uptake in the thalamus, anterior cingulate gyrus and caudate nucleus (Jokinen et al., 2013). Hence, dopaminergic dysfunction (a key characteristic of PD and DLB) within neural networks communicating between the brainstem, striatum and cortex such as the corticothalamic and corticostriatal systems may be involved in gait arrhythmicity. Therefore, given DLB patients have greater cognitive impairments than PD patients, it is not surprising Early DLB patients exhibited greater deficits in rhythm compared to Early PD patients (Lippa et al., 2007).

Group differences approached but did not reach statistical significance for elements of variability (step velocity CV) and postural control (step width) during normal self-paced gait. However, both step velocity variability and step width demonstrated that disease group had a moderate effect on step velocity CV (partial $\eta 2 = 0.116$) and step width (partial $\eta 2 = 0.069$). Early DLB patients demonstrated increased step velocity variability and step width compared to individuals with Early PD which aligns closely with the walking behaviors hypothesized. An increase in gait variability is thought to arise from a compensatory shift from automatic to more voluntary motor control (Peterson & Horak, 2016). Thus, the larger spatiotemporal deficit in variability during simple forward walking suggests Early DLB patients rely more heavily on cortical compensation to maintain safe and effective walking. Step width also approached statistical significance showing Early DLB patients took wider steps than Early PD patients during simple forward walking. Step width is thought to be implicated in balance control where wider steps lead to greater stability and may be a compensatory response to instability (Gabell & Nayak, 1984). Thus, findings suggest Early DLB may have employed greater voluntary control over their gait, widening their steps to compensate for their greater impairments in postural stability compared to Early PD patients (Allan et al., 2005; Peterson & Horak, 2016).

Lastly, during self-paced gait, contrary to the behaviors hypothesized no differences in asymmetry were seen between PD and DLB groups. The results of this study differ from past work showing PDD patients have greater swing and stance time asymmetry compared to advanced DLB

patients. A potential reason for this discrepancy may be due to the effectiveness of medication at a specific stage of the disease. Levodopa at the initial stages of PD is more successful at alleviating motor symptoms than at the advanced disease stages (Thanvi & Lo, 2004). Evidence shows increased levodopa is associated with reduced asymmetry (step time asymmetry and swing time asymmetry) in PD patients (Galna et al., 2015). Therefore, aspects of asymmetry may have been normalized in the Early PD group given individuals were tested in their 'ON' state.

5.1.3 Accuracy of gait characteristics in discriminating Early DLB from Early PD patients

An examination of the sensitivity and specificity of select gait characteristics that reached or approached statistical significance during normal walking revealed rhythm (step time and stance time) and variability (step velocity CV) discriminated Early DLB patients from Early PD patients with moderate accuracy. While pace (velocity and step length) had no discriminatory power and postural control (step width) had poor accuracy in distinguishing Early DLB patients from Early PD patients. Thus, highlighting the need to look beyond traditionally used gait outcome measures like speed, especially at the early stages of the disease. The notion of looking beyond gait speed is further exemplified by recent work done in PD patients and healthy controls (Vitorio et al., 2021). Vitorio and colleagues found dual tasking affected arm range of motion and foot strike angle more in PD patients than healthy controls. Interestingly their ROC analysis revealed the dual task cost for arm range of motion and foot strike angle were the top two metrics able to discriminate healthy controls from PD patients with moderate to high accuracy (Vitorio et al., 2021). Additionally, in contrast to the current study findings, Vitorio et al., 2021 found gait speed and stride length had high accuracy in discriminating PD patients from controls during simple forward walking, However, turn velocity, turn duration, foot strike angle and arm range of motion showed higher accuracy than gait speed and stride length when discriminating PD from healthy older adults during normal walking. Future work comparing PD and DLB should consider measuring arm range of motion and foot strike angle as well as features related to turning such as turn velocity and turn duration as gait outcomes measures that may improve discrimination between Lewy body disease groups. This study replicated previous work using ROC analysis between advanced PD with dementia and DLB patients showing features of pace had poor discriminatory power but aspects of variability displayed a moderate ability to accurately dissociate DLB from PDD patients (Mc Ardle et al., 2020). However, contrary to Mc Ardle and colleagues, this study revealed elements of rhythm could discriminate Early DLB patients from Early

PD patients with moderate accuracy. This suggests Early DLB have may have selective impairments in maintaining gait automaticity compared to Early PD. A selective change in gait rhythmicity may reflect distinct impaired neural systems found at the early stages of the disease. However, further work is needed to determine the neural correlates associated with features of rhythm. Studies assessing the relationship between gray matter volume and rhythm characteristics show mixed findings (Wilson et al., 2019). For example, one study found that increased double support time was related to decreased gray matter volume in areas including the prefrontal cortex, parietal lobe, sensorimotor cortex and motor cortex (Rosano et al., 2008). Conversely, another study revealed no relationship between double support time and gray matter volumes in the cerebellum, prefrontal cortex or basal ganglia (Manor et al., 2012).

5.1.4 Gait differences between groups as task complexity increases

A novel feature of this study was the investigation into whether increasing cognitive complexity during dual tasking influenced gait performance between Early PD and Early DLB patients. In contrast to the hypothesis, the results of this study showed that increasing cognitive load during dual-task walking from serial 1s to serial 7s did not expose any additional gait differences between Early PD and Early DLB One reason for this finding may be due to the 25% (5/25) of Early DLB patients who were unable to complete the serial 7s dual task. This substantial dropout is important to consider when assessing the practical significance of using a serial 7s secondary task to assess the diagnostic implications of increasing cognitive load to help unmask potential differences in gait between PD and DLB during the early stages of the disease. From a clinical standpoint, the substantial dropout of DLB patients could mean the serial 7s dual task can discriminate the groups quite well; if an individual cannot complete the serial 7s dual task it may indicate they likely have DLB rather than PD. However, if gait is every to be used as a diagnostic marker it is important to be able to detect differences in gait between the two Lewy body disease groups. Thus. the large portion of DLB patients unable to successfully complete the serial 7s dual task may indicate that serial 7s dual tasking may be too challenging and complex to draw out the desired effect. Gait differences may not have been as salient as hypothesized when cognitive complexity increased because participants may have prioritized their gait while secondary task performance suffered as a result of the dual task being too challenging.. Additionally, the clinical heterogeneity within the early LB disease groups may have contributed to the lack of findings throughout the study. Evidence demonstrates the existence of clinical heterogeneity within the early stages of PD (Lewis et al., 2005) and DLB

(Morenas-Rodríguez et al., 2018). Studies also suggest distinct neuropathological changes may underlie the myriad of symptoms (Haaxma et al., 2010; Pirker, 2003; Wang et al., 2015). Therefore, clinical heterogeneity within a group may have contributed to an increased error variance and in turn reduced statistical power (Norton et al., 2001). The moderate to large effect sizes seen for velocity, step length, stance time CV, step time, stance time, step velocity CV, and step width during normal walking suggest these gait metrics may be the most helpful in future work differentiating gait behaviors between Lewy body disease groups.

Research shows task complexity does differentially affect walking due to the various degrees of challenge imposed by different cognitive loads (Montero-Odasso et al., 2012). Past work shows PD patients demonstrated increased arrhythmicity (greater stride time and swing time variability) when walking while performing serial 7 subtractions (Hausdorff et al., 2005). The study by Hausdorff and colleagues (2005) also found the effect of dual tasking on gait variability increased in PD patients across dual task walking conditions but not in controls. Similarly, work by Rochester et al., 2014 showed that controls took wider steps and had increased step width variability relative to PD patients. Evidence from Rochester et al., 2014 suggest dual task interference impacts certain gait characteristics within domains of variability and postural control rather than global gait behaviors. This supports the notion that dual tasking may differentially impact certain aspects of gait, whereby stride-to-stride variability, which is believed to be more cortically influenced, may be more profoundly impacted by dual tasking in clinical populations with greater cognitive deficits like those with DLB (Lippa et al., 2007; Wilson et al., 2019).

Given 25% of DLB patients were unable to complete the serial 7s dual task a sub-analysis in only serial 1s, where all Early DLB patients were able to adequately perform the task was completed to assess if dual tasking could reveal any additional gait differences not previously observed during normal walking. The results of this sub-analysis revealed stance time variability and step length variability not previously seen during normal walking differed between Early PD and Early DLB during the serial 1s dual task with variability higher for the DLB group. A comparison of effect sizes revealed a larger moderate effect for stance time variability during the serial 1s dual task condition than during normal walking (normal: partial $\eta 2 = 0.078$; serial 1s : partial $\eta 2 = 0.089$). In addition, serial 1s dual tasking demonstrated a moderate effect on step length CV (partial $\eta 2 = 0.132$) not previously seen during normal walking (partial $\eta 2 = 0.003$) which suggest the type of disease group may have a greater effect on stance time variability and step length variability during dual tasking.

Furthermore, the current study suggests that dual-task gait may impact aspects of variability, similar to findings in previous work, and can help dissociate between PD and DLB (Kelly et al., 2012). Research suggests individuals with PD compared to controls have greater challenges in automaticity due to dysfunction in basal ganglia circuity and thus employ more cognitive control to maintain safe and effective walking (Bohnen et al., 2013). The reduction in automaticity is reflected in greater stride-to-stride variability (Kelly et al., 2012). Dual tasking divides attention and provides an opportunity to exacerbate walking deficits that may have been masked due to this compensatory shift away from automatic control (Kelly et al., 2012; Horak et al., 2016). The results of this sub-analysis support the idea that divided attention during dual-task gait may exacerbate walking differences that are more cortically controlled than normal walking (Kelly et al., 2012). Taken together, this study in contrast to previous work demonstrated that increased dual-task complexity from a low cognitive load to a high cognitive load does not help exacerbate walking impairments in Early PD and Early DLB patients. However, dual tasking, shown by the serial 1s dual task was able to differentiate between PD and DLB patients revealing gait differences not previously seen in normal walking.

5.1.5 Limitations and Future Considerations

While this study was the first to compared PD and DLB gait at the early stages, it also had several limitations worth noting.. Patients within this study were tested on their medications with 26 Early PD patients on levodopa or dopamine agonist medication and 19 Early DLB patients on cholinesterase inhibitors of which 7 Early DLB patients were also taking dopaminergic medications. Research shows that dopaminergic medications can improve stride length and gait velocity while postural elements like step width are resistant to dopaminergic therapies (Bohnen & Cham, 2006; Lord et al., 2014). Similarly, research demonstrates increased levels of levodopa are associated with reduced asymmetry (step time asymmetry and swing time asymmetry) in individuals with PD (Galna et al., 2015). Cholinesterase inhibitors are typically employed by clinicians to improve cognition in PD patients with dementia (Chen et al., 2021). Given the potential overlap in cognitive and motor circuitry it is not surprising cholinesterase inhibitors have been shown to improve features of gait variability (Chen et al., 2021). Taken together, aspects of asymmetry may have been normalized in the Early PD group since patients were tested in their ‘ON’ state and features of gait variability in Early DLB patients may have been underestimated due to the influence of cholinergic medication. Research studies may want to consider performing a cross-sectional assessment of walking in de novo PD and DLB patients who are not on levodopa and/or cholinesterase inhibitors to account for the

possibility that the ON medication state impacted current study findings. Furthermore, a longitudinal assessment of walking in newly diagnosed unmedicated PD and DLB patients is another area for future consideration given the rate of change may reflect a specific disease trajectory (for example, DLB gait impairments may worsen faster than PD) (Postuma et al., 2012). A longitudinal study in unmedicated PD and DLB patients may help elucidate the prognostic utility of a quantitative assessment of gait.

Another limitation of this study is the greater ratio of males to females for Early DLB patients compared to Early PD patients. The larger ratio of males to females within the DLB groups may have impacted the study findings given certain spatiotemporal measures of gait like velocity and step length will be greater in males than females due to their greater leg length. Given there were more males than females in the DLB group, effects may have been underestimated for velocity and step length. To address this limitation future studies should consider recording and normalizing gait metrics to leg length.

In addition, this study restricted the quantification of walking behaviors to only aspects of the lower limbs. Research demonstrates PD patients have reduced arm swing amplitude and that asymmetry in spatiotemporal features of arm swing during walking may be an early sign gait abnormalities in PD (Mirelman et al., 2016). Furthermore, outcome measures such as turn velocity, turn duration, arm range of motion and foot strike angle have been shown to have high accuracy in discriminating PD from healthy control (Vitorio et al., 2021). Taken together, it is recommended that future work quantify upper-limb arm swing and range of motion as well as aspects of turning and foot strike angles as gait outcomes to investigate further as a potential way to improve discrimination. Wearable sensors may be a more cost-effective way to capture upper and lower limb movement during gait.

Finally, given, 25% of Early DLB patients were unable to complete the serial 7s dual, future research should explore an optimal dual task condition that would provide sufficient cognitive complexity to observe a graded decline in gait performance without the loss of participants due to inability to complete the more cognitive demanding dual task. An observation of secondary task performance will also aid in understanding if gait performance was better as a consequence of poor cognitive performance.

Overall, the implications of this research study include helping to lay the foundation for using gait as a prognostic and diagnostic marker for neurodegeneration. An understanding of distinct gait profiles between Lewy body disease groups at the early stages of the disease helps generate potential endpoints of phenoconversion in high-risk populations like those with isolated RBD. If gait can one day be used as a prognostic marker for neurodegeneration, quantitative motor assessments may be a cost-effective approach to diagnosing disease trajectory in those at risk and may serve as a marker in the development of neuroprotective therapies used to slow or halt disease progression. Future research should explore using a multimodal approach including imaging techniques and quantitative movement assessments to understand if gait can be used as a potential proxy marker for predicting a specific neurodegenerative disease.

5.2 Conclusion

In conclusion, this study aimed to investigate whether signatures of walking existed between Early PD and Early DLB patients under single and dual-task gait conditions. By comprehensively examining gait behaviors, this study revealed the presence of distinct gait differences between PD and DLB patients at the early stages of the disease specifically that Early DLB patients have greater deficits in pace, rhythm, variability and postural control compared to Early PD. This study also showed that aspects of variability like step velocity CV and rhythm such as step time and stance time have moderate accuracy when discriminating Early DLB from Early PD patients. Finally, dual tasking (serial 1s) may help unmask gait deficits specific to variability which may reflect greater cortical pathology. Overall, our work supports previous research, showing differences in gait behaviors exist between PD and DLB. This study extends past work by assessing these differences at the early stages of disease as well as investigating how increasing cognitive complexity affects gait performance between the two groups. Our research provides evidence for the potential utility of gait in tracking and predicting conversion to overt synucleinopathies in high-risk individuals and helps build our knowledge of unique gait profiles for neurodegenerative disorders.

References

Aarsland, D. (2016). Cognitive impairment in Parkinson's disease and dementia with Lewy bodies. *Parkinsonism & Related Disorders*, *22*, S144–S148. https://doi.org/10.1016/J.PARKRELDIS.2015.09.034

Adler, C. H., Beach, T. G., Zhang, N., Shill, H. A., Driver-Dunckley, E., Caviness, J. N., Mehta, S. H., Sabbagh, M. N., Serrano, G. E., Sue, L. I., Belden, C. M., Powell, J., Jacobson, S. A., Zamrini, E., Shprecher, D., Davis, K. J., Dugger, B. N., & Hentz, J. G. (2019). Unified Staging System for Lewy Body Disorders: Clinicopathologic Correlations and Comparison to Braak Staging. *Journal of Neuropathology and Experimental Neurology*, *78*(10), 891. https://doi.org/10.1093/JNEN/NLZ080

Allan, L. M., Ballard, C. G., Burn, D. J., & Kenny, R. A. (2005). Prevalence and Severity of Gait Disorders in Alzheimer's and Non-Alzheimer's Dementias. *Journal of the American Geriatrics Society*, *53*(10), 1681–1687. https://doi.org/10.1111/J.1532-5415.2005.53552.X

Antonini, A., Moeller, J. R., Nakamura, T., Spetsieris, P., Dhawan, V., & Eidelberg, D. (1998). The metabolic anatomy of tremor in Parkinson's disease. *Neurology*, *51*(3), 803–810. https://doi.org/10.1212/WNL.51.3.803

Ballanger, B., Lozano, A. M., Moro, E., Van Eimeren, T., Hamani, C., Chen, R., Cilia, R., Houle, S., Poon, Y. Y., Lang, A. E., & Strafella, A. P. (2009). Cerebral blood flow changes induced by pedunculopontine nucleus stimulation in patients with advanced Parkinson's disease: A [15O] H2O PET study. *Human Brain Mapping*, *30*(12), 3901. https://doi.org/10.1002/HBM.20815

Baltadjieva, R., Giladi, N., Gruendlinger, L., Peretz, C., & Hausdorff, J. M. (2006). Marked alterations in the gait timing and rhythmicity of patients with de novo Parkinson's disease. *European Journal of Neuroscience*, *24*(6), 1815–1820. https://doi.org/10.1111/J.1460-9568.2006.05033.X

Baradaran, N., Tan, S. N., Liu, A., Ashoori, A., Palmer, S. J., Wang, Z. J., Oishi, M. M. K., & McKeown, M. J. (2013). Parkinson's Disease Rigidity: Relation to Brain Connectivity and Motor Performance. *Frontiers in Neurology*, *4*. https://doi.org/10.3389/FNEUR.2013.00067

Beach, T. G., Adler, C. H., Lue, L. F., Sue, L. I., Bachalakuri, J., Henry-Watson, J., Sasse, J., Boyer,

S., Shirohi, S., Brooks, R., Eschbacher, J., White, C. L., Akiyama, H., Caviness, J., Shill, H. A., Connor, D. J., Sabbagh, M. N., & Walker, D. G. (2009). Unified Staging System for Lewy Body Disorders: Correlation with Nigrostriatal Degeneration, Cognitive Impairment and Motor Dysfunction. *Acta Neuropathologica*, *117*(6), 613. https://doi.org/10.1007/S00401-009-0538-8

Benninger, D. H., Thees, S., Kollias, S. S., Bassetti, C. L., & Waldvogel, D. (2009). Morphological differences in Parkinson's disease with and without rest tremor. *Journal of Neurology*, *256*(2), 256–263. https://doi.org/10.1007/S00415-009-0092-2

Berardelli, A., Rothwell, J. C., Thompson, P. D., & Hallett, M. (2001). Pathophysiology of bradykinesia in Parkinson's disease. *Brain*, *124*(11), 2131–2146. https://doi.org/10.1093/BRAIN/124.11.2131

Berman, S. B., & Miller-Patterson, C. (2019). PD and DLB: Brain imaging in Parkinson's disease and dementia with Lewy bodies. *Progress in Molecular Biology and Translational Science*, *165*, 167–185. https://doi.org/10.1016/BS.PMBTS.2019.07.009

Boeve, B. F., Silber, M. H., Saper, C. B., Ferman, T. J., Dickson, D. W., Parisi, J. E., Benarroch, E. E., Ahlskog, J. E., Smith, G. E., Caselli, R. C., Tippman-Peikert, M., Olson, E. J., Lin, S. C., Young, T., Wszolek, Z., Schenck, C. H., Mahowald, M. W., Castillo, P. R., Del Tredici, K., & Braak, H. (2007). Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. *Brain*, *130*(11), 2770–2788. https://doi.org/10.1093/BRAIN/AWM056

Bohnen, N. I., & Cham, R. (2006). Postural Control, Gait, and Dopamine Functions in Parkinsonian Movement Disorders. *Clinics in Geriatric Medicine*, *22*(4), 797–812. https://doi.org/10.1016/J.CGER.2006.06.009

Bohnen, N. I., Frey, K. A., Studenski, S., Kotagal, V., Koeppe, R. A., Scott, P. J. H., Albin, R. L., & Müller, M. L. T. M. (2013). Gait speed in Parkinson disease correlates with cholinergic degeneration. *Neurology*, *81*(18), 1611–1616. https://doi.org/10.1212/WNL.0B013E3182A9F558

Bohnen, N. I., Kanel, P., & Müller, M. L. T. M. (2018). Molecular Imaging of the Cholinergic system in Parkinson's disease. *International Review of Neurobiology*, *141*, 211. https://doi.org/10.1016/BS.IRN.2018.07.027

Bohnen, N. I., Kaufer, D. I., Hendrickson, R., Ivanco, L. S., Lopresti, B. J., Constantine, G. M., Mathis, C. A., Davis, J. G., Moore, R. Y., & DeKosky, S. T. (2005). Cognitive correlates of cortical cholinergic denervation in Parkinson's disease and parkinsonian dementia. *Journal of Neurology 2005 253:2*, *253*(2), 242–247. https://doi.org/10.1007/S00415-005-0971-0

Braak, H., Bohl, J. R., Müller, C. M., Rüb, U., de Vos, R. A. I., & Del Tredici, K. (2006). The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. *Movement Disorders*, *21*(12), 2042–2051. https://doi.org/10.1002/MDS.21065

Braak, H., Del Tredici, K., Rüb, U., De Vos, R. A. I., Jansen Steur, E. N. H., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging*, *24*(2), 197–211. https://doi.org/10.1016/S0197-4580(02)00065-9

Burn, D. J., Rowan, E. N., Allan, L. M., Molloy, S., O'Brien, J. T., & McKeith, I. G. (2006). Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. *Journal of Neurology, Neurosurgery, and Psychiatry*, *77*(5), 585. https://doi.org/10.1136/JNNP.2005.081711

Chen, J. H., Huang, T. W., & Hong, C. T. (2021). Cholinesterase inhibitors for gait, balance, and fall in Parkinson disease: a meta-analysis. *Npj Parkinson's Disease 2021 7:1*, *7*(1), 1–7. https://doi.org/10.1038/s41531-021-00251-1

Cheng, H. C., Ulane, C. M., & Burke, R. E. (2010). Clinical Progression in Parkinson's Disease and the Neurobiology of Axons. *Annals of Neurology*, *67*(6), 715. https://doi.org/10.1002/ANA.21995

De Laat, K. F., Tuladhar, A. M., Van Norden, A. G. W., Norris, D. G., Zwiers, M. P., & De Leeuw, F. E. (2011). Loss of white matter integrity is associated with gait disorders in cerebral small vessel disease. *Brain*, *134*(1), 73–83. https://doi.org/10.1093/BRAIN/AWQ343

Deuschl, G., Bain, P., Brin, M., Agid, Y., Benabid, L., Benecke, R., Berardelli, A., Brooks, D. J., Elble, R., Fahn, S., Findley, L. J., Hallett, M., Jankovic, J., Koller, W. C., Krack, P., Lang, A. E., Lees, A., Lucking, C. H., Marsden, C. D., … Toloso, E. (1998). Consensus Statement of the Movement Disorder Society on Tremor. *Movement Disorders*, *13*(S3), 2–23. https://doi.org/10.1002/MDS.870131303

Dickson, D. W., Uchikado, H., Fujishiro, H., & Tsuboi, Y. (2010). Evidence in favor of Braak staging

of Parkinson's disease. *Movement Disorders*, *25*(S1), S78–S82. https://doi.org/10.1002/MDS.22637

Doty, R. (2012). Olfactory dysfunction in Parkinson disease. *NATURE REVIEWS | NEUROLOGY*, *8*, 329–339. https://doi.org/10.1038/nrneurol.2012.80

French, I. T., & Muthusamy, K. A. (2018). A review of the pedunculopontine nucleus in Parkinson's disease. *Frontiers in Aging Neuroscience*, *10*(APR), 99. https://doi.org/10.3389/FNAGI.2018.00099/XML/NLM

Fritz, N. E., Kegelmeyer, D. A., Kloos, A. D., Linder, S., Park, A., Kataki, M., Adeli, A., Agrawal, P., Scharre, D. W., & Kostyk, S. K. (2016). Motor performance differentiates individuals with Lewy body dementia, Parkinson's and Alzheimer's disease. *Gait & Posture*, *50*, 1–7. https://doi.org/10.1016/J.GAITPOST.2016.08.009

Gabell, A., & Nayak, U. S. L. (1984). The effect of age on variability in gait. *Journal of Gerontology*, *39*(6), 662–666. https://doi.org/10.1093/GERONJ/39.6.662

Galna, B., Lord, S., Burn, D. J., & Rochester, L. (2015). Progression of gait dysfunction in incident Parkinson's disease: impact of medication and phenotype. *Movement Disorders : Official Journal of the Movement Disorder Society*, *30*(3), 359–367. https://doi.org/10.1002/MDS.26110

Galna, B., Lord, S., & Rochester, L. (2013). Is gait variability reliable in older adults and Parkinson's disease? Towards an optimal testing protocol. *Gait & Posture*, *37*(4), 580–585. https://doi.org/10.1016/J.GAITPOST.2012.09.025

Geser, F., Wenning, G. K., Poewe, W., & McKeith, I. (2005). How to diagnose dementia with Lewy bodies: State of the art. *Movement Disorders*, *20*(S12), S11–S20. https://doi.org/10.1002/MDS.20535

Getz, S. J., & Levin, B. (2017). Cognitive and Neuropsychiatric Features of Early Parkinson's Disease. *Archives of Clinical Neuropsychology*, *32*(7), 769–785. https://doi.org/10.1093/ARCLIN/ACX091

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Nyenhuis, D., … Zweig, R. M. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale

(MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders*, *23*(15), 2129–2170. https://doi.org/10.1002/MDS.22340

Golbe, L. I., & Leyton, C. E. (2018). Life expectancy in Parkinson disease. *Neurology*, *91*(22), 991–992. https://doi.org/10.1212/WNL.0000000000006560

Goldman, J. G., Holden, S., Ouyang, B., Bernard, B., Goetz, C. G., & Stebbins, G. T. (2015). Diagnosing PD-MCI by MDS Task Force criteria: how many and which neuropsychological tests? *Movement Disorders : Official Journal of the Movement Disorder Society*, *30*(3), 402. https://doi.org/10.1002/MDS.26084

Gomperts, S. N. (2016). Lewy Body Dementias: Dementia With Lewy Bodies and Parkinson Disease Dementia. *Continuum : Lifelong Learning in Neurology*, *22*(2 Dementia), 435. https://doi.org/10.1212/CON.0000000000000309

Grillner, S., & Wallén, P. (1985). Central pattern generators for locomotion, with special reference to vertebrates. *Annual Review of Neuroscience*, *8*(1), 233–261. https://doi.org/10.1146/ANNUREV.NE.08.030185.001313

Gupta, D., & Kuo, S.-H. (2018). Prevalence and patterns of rest, postural and action tremor in drug-naïve Parkinson's disease (P2.066). *Neurology*, *90*(15 Supplement).

Haaxma, C. A., Helmich, R. C. G., Borm, G. F., Kappelle, A. C., Horstink, M. W. I. M., & Bloem, B. R. (2010). Side of symptom onset affects motor dysfunction in Parkinson's disease. *Neuroscience*, *170*(4), 1282–1285. https://doi.org/10.1016/J.NEUROSCIENCE.2010.07.030

Hausdorff, J. M., Yogev, G., Springer, S., Simon, E. S., & Giladi, N. (2005). Walking is more like catching than tapping: gait in the elderly as a complex cognitive task. *Experimental Brain Research 2005 164:4*, *164*(4), 541–548. https://doi.org/10.1007/S00221-005-2280-3

Helmich, R. C., Janssen, M. J. R., Oyen, W. J. G., Bloem, B. R., & Toni, I. (2011). Pallidal dysfunction drives a cerebellothalamic circuit into Parkinson tremor. *Annals of Neurology*, *69*(2), 269–281. https://doi.org/10.1002/ANA.22361

Henderson, E. J., Lord, S. R., Brodie, M. A., Gaunt, D. M., Lawrence, A. D., Close, J. C. T., Whone, A. L., & Ben-Shlomo, Y. (2016). Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet. Neurology*, *15*(3), 249–258. https://doi.org/10.1016/S1474-4422(15)00389-0

Hollman, J. H., McDade, E. M., & Petersen, R. C. (2011). Normative Spatiotemporal Gait Parameters in Older Adults. *Gait & Posture*, *34*(1), 111. https://doi.org/10.1016/J.GAITPOST.2011.03.024

Horak, F. B., Nutt, J. G., & Nashner, L. M. (1992). Postural inflexibility in parkinsonian subjects. *Journal of the Neurological Sciences*, *111*(1), 46–58. https://doi.org/10.1016/0022-510X(92)90111-W

Horning, S., & Davis, H. P. (2012). Aging and Cognition. *Encyclopedia of Human Behavior: Second Edition*, 44–52. https://doi.org/10.1016/B978-0-12-375000-6.00007-0

Ishihara, L. S., Cheesbrough, A., Brayne, C., & Schrag, A. (2007). Estimated life expectancy of Parkinson's patients compared with the UK population. *Journal of Neurology, Neurosurgery & Psychiatry*, *78*(12), 1304–1309. https://doi.org/10.1136/JNNP.2006.100107

Jellinger, K. A. (2003). Neuropathological spectrum of synucleinopathies. *Movement Disorders*, *18*(S6), 2–12. https://doi.org/10.1002/MDS.10557

Jellinger, K. A., & Korczyn, A. D. (2018). Are dementia with Lewy bodies and Parkinson's disease dementia the same disease? *BMC Medicine*, *16*(1), 1–16. https://doi.org/10.1186/s12916-018-1016-8

Jiang, Y., & Zsombok, A. (2014). Regulation of neurons in the dorsal motor nucleus of the vagus by SIRT1. *Frontiers in Neuroscience*, *0*(8 JAN), 270. https://doi.org/10.3389/FNINS.2013.00270/XML/NLM

Jokinen, P., Karrasch, M., Brück, A., Johansson, J., Bergman, J., & Rinne, J. O. (2013). Cognitive slowing in Parkinson's disease is related to frontostriatal dopaminergic dysfunction. *Journal of the Neurological Sciences*, *329*(1–2), 23–28. https://doi.org/10.1016/J.JNS.2013.03.006

Kao, A. W., Racine, C. A., Quitania, L. C., Kramer, J. H., Christine, C. W., & Miller, B. L. (2009). Cognitive and Neuropsychiatric Profile of the Synucleinopathies: Parkinson's Disease, Dementia with Lewy Bodies and Multiple System Atrophy. *Alzheimer Disease and Associated Disorders*, *23*(4), 365. https://doi.org/10.1097/WAD.0B013E3181B5065D

Kelly, V. E., Eusterbrock, A. J., & Shumway-Cook, A. (2012). A review of dual-task walking deficits in people with Parkinson's disease: Motor and cognitive contributions, mechanisms, and clinical implications. *Parkinson's Disease, 918719*. https://doi.org/10.1155/2012/918719

Kim, S. D., Allen, N. E., Canning, C. G., & Fung, V. S. C. (2012). Postural Instability in Patients with Parkinson's Disease. *CNS Drugs 2012 27:2*, *27*(2), 97–112. https://doi.org/10.1007/S40263-012-0012-3

Lanciego, J. L., Luquin, N., & Obeso, J. A. (2012). Functional Neuroanatomy of the Basal Ganglia. *Cold Spring Harbor Perspectives in Medicine*, *2*(12), a009621. https://doi.org/10.1101/CSHPERSPECT.A009621

Larsson, V., Torisson, G., & Londos, E. (2018). Relative survival in patients with dementia with Lewy bodies and Parkinson's disease dementia. *PloS One*, *13*(8). https://doi.org/10.1371/JOURNAL.PONE.0202044

Lewis, S. J.G., Foltynie, T., Blackwell, A. D., Bobbins, T. W., Owen, A. M., & Barker, R. A. (2005). Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. *Journal of Neurology, Neurosurgery & Psychiatry*, *76*(3), 343–348. https://doi.org/10.1136/JNNP.2003.033530

Lewis, Simon J.G., & Shine, J. M. (2016). The Next Step: A Common Neural Mechanism for Freezing of Gait. *The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *22*(1), 72–82. https://doi.org/10.1177/1073858414559101

Lippa, C. F., Duda, J. E., Grossman, M., Hurtig, H. I., Aarsland, D., Boeve, B. F., Brooks, D. J., Dickson, D. W., Dubois, B., Emre, M., Fahn, S., Farmer, J. M., Galasko, D., Galvin, J. E., Goetz, C. G., Growdon, J. H., Gwinn-Hardy, K. A., Hardy, J., Heutink, P., … Wszolek, Z. K. (2007). DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. *Neurology*, *68*(11), 812–819. https://doi.org/10.1212/01.WNL.0000256715.13907.D3

Lord, S., Galna, B., Coleman, S., Yarnall, A., Burn, D., & Rochester, L. (2014). Cognition and Gait Show a Selective Pattern of Association Dominated by Phenotype in Incident Parkinson's Disease. *Frontiers in Aging Neuroscience*, *6*(OCT). https://doi.org/10.3389/FNAGI.2014.00249

Lord, S., Galna, B., & Rochester, L. (2013). Moving forward on gait measurement: Toward a more refined approach. *Movement Disorders*, *28*(11), 1534–1543. https://doi.org/10.1002/MDS.25545

Lord, S., Galna, B., Verghese, J., Coleman, S., Burn, D., & Rochester, L. (2013). Independent domains of gait in older adults and associated motor and nonmotor attributes: validation of a

factor analysis approach. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *68*(7), 820–827. https://doi.org/10.1093/GERONA/GLS255

MacKay-Lyons, M. (2002). Central Pattern Generation of Locomotion: A Review of the Evidence. *Physical Therapy*, *82*(1), 69–83. https://doi.org/10.1093/PTJ/82.1.69

Magrinelli, F., Picelli, A., Tocco, P., Federico, A., Roncari, L., Smania, N., Zanette, G., & Tamburin, S. (2016). Pathophysiology of Motor Dysfunction in Parkinson's Disease as the Rationale for Drug Treatment and Rehabilitation. *Parkinson's Disease*, *2016*. https://doi.org/10.1155/2016/9832839

Mancini, M., & Horak, F. B. (2010). The relevance of clinical balance assessment tools to differentiate balance deficits. *European Journal of Physical and Rehabilitation Medicine*, *46*(2), 239. /pmc/articles/PMC3033730/

Manor, B., Abduljalil, A., Newton, E., & Novak, V. (2012). The Relationship Between Brain Volume and Walking Outcomes in Older Adults With and Without Diabetic Peripheral Neuropathy. *Diabetes Care*, *35*(9), 1907. https://doi.org/10.2337/DC11-2463

Mc Ardle, R, Del Din, S., Galna, B., Thomas, A., & Rochester, L. (2020). Differentiating dementia disease subtypes with gait analysis: feasibility of wearable sensors? *Gait & Posture*, *76*, 372–376. https://doi.org/10.1016/J.GAITPOST.2019.12.028

Mc Ardle, Ríona, Del Din, S., Galna, B., Thomas, A., & Rochester, L. (2020). Differentiating dementia disease subtypes with gait analysis: feasibility of wearable sensors? *Gait & Posture*, *76*, 372–376. https://doi.org/10.1016/J.GAITPOST.2019.12.028

McKeith, I. (2004). Dementia with Lewy bodies. *Dialogues in Clinical Neuroscience*, *6*(3), 333. https://doi.org/10.31887/DCNS.2004.6.3/IMCKEITH

McKeith, I., Boeve, B. F., DIckson, D. W., Halliday, G., Taylor, J. P., Weintraub, D., Aarsland, D., Galvin, J., Attems, J., Ballard, C. G., Bayston, A., Beach, T. G., Blanc, F., Bohnen, N., Bonanni, L., Bras, J., Brundin, P., Burn, D., Chen-Plotkin, A., … Kosaka, K. (2017). Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology*, *89*(1), 88–100. https://doi.org/10.1212/WNL.0000000000004058

Merory, J. R., Wittwer, J. E., Rowe, C. C., & Webster, K. E. (2007). Quantitative gait analysis in patients with dementia with Lewy bodies and Alzheimer's disease. *Gait & Posture*, *26*(3), 414–

419. https://doi.org/10.1016/J.GAITPOST.2006.10.006

Mirelman, A., Bernad-Elazari, H., Thaler, A., Giladi-Yacobi, E., Gurevich, T., Gana-Weisz, M., Saunders-Pullman, R., Raymond, D., Doan, N., Bressman, S. B., Marder, K. S., Alcalay, R. N., Rao, A. K., Berg, D., Brockmann, K., Aasly, J., Waro, B. J., Tolosa, E., Vilas, D., … Giladi, N. (2016). Arm swing as a potential new prodromal marker of Parkinson's disease. *Movement Disorders : Official Journal of the Movement Disorder Society*, *31*(10), 1527–1534. https://doi.org/10.1002/MDS.26720

Molano, J., Boeve, B., Ferman, T., Smith, G., Parisi, J., Dickson, D., Knopman, D., Graff-Radford, N., Geda, Y., Lucas, J., Kantarci, K., Shiung, M., Jack, C., Silber, M., Pankratz, V. S., & Petersen, R. (2010). Mild cognitive impairment associated with limbic and neocortical lewy body disease: a clinicopathological study. *Brain*, *133*(2), 540–556. https://doi.org/10.1093/BRAIN/AWP280

Montero-Odasso, M., Muir, S. W., & Speechley, M. (2012). Dual-Task Complexity Affects Gait in People With Mild Cognitive Impairment: The Interplay Between Gait Variability, Dual Tasking, and Risk of Falls. *Archives of Physical Medicine and Rehabilitation*, *93*(2), 293–299. https://doi.org/10.1016/J.APMR.2011.08.026

Morenas-Rodríguez, E., Sala, I., Subirana, A., Pascual-Goñi, E., Sánchez-Saudinós, M. B., Alcolea, D., Illán-Gala, I., Carmona-Iragui, M., Ribosa-Nogué, R., Camacho, V., Blesa, R., Fortea, J., & Lleó, A. (2018). Clinical Subtypes of Dementia with Lewy Bodies Based on the Initial Clinical Presentation. *Journal of Alzheimer's Disease*, *64*(2), 505–513. https://doi.org/10.3233/JAD-180167

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

Mussa, B. M., & Verberne, A. J. M. (2013). The dorsal motor nucleus of the vagus and regulation of pancreatic secretory function. *Experimental Physiology*, *98*(1), 25–37. https://doi.org/10.1113/EXPPHYSIOL.2012.066472

Nadkarni, N. K., McIlroy, W. E., Mawji, E., & Black, S. E. (2009). Gait and Subcortical Hyperintensities in Mild Alzheimer's Disease and Aging. *Dementia and Geriatric Cognitive*

Disorders, *28*(4), 295–301. https://doi.org/10.1159/000245158

Norton, B.), Strube, M.), & D2, P. (2001). Understanding Statistical Power. *Journal of Orthopaedic & Sports Physical Therapy*, *31*(6), 307–315. www.jospt.org

O'Brien, J. T., Colloby, S., Fenwick, J., Williams, E. D., Firbank, M., Burn, D., Aarsland, D., & McKeith, I. G. (2004). Dopamine Transporter Loss Visualized With FP-CIT SPECT in the Differential Diagnosis of Dementia With Lewy Bodies. *Archives of Neurology*, *61*(6), 919–925. https://doi.org/10.1001/ARCHNEUR.61.6.919

O'Shea, S., Morris, M. E., & Iansek, R. (2002). Dual Task Interference During Gait in People With Parkinson Disease: Effects of Motor Versus Cognitive Secondary Tasks. *Physical Therapy*, *82*(9), 888–897. https://doi.org/10.1093/PTJ/82.9.888

Pahapill, P. A., & Lozano, A. M. (2000). The pedunculopontine nucleus and Parkinson's disease. *Brain*, *123*(9), 1767–1783. https://doi.org/10.1093/BRAIN/123.9.1767

Parkinson's Disease vs. Parkinsonism. (2022). Parkinson's Foundation. https://www.parkinson.org/library/fact-sheets/parkinsonism

Peterson, D. S., & Horak, F. B. (2016). Neural Control of Walking in People with Parkinsonism. *Physiology*, *31*(2), 95. https://doi.org/10.1152/PHYSIOL.00034.2015

Pirker, W. (2003). Correlation of dopamine transporter imaging with parkinsonian motor handicap: how close is it? *Movement Disorders : Official Journal of the Movement Disorder Society*, *18 Suppl 7*(SUPPL. 7). https://doi.org/10.1002/MDS.10579

Pistacchi, M., Gioulis, M., Sanson, F., de Giovannini, E., Filippi, G., Rossetto, F., & Marsala, S. Z. (2017). Gait analysis and clinical correlations in early Parkinson's disease. *Functional Neurology*, *32*(1), 28–34. https://doi.org/10.11138/FNEUR/2017.32.1.028

Postuma, R. B., Lang, A. E., Gagnon, J. F., Pelletier, A., & Montplaisir, J. Y. (2012). How does parkinsonism start? Prodromal parkinsonism motor changes in idiopathic REM sleep behaviour disorder. *Brain*, *135*(6), 1860–1870. https://doi.org/10.1093/BRAIN/AWS093

Postuma, R., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A. E., Halliday, G., Goetz, C. G., Gasser, T., Dubois, B., Chan, P., Bloem, B. R., Adler, C. H., & Deuschl, G. (2015). MDS clinical diagnostic criteria for Parkinson's disease.

Movement Disorders, *30*(12), 1591–1601. https://doi.org/10.1002/MDS.26424

Rajmohan, V., & Mohandas, E. (2007). The limbic system. *Indian Journal of Psychiatry*, *49*(2), 132. https://doi.org/10.4103/0019-5545.33264

Rochester, L., Yarnall, A. J., Baker, M. R., David, R. V., Lord, S., Galna, B., & Burn, D. J. (2012). Cholinergic dysfunction contributes to gait disturbance in early Parkinson's disease. *Brain*, *135*(9), 2779. https://doi.org/10.1093/BRAIN/AWS207

Rosano, C., Aizenstein, H., Brach, J., Longenberger, A., Studenski, S., & Newman, A. B. (2008). Gait Measures Indicate Underlying Focal Gray Matter Atrophy in the Brain of Older Adults. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *63*(12), 1380. https://doi.org/10.1093/GERONA/63.12.1380

Rosano, C., Simonsick, E. M., Harris, T. B., Kritchevsky, S. B., Brach, J., Visser, M., Yaffe, K., & Newman, A. B. (2005). Association between physical and cognitive function in healthy elderly: the health, aging and body composition study. *Neuroepidemiology*, *24*(1–2), 8–14. https://doi.org/10.1159/000081043

Spillantini, M. G., Crowther, R. A., Jakes, R., Hasegawa, M., & Goedert, M. (1998). α-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(11), 6469. https://doi.org/10.1073/PNAS.95.11.6469

St Louis, E. K., & Boeve, B. F. (2017). REM Sleep Behavior Disorder: Diagnosis, Clinical Implications, and Future Directions. *Mayo Clinic Proceedings*, *92*(11), 1723. https://doi.org/10.1016/J.MAYOCP.2017.09.007

Surmeier, D. J., Obeso, J. A., & Halliday, G. M. (2017). Selective neuronal vulnerability in Parkinson disease. *Nature Reviews. Neuroscience*, *18*(2), 101. https://doi.org/10.1038/NRN.2016.178

Takakusaki, K. (2017). Functional Neuroanatomy for Posture and Gait Control. *Journal of Movement Disorders*, *10*(1), 1. https://doi.org/10.14802/JMD.16062

Thanvi, B. R., & Lo, T. C. N. (2004). Long term motor complications of levodopa: clinical features, mechanisms, and management strategies. *Postgraduate Medical Journal*, *80*(946), 452–458. https://doi.org/10.1136/PGMJ.2003.013912

Tombu, M., & Jolicoeur, P. (2003). A Central Capacity Sharing Model of Dual-Task Performance. *Experimental Psychology: Human Perception and Performance*, *29*(1), 3–18. https://doi.org/10.1037/0096-1523.29.1.3

Tucker, D. M., & Williamson, P. A. (1984). Asymmetric neural control systems in human self-regulation. *Psychological Review*, *91*(2), 185–215. https://doi.org/10.1037/0033-295X.91.2.185

Verghese, J., Wang, C., Lipton, R., Holtzer, R., & Xue, X. (2007). Quantitative gait dysfunction and risk of cognitive decline and dementia. *Journal of Neurology, Neurosurgery, and Psychiatry*, *78*(9), 929–935. https://doi.org/10.1136/JNNP.2006.106914

Verlinden, V. J. A., Van Der Geest, J. N., Hofman, A., & Ikram, M. A. (2014). Cognition and gait show a distinct pattern of association in the general population. *Alzheimer's & Dementia*, *10*(3), 328–335. https://doi.org/10.1016/J.JALZ.2013.03.009

Vitorio, R., Hasegawa, N., Carlson-Kuhta, P., Nutt, J. G., Horak, F. B., Mancini, M., & Shah, V. V. (2021). Dual-Task Costs of Quantitative Gait Parameters While Walking and Turning in People with Parkinson's Disease: Beyond Gait Speed. *Journal of Parkinson's disease*, *11*(2), 653–664. https://doi.org/10.3233/JPD-202289

Walker, Z., Costa, D. C., Walker, R. W. H., Lee, L., Livingston, G., Jaros, E., Perry, R., McKeith, I., & Katona, C. L. E. (2004). Striatal dopamine transporter in dementia with Lewy bodies and Parkinson disease. *Neurology*, *62*(9), 1568–1572. https://doi.org/10.1212/01.WNL.0000123248.39847.1D

Wang, J., Yang, Q. X., Sun, X., Vesek, J., Mosher, Z., Vasavada, M., Chu, J., Kanekar, S., Shivkumar, V., Venkiteswaran, K., & Subramanian, T. (2015). MRI evaluation of asymmetry of nigrostriatal damage in the early stage of early-onset Parkinson's disease. *Parkinsonism & Related Disorders*, *21*(6), 590–596. https://doi.org/10.1016/J.PARKRELDIS.2015.03.012

Wilkins, K. B., Parker, J. E., & Bronte-Stewart, H. M. (2020). Gait variability is linked to the atrophy of the Nucleus Basalis of Meynert and is resistant to STN DBS in Parkinson's disease. *Neurobiology of Disease*, *146*. https://doi.org/10.1016/J.NBD.2020.105134

Wilson, J., Allcock, L., Mc Ardle, R., Taylor, J. P., & Rochester, L. (2019). The neural correlates of discrete gait characteristics in ageing: A structured review. *Neuroscience and Biobehavioral Reviews*, *100*, 344–369. https://doi.org/10.1016/J.NEUBIOREV.2018.12.017

Yogev, G., Giladi, N., Peretz, C., Springer, S., Simon, E. S., & Hausdorff, J. M. (2005). Dual tasking, gait rhythmicity, and Parkinson's disease: Which aspects of gait are attention demanding? *European Journal of Neuroscience*, *22*(5), 1248–1256. https://doi.org/10.1111/J.1460-9568.2005.04298.X

Yogev, G., Plotnik, M., Peretz, C., Giladi, N., & Hausdorff, J. M. (2007). Gait asymmetry in patients with Parkinson's disease and elderly fallers: when does the bilateral coordination of gait require attention? *Experimental Brain Research*, *177*(3), 336–346. https://doi.org/10.1007/S00221-006-0676-3

Zaccai, J., Brayne, C., McKeith, I., Matthews, F., & Ince, P. G. (2008). Patterns and stages of α-synucleinopathy. *Neurology*, *70*(13), 1042–1048. https://doi.org/10.1212/01.WNL.0000306697.48738.B6