Universidade Estadual Paulista
"Júlio de Mesquita Filho"
Faculdade de Ciências - Bauru

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DO MOVIMENTO – INTERUNIDADES

ALINE PRIETO SILVEIRA CIOLA

ASYMMETRY, DUAL TASK AND INTERSEGMENTAL COORDINATION IN GAIT OF PEOPLE WITH PARKINSON'S DISEASE

Bauru - SP

2024

Universidade Estadual Paulista
"Júlio de Mesquita Filho"
Faculdade de Ciências - Bauru

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DO MOVIMENTO – INTERUNIDADES

ALINE PRIETO SILVEIRA CIOLA

ASYMMETRY, DUAL TASK AND INTERSEGMENTAL COORDINATION IN GAIT OF PEOPLE WITH PARKINSON'S DISEASE

Thesis presented to the Faculty of Sciences of the Bauru Campus, São Paulo State University, as part of the requirements for obtaining the title of Doctor of Movement Sciences.

Advisor: Fabio Augusto Barbieri

Bauru

2024

UNIVERSIDADE ESTADUAL PAULISTA

Câmpus de Bauru

ATA DA DEFESA PÚBLICA DA TESE DE DOUTORADO DE ALINE PRIETO SILVEIRA CIOLA, DISCENTE DO PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DO MOVIMENTO, DA FACULDADE DE CIÊNCIAS - CÂMPUS DE BAURU.

Aos 18 dias do mês de dezembro do ano de 2024, às 13h, por meio de Videoconferência, realizou-se a defesa de TESE DE DOUTORADO de ALINE PRIETO SILVEIRA CIOLA, intitulada **ASYMMETRY, DUAL TASK AND INTERSEGMENTAL COORDINATION IN GAIT OF PEOPLE WITH PARKINSON'S DISEASE**. A Comissão Examinadora foi constituída pelos seguintes membros: Profa. Dra. PAULA FAVARO POLASTRI ZAGO (Participação Presencial) do(a) Departamento de Educação Física / UNESP - Faculdade de Ciências de Bauru - SP, Dra. CAMILA TORRIANI-PASIN (Participação Virtual) do(a) Physical Therapy and Movement Sciences / The University of Texas at El Paso (UTEP), Profa. Dra. NATALIA MADALENA RINALDI (Participação Virtual) do(a) Centro de Educação Física e Desportos / Universidade Federal do Espirito Santo - ES, Profa. Dra. ANA MARIA FORTI BARELA (Participação Virtual) do(a) Departamento de Educação Física / Universidade Cruzeiro do Sul de São Paulo - SP, Prof. Dr. RODRIGO VITORIO (Participação Virtual) do(a) Docente credenciado no Programa de Ciências da Motricidade / Northumbria University – Reino Unido. Após a exposição pela doutoranda e arguição pelos membros da Comissão Examinadora que participaram do ato, de forma presencial e/ou virtual, a discente recebeu o conceito final: APROVADA . Nada mais havendo, foi lavrada a presente ata, que após lida e aprovada, foi assinada pelo(a) Presidente(a) da Comissão Examinadora.

Profa. Dra. PAULA FAVARO POLASTRI ZAGO

Documento assinado digitalmente
gov.br
PAULA FAVARO POLASTRI ZAGO
Data: 19/12/2024 12:25:17-0300
Verifique em https://validar.iti.gov.br

C576a

Ciola, Aline Prieto Silveira
Asymmetry, dual task and intersegmental coordination in gait of people with Parkinson's disease / Aline Prieto Silveira Ciola. -- Bauru, 2024
150 f.

Tese (doutorado) - Universidade Estadual Paulista (UNESP), Faculdade de Ciências, Bauru
Orientador: Fabio Augusto Barbieri

1. Motor control. 2. Asymmetry. 3. Movement disorders. 4. Cognition. 5. Electroencephalography. I. Título.

Sistema de geração automática de fichas catalográficas da Unesp. Dados fornecidos pelo autor(a).

POTENTIAL IMPACT OF THIS RESEARCH

This thesis contributes to the Sustainable Development Goal 3 (SDG-3) by addressing health and well-being. Through the investigation of asymmetry, intersegmental coordination, and dual-task effects on the gait of individuals with Parkinson's disease, this work aims to enhance our understanding of their motor behavior and identify tasks that pose significant risks. The findings can inform future research and guide rehabilitation professionals in developing targeted strategies to slow disease progression and mitigate related consequences, such as falls, thereby improving the quality of life for this population.

IMPACTO POTENCIAL DESTA PESQUISA

Essa tese contribui com os Objetivos de Desenvolvimento Sustentável (ODS - 3). Ao investigar os efeitos da assimetria, coordenação intersegmentar e duplas tarefas no andar de pessoas com doença de Parkinson, esperamos contribuir com a saúde e bem-estar desses indivíduos. Estabelecendo informações de como é o comportamento motor desses indivíduos e quais tarefas representam riscos, é possível que estudos futuros e profissionais da reabilitação usem tais informações para desenvolver estratégias de tratamento para frear a evolução da doença e prevenir consequências relacionadas, como as quedas.

Dedico este trabalho a todos os participantes do Ativa Parkinson, a minha família e a Deus.

AGRADECIMENTOS

Agradeço a Deus pelo dom da vida e por permitir que eu tivesse saúde e energia para realizar esse trabalho. Desejo que essas descobertas possam ajudar muitas pessoas e que toda a honra e glória seja destinada à Ele.

Agradeço meu esposo (Tobias) pelo amor e suporte no dia a dia, pelos incentivos quando eu estava fraca e pela sua paciência quando inúmeras vezes precisei dedicar minha atenção e tempo à tese.

Agradeço a meus pais (Paulo e Tânia) por sempre acreditarem em mim, incentivarem meu estudo e dar todo amor e apoio emocional necessário. Vocês são minha inspiração de perseverança, ética e trabalho.

Agradeço também ao meu irmão Bruno, meus sogros Carla e Beto e aos demais familiares e amigos queridos que me ajudaram em diferentes fases da tese. Não citarei todos os nomes, mas vocês também foram essenciais em diversos momentos. Poder compartilhar alegrias e angústias com vocês fez parte desse processo.

Agradeço imensamente ao meu orientador. Fabinho, obrigada por todo o conhecimento compartilhado e por inúmeras vezes me tirar da zona de conforto. Hoje vejo a grande evolução acadêmica e profissional que tive graças a tantas oportunidades que você fornece a nós, seus alunos. Espero ter contribuído e deixado minha marca no MOVI-LAB.

Agradeço aos meus amigos e companheiros de laboratório pelo auxílio nas atividades e por todas as conversas e momentos compartilhados. As risadas e desabafos sempre me deram forças para continuar.

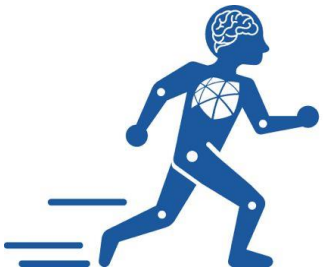
Agradeço aos participantes do Projeto Ativa Parkinson. Estar com vocês sempre foi um momento importante da minha semana. O “Ativa” não é só um projeto, ele se tornou uma família. Obrigada por todo o carinho nesses anos que acompanhei vocês de perto. Sentirei saudades.

Agradeço aos alunos da graduação que passaram pelo meu caminho. Poder ministrar aulas na graduação despertou o meu carinho pela docência e abriu uma porta que quero ultrapassar.

Não posso deixar de agradecer a Mauriceia, minha companheira quinzenal nesse processo. Estar com a mente saudável durante a pós-graduação, é um enorme privilégio atualmente.

Agradeço ao Prof. Christian Schenstedt e à Jana Seuthe por terem me recebido com acolhimento durante o período de intercâmbio na Alemanha.

Por fim, agradeço ao apoio da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Código de Financiamento 001 que financiou o meu período de doutorado no Brasil e, também, na Alemanha. Essa foi uma experiência valiosa que não teria vivido se não fosse o incentivo da CAPES para a internacionalização dos alunos.



MOVI-LAB

Laboratório de Pesquisa em Movimento Humano



ativa PARKINSON

DEF - UNESP

ABSTRACT

Motor disorders caused by asymmetry in Parkinson's disease (PD) are not limited to classic motor symptoms; they are also evident in the gait of people with PD (pwPD). Gait asymmetry (GA) tends to intensify in scenarios involving obstacles or dual-task conditions, where increased cognitive demands can interfere with gait control and diminish its automaticity. As the disease progresses, disruptions in cortical connectivity may further exacerbate asymmetry and reduce coordination. These findings suggest that higher-level cognitive functions may influence specific aspects of gait. The primary goal of this thesis (study #1) was to examine the effects of asymmetry, dual-tasking, and intersegmental coordination on the gait of pwPD. To achieve this, three studies were conducted. The first study aimed to systematically review the current literature and perform a meta-analysis to compare GA in pwPD to neurologically healthy older individuals (NHI). Additionally, the study evaluated the impact of dopaminergic medication on GA. Study #2 investigated whether obstacle circumvention to the more or less affected side in pwPD, performed concomitantly with a dual task (DT), would lead to worse intersegmental coordination. Seventeen pwPD and 17 NHI were asked to avoid an obstacle while listening to an audio recording of random numbers. Before starting the task, participants were instructed to focus on a specific number. At the end of each trial, their response was recorded. A total of 20 trials were conducted—10 for each side—with half performed under DT conditions. Parameters of asymmetry and intersegmental coordination, including axial coordination and coordination between the lower limbs, were analyzed. Study #3 evaluated gait under various DT conditions in 15 pwPD and 15 NHI. The level of task difficulty was categorized into six conditions: no dual task, very easy, easy, moderate, reasonably difficult, and difficult task. Similar to Study #2, participants listened to an audio recording of random numbers and were asked to memorize how many times a specific number appeared. The level of difficulty increased with the number of digits to be memorized. Spatial-temporal asymmetry and cortical activity were analyzed during these tasks. The main findings are highlighted as follow: Study #1 revealed that pwPD exhibited greater gait asymmetry across most spatial-temporal variables compared to NHI. Swing time asymmetry was identified as the most sensitive indicator of gait asymmetry in PD. Study #2 demonstrated group differences, with pwPD displaying worse intersegmental coordination, particularly axial coordination, compared to NHI. However, the most affected side did not significantly impair coordination during obstacle circumvention. Study #3 revealed greater spatial-temporal and cortical asymmetry in pwPD compared to NHI. The effects of task difficulty on cortical asymmetry were observed exclusively in pwPD. This thesis confirms that pwPD are more asymmetric in both spatial-temporal and cortical parameters compared to NHI. Furthermore, intersegmental coordination, particularly axial coordination, is more affected in PD. However, the influence of challenging environments and dual-task conditions warrants further investigation.

Key words: Motor Control; Asymmetry; Movement Disorders; Cognition; Electroencephalography.

RESUMO

As alterações ocasionadas pela assimetria não se limitam aos sinais motores clássicos, ela também é verificada no andar de pessoas com DP. Em situações com a presença de obstáculos ou sob a condição de duplas tarefas, a assimetria no andar (GA) parece ser ainda mais intensificada. Em ambas as situações altas demandas cognitivas podem influenciar no controle da marcha, comprometendo sua automaticidade. Com o avanço da doença, alterações na conectividade de áreas corticais também podem ser comprometidas. Com isso, manifestações assimétricas e menos coordenadas podem ocorrer, sugerindo que alguns aspectos da marcha podem ser influenciados por funções cognitivas de nível superior. Sendo assim, o objetivo dessa tese foi verificar o efeito da assimetria, dupla tarefa e coordenação intersegmentar no andar de indivíduos com doença de Parkinson. Para isso, uma sequência de três estudos foi desenvolvida. O estudo #1 teve como objetivo verificar sistematicamente a literatura atual e realizar uma meta-análise para investigar as diferenças entre a GA em pwPD em comparação com idosos neurologicamente saudáveis (GC) e avaliar o efeito da medicação dopaminérgica na GA. O estudo #2 verificou se o desvio para o lado mais ou menos afetado pela DP concomitante a uma DT levaria a uma pior coordenação intersegmentar. Dezessete indivíduos com DP e 17 NHI realizaram o desvio de um obstáculo enquanto um áudio contendo números aleatórios era falado. Antes de iniciar a avaliação do andar, era dito ao indivíduo qual o número ele deveria prestar atenção. Ao final da tentativa, foi verificado contabilizada a resposta. Foram realizadas 20 tentativas no total, 10 para cada lado, sendo metade delas com a realização da dupla tarefa concomitante. Os parâmetros de assimetria e coordenação intersegmentar axial e entre membros inferiores foi verificado. No estudo #3, 15 indivíduos com DP e 15 GC realizaram a avaliação do andar livre sob várias condições de dupla tarefa. O grau de dificuldade foi caracterizado em 6 condições: sem dupla tarefa (ST), muito fácil, fácil, moderada, razoavelmente difícil e difícil. Assim como no estudo #2, os indivíduos deveriam escutar um áudio contendo números aleatórios e memorizar quantas vezes um número “x” era falado. Com o aumento do nível de dificuldade da tarefa, a quantidade de números a memorizar era aumentada. Durante a realização dessas tarefas, foi analisada a assimetria espaço-temporal e da atividade cortical. Os resultados do estudo #1 evidenciaram que indivíduos com DP apresentaram maior assimetria dos parâmetros espaço-temporais comparados ao GC. A variável mais sensível para detectar a assimetria no andar de indivíduos com DP é o tempo de balanço. O estudo #2 também revelou diferenças entre os grupos: pessoas com DP apresentaram pior coordenação intersegmentar axial e de membros inferiores que o GC. Entretanto, o lado mais afetado pela DP não comprometeu o padrão de coordenação com grandes impactos durante o desvio de um obstáculo. Por fim, no estudo #3, indivíduos com DP exibiram maior assimetria dos parâmetros espaço-temporais e corticais comparados ao GC. Embora, os efeitos da dificuldade da tarefa na assimetria cortical tenham sido exclusivos em indivíduos com DP. Como principal conclusão da tese, é possível assumir que indivíduos com DP são mais assimétricos que seus pares neurologicamente sadios para os parâmetros espaço-temporais e corticais. Além disso, a coordenação intersegmentar, especialmente a axial, é mais comprometida. Os efeitos de ambientes desafiadores e duplas tarefas precisam de mais investigações.

Palavras-chave: Controle Motor; Assimetria; Desordens do movimento; Cognição; Eletroencefalografia.

LIST OF FIGURES

Figure 1. Flowchart including literature search and selection steps following PRISMA statement 39

Figure 2. Cumulative amount of the included articles per year. 40

Figure 3. On the left there are the type of outcomes and the respective number of studies that investigated each one. On the right, the number of studies showing significant (or non-significant) results in GA when comparing pwPD vs NHI. The arrow graphic represents significant greater asymmetry in pwPD compared to NHI 62

Figure 4. Forest plots of GA for (a) step length asymmetry, (b) swing time asymmetry, and (c) step time asymmetry for the comparison between pwPD at OFF state vs. NHI. PD: people with Parkinson's disease; NHI: neurologically age-matched healthy individuals; SMD: Standardized mean difference; CI: Confidence interval. 65

Figure 5. Forest plots of GA for (a) step length asymmetry, (b) swing time asymmetry, (c) step time asymmetry, and (d) stance time asymmetry for the comparison between pwPD at ON state vs. NHI. PD: people with Parkinson's disease; NHI: neurologically age-matched healthy individuals; SMD: Standardized mean difference; CI: Confidence interval. 66

Figure 6. Forest plots of GA for (a) step length asymmetry, (b) swing time asymmetry, and (c) and step time asymmetry for the comparison between PD at ON vs. OFF state of dopaminergic medication. PD: people with Parkinson's disease; SMD: Standardized mean difference; CI: Confidence interval 67

Figure 7. A) illustration of the task performed by the individuals (two steps of aprroach and two steps of circumvention phases). B) and C) displays data captured by VICON cameras using Nexus software. The left panels (B) provide a lateral view, while the right panels (C) present a top-down view, illustrating the individual, the obstacle, and the walkway. 91

Figure 8. Intersegmental coordination between thighs, legs and feet during an obstacle cirvumvention with and without a dual task to the more and less affected side. *: indicates main effects of group; #: # Indicates main effects of task; Combination of continuous rectangles indicates interaction effects between Group x side 94

Figure 9. Intersegmental coordination between head-pelvis (1), head-trunk (2) and trunk-pelvis (3) during an obstacle cirvumvention with and without a dual task to the more and less affected side. *: indicates main effects of group; #: # Indicates main effects of task 95

Figure 10. Asymmetry of spatial-temporal variables during gait without a dual task (ST) and with different difficulties of dual task 115

Figure 11. The figure below presents the values of ΔPSD asymmetry index of theta, alpha, beta and gamma bands. Those values were calculated in three cortical regions: Prefrontal, Sensoriomotor and Occipital cortex during gait without a dual task (ST) and with different difficulties of dual task 117

LIST OF TABLES

Table 1. Demographic and clinical characteristics of the included studies 42

Table 2. Gait protocols, GA index and main findings of the studies included in the review . 48

Table 3. Gait variables investigated in each study according to kinematic, kinetic, muscular (EMG) and/or neural gait feature. The third column shows the results presented only for GA values when comparing NHI and pwPD or GA with correlate variables..... 55

Table 4. Table 4 shows the scores for the participants' anthropometric characteristics and clinical assessments 92

Table 5. Mean and standard deviation values for the sample's anthropometric and clinical data 113

Table 6. Absolute error values presented by both groups when performing the cognitive task while seated and while walking..... 114

Table 7. The table presents a synthesis of data from the current literature, highlighting the main findings of this thesis and offering recommendations for future studies 131

SUMMARY

CHAPTER 1 – Contextualization **16**
1.1 Introduction 17
1.1.1 Asymmetry in people with PD 18
1.1.2 Asymmetry on gait of people with PD 20
1.1.3 Dual task and gait asymmetry: what the literature shows and what we can do to move forward? 21
1.2 Objectives and design of the thesis 23
1.3 Hypotheses 24
References 26
CHAPTER 2 – Study 1: Gait Asymmetry in Parkinson's Disease – A systematic review and meta-analysis (AsymmGait-Parkinson study) 31
Abstract 32
2.1 Introduction 33
2.2 Methods 34
2.2.1 Protocol and registration 34
2.2.2 Search strategy 35
2.2.3 Study selection and eligibility 35
2.2.4 Quality assessment 36
2.2.5 Data extraction and analysis 37
2.2.6 Quantitative data synthesis and analysis 37
2.3 Results 38
2.3.1 Study selection 38
2.3.2 Quality assessment 39
2.3.3 Research paradigm 40
a) Distribution of studies published per year 40
b) Sample characteristics 40
c) GA studies' comparison 46
d) Walking task 46
e) GA index's calculation 46
f) Outcomes analyzed 47
2.3.4 Overview of main findings of the systematic review 62
a) kinematic outcomes 62
b) kinetic outcomes 63

c) muscular outcomes 63
d) neural outcomes 64
2.3.5 Meta-analysis 64
a) PD OFF vs. controls 64
a) PD ON vs. controls 64
a) PD ON vs. PD OFF 65
2.4 Discussion 68
2.4.1 Dopaminergic medication partly improves gait asymmetry 70
2.4.2 Methodological quality 70
Wide variability among experimental protocols to assess GA in pwPD 71
2.4.3 Clinical implications, study limitations and future directions 72
2.5 Conclusion 73
References 73

CHAPTER 3 – Study 2: Intersegmental coordination during an obstacle circumvention is not affected by side of symptoms and a dual task in people with Parkinson's disease 83
Abstract 84
3.1 Introduction 85
3.2 Methods 86
3.2.1 Participants 86
3.2.2 Experimental design 87
3.2.3 Clinical evaluations 87
3.2.4 Gait evaluation 88
3.2.5 Data analysis 89
3.2.6 Statistical analysis 90
3.3 Results 92
3.3.1 Sample characteristics and clinical parameters 92
3.3.2 Intersegmental coordination during OC to the most and least affected side with ir without a dual task 92
Coupling between left x right thigh 92
Coupling between left x right leg 92
Coupling between left x right foot 93
Coupling between head x pelvis 93
Coupling between head x trunk 93
Coupling between trunk x pélvis 93
3.4 Discussion 96

3.5 Conclusion 99
References 100
4. CHAPTER 4 – Study 3: Influence of the difficulty of the cognitive task during walking on the asymmetry of spatial-temporal parameters and cortical activity in individuals with Parkinson's disease **104**
Abstract 105
4.1 Introduction 106
4.2 Methods 107
4.2.1 Participants and experimental design 107
4.2.2 Clinical assessment 108
4.2.3 Gait assessment 109
4.2.4 Data Analysis 110
Spatial-temporal data 110
Cortical activity data 111
4.2.5 Análise estatística 112
4.3 Results 112
4.2.1 Clinical evaluation and performance in the cognitive dual task 112
4.2.1 Effects of dual task difficulty on asymmetry of spatial-temporal and cortical parameters 114
Spatial-temporal parameters 114
Cortical parameters 115
4.4 Discussion 117
4.5 Conclusion 120
References 121
5 CHAPTER 5 – Final remarks 127
5.1 Final remarks 128
a) Are individuals with PD always asymmetrical? 128
b) Dual task as a model to study gait asymmetry in PD 128
c) Intersegmental coordination and gait asymmetry in gait of pwPD 129
d) Limitations, future suggestions and practical applications 129
References 132
APPENDICES 133
Appendix A - Description of the terms used for paper searching in each database 134
Appendix B - Questions of appraisal tool adapted from Galna et al. (2015) 135
Appendix C - Basic information about the studies included at systematic review. 136

Appendix D - Methodological quality appraisal results. Each question is the average of the evaluation of three authors. The last column presents the total score for each paper. The last line presents the average for each question 139

Appendix E - Equations, indexes, and other methods employed to calculate asymmetry during gait 140

Appendix F - Funnel plots of step length asymmetry, swing time asymmetry, step time asymmetry and stance time asymmetry for the comparison between pwPD at ON state vs. NHI 144

Appendix G - Asymmetric spatial-temporal parameters of PG compared to CG during the approach and circumvention phases to the more and less affected side during the obstacle circumvention with and without a dual task 145

ANNEXES 146

Annex I - Ethics Committee approval 147

Annex II – PROSPERO registration number 150

CHAPTER 1 –
CONTEXTUALIZATION

1.1 INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease in the world, affecting 1-2 out of every 1000 individuals (Tysnes; Storstein, 2017). In Brazil, estimates projected a prevalence of 340,000 people with the disease in the country by 2020 (Dorsey *et al*., 2006). Therefore, studies involving PD have been growing and are being highlighted by various research groups around the world, with the aim of helping with early diagnosis, understanding the mechanisms of the disease and possible treatments to mitigate its progression.

PD is characterized by the asymmetrical degeneration of dopaminergic cells in the substantia nigra of the midbrain (Lewis *et al.*, 2009). This degeneration causes motor signs/symptoms such as bradykinesia (slowness of movement), muscle rigidity, resting tremor and postural instability (Sant *et al*., 2008; Hughes, *et al.*, 2002; Hess, Hallett, 2017), which appear when there has already been a loss of 50-70% of the nigral neurons (Obeso *et al.*, 2000; Takakusaki *et al.*, 2004). At the beginning of the disease, signs and symptoms are present unilaterally (Djaldetti; Melamed, 2006; Segarra *et al.*, 2016; Kempster *et al.*, 1989; Uitti, 2005). As the disease progresses, symptoms can become bilateral, with changes predominating on the side where the disease began. In addition to motor impairments, changes in cortical activity are also present in PD, with patterns of cortical atrophy differing between the cerebral hemispheres throughout the course of the disease (Claassen *et al.*, 2016).

Locomotion, one of the main motor aspects affected in PD, can also manifest itself asymmetrically in tasks involving walking (Plotnik *et al*., 2008), for example during walking with crossing and avoiding obstacles (Barbieri *et al*., 2018a; Barbieri *et al*., 2018b). Asymmetrical gait in the elderly is directly related to a higher number of falls (Laroche; Cook; Mackala, 2012). Furthermore, in situations where tasks are concomitant with walking - dual tasks - the asymmetry seems to intensify even more (Yogev *et al*., 2007; Plotnik *et al*., 2005; Plotnik *et al*., 2009). Dual-tasking (DT) involves combining two tasks (each aimed at different goals), either motor or cognitive (Broeder *et al*., 2014). In PD, performing DTs in daily life impairs not only the spatial-temporal variables of gait (Yamada *et al*., 2020) but also bilateral symmetry and coordination during walking (Yogev *et al*., 2007). Asymmetry and reduced coordination during gait have been described as contributing to episodes of freezing (Plotnik *et al*., 2005; Plotnik; Giladi; Hausdorff, 2008), one of the most disabling signs of the disease.

However, in most studies, the DTs are performed under free walking conditions, without the major challenges of everyday life. There is considerable methodological variability in studies within the current literature (Kelly, Eusterbrock, Shumway-Cook, 2012), including a lack of standardization in the types of cognitive tasks used, their difficulty levels, and their effects on gait. Although cognitive deficits in PD and their impact on locomotor activities are well-documented (Raffegeau *et al*., 2019), the influence of task difficulty on gait dynamics remains a relatively unexplored area. Investigating cortical activity during cognitive dual tasks (DTs) offers valuable insights into capacity-sharing theories and the competition for attentional resources. Moreover, understanding the asymmetry in PD gait requires further exploration of contributing factors, such as reduced automaticity, altered cortical activity recruitment, and its impact on intersegmental coordination. This knowledge is essential for designing preventive measures to enhance safety and independence in individuals with PD. Furthermore, it can inform the development of locomotion-specific interventions, ultimately reducing hospitalization rates and associated healthcare costs from falls within this population.

The subsequent sections of this general introduction will provide an overview of asymmetry in Parkinson's disease (PD) and its implications for walking. Additionally, the topics will highlight current findings in the literature and explore areas where advancements can be made, particularly in understanding dual-tasking and asymmetry during gait in individuals with PD. Finally, the study's objectives and hypotheses will be presented.

1.1.1 Asymmetry in PD

Symmetry is often seen as a characteristic of a healthy system, while asymmetry can be indicative of harmful alterations to a system (McManus, 2005). Although the reason for the unilateral degenerative process in PD is unknown, possible genetic, structural, environmental, toxic and metabolic causes have been raised. Two main hypotheses have been proposed to explain the asymmetry: (I) the variation in the number of nigral dopaminergic cells between the hemispheres from birth and (II) the greater vulnerability of one side of the substantia nigra to neuronal death (Djaldetti; Melamed, 2006). According to the first hypothesis, the number of nigral neurons is different between the hemispheres from birth. With the degenerative process of PD,

both hemispheres are affected in a similar way; however, due to the baseline difference in the number of cells, one hemisphere reaches vulnerability first. The second hypothesis argues that as the degenerative process begins, one side of the substantia nigra is more susceptible to degeneration. Therefore, both sides are affected, but degeneration is more pronounced on one side. However, none of the hypotheses raised have been confirmed as a causal factor for the origin of the asymmetry.

Unilateral motor impairment in people with PD (pwPD) is present in more than half of all individuals (Uitti *et al*., 2005). This unilateral predominance of signs and symptoms affects people in the early stages and can persist throughout the progression of the disease, around 20 to 30 years (Djaldetti *et al*., 2006; Verreyt *et al*., 2011). The changes caused by asymmetry are not limited to the classic motor signs of the disease (Miller-Patterson *et al*., 2018); it extends to everyday locomotor activities (Barbieri *et al*., 2018a, Boonstra *et al*., 2014), as well as leading to functional and structural changes in the cerebral cortex (Claassen *et al*., 2016).

Cerebral asymmetry is defined by the functional, anatomical or neurochemical difference between the two hemispheres. In the early stages of PD, asymmetrical neurodegeneration of the nigrostriatal pathways occurs bilaterally (Wang *et al*., 2015). As the disease progresses, changes in the connectivity of cortical areas can also be compromised (Hawkes; Del Tredici; Braak, 2010). Contralateral structural and/or functional alterations in the nigrostriato-cortical circuit may be related to asymmetry in PD (De La Fuente-Fernandéz *et al*., 2000), which is one of the explanations for the asymmetrical negative effects on walking. The initial onset of symptoms in the right or left hemisphere may indicate a relationship between the laterality of motor symptoms and neural asymmetries. People with left-sided motor symptoms showed a “healthier” pattern of motor responses (Heinrichs-Graham *et al*., 2017). In addition, the laterality of symptoms can alter the response of cognitive functions, since the predominance of motor symptoms on the right is related to alterations in speech and verbal memory, while the predominant symptoms on the left reflect deficits in attention, visuospatial orientation and programming (Verreyt *et al*., 2011).

Moreover, cerebral atrophy in PD appears to be time-dependent, manifesting in different brain areas as the disease progresses. Specific cortical regions seem to experience atrophy with increasing disease duration, with frontal brain regions being more susceptible in the early stages, while posterior regions are more affected as the

disease advances (Kempster *et al*., 1989; Wang *et al*., 2015). Additionally, during the initial course of the disease, cortical atrophy is observed in regions of the left hemisphere, apparently independent of symptom dominance or severity. In later stages, this atrophy extends to the right hemisphere and posterior brain regions (Claassen *et al*., 2016). Despite these insights, significant gaps remain regarding the cortical effects, their relationship with gait asymmetry, and the specific walking functions affected.

1.1.2 Gait asymmetry among individuals with Parkinson's disease

Numerous studies have shown that gait is significantly impaired in individuals with Parkinson's disease, even in its early stages, characterized by reduced walking speed and shorter stride length, progressing to moderate levels of impairment (Yang *et al*., 2008). In advanced stages of the disease, individuals often lose the ability to walk independently, making it impossible to assess gait asymmetry. Consequently, individuals with PD experience compromised daily activities, as gait is essential for maintaining independence and quality of life (Viteckova *et al*., 2018). Therefore, gait alterations, such as asymmetry, may serve as indicators for early diagnosis of PD (Maetzler; Hausdorff, 2012) and can also be a useful tool for evaluating the benefits of training (Alam *et al*., 2017).

People with PD may exhibit asymmetry in arm swing (Roggendorf *et al*., 2012; KWON *et al*., 2014), step duration (Barbieri *et al*., 2018a), step length (ROEMMICH *et al*., 2014), and swing phase of the legs (Yogev *et al*., 2007). Additionally, impairments involving asymmetric postural control and motor coordination (Beretta *et al*., 2015; Frazzitta *et al*., 2013; Plotnik; Giladi; Hausdorff, 2008; Boonstra *et al*., 2014; Barbieri *et al*., 2018b) may further damage locomotion in individuals with PD. Greater asymmetry has also been linked to the occurrence of freezing episodes during walking (Plotnik *et al*., 2005).

The limitations induced by gait asymmetry range from unrestricted walking (Plotnik; Giladi; Hausdorff, 2008) to more complex activities, such as crossing horizontal obstacles (Barbieri *et al*., 2018b). Barbieri and colleagues (2018b) observed that during obstacle crossing, there is an increase in asymmetry in the leading foot. In another study, Barbieri and colleagues (2018a) also found an increase in asymmetry during avoidance of vertical obstacles. The latter study concluded that individuals with PD adopted riskier obstacle avoidance strategies on the more affected side compared to

the less affected side of the body. Similar results were observed in neurologically healthy older adults; however, the changes were more pronounced in individuals with PD.

Another critical factor is the relationship between spatial-temporal gait asymmetries and reduced integrity of corpus callosum tracts that connect the supplementary motor area (SMA) and pre-SMA (Fling; Curtze; Horak, 2018). A lack of integrity in these structures may further impair the conception and sequential planning of movements. Moreover, increased interhemispheric synchronization in the brain may accompany the asymmetric symptoms of PD during walking, potentially resulting from asymmetric neural degeneration (Miron-Shahar *et al*., 2019). Given that cortical-level impairments are present in PD, tasks requiring competition for cortical attentional resources, such as dual-task activities, may exacerbate gait execution difficulties.

1.1.3 Dual Task and Gait Asymmetry: What the Literature Presents and Possible Advances

The ability to perform two activities simultaneously is defined as a dual task (Sala *et al*., 1995). DTs are integrated into various everyday contexts, including locomotor activities such as walking while conversing (a cognitive task) or holding an object (a motor task). Their effects appear to impair the performance of spatial-temporal gait variables in elderly individuals with PD (Yamada *et al*., 2020); for instance, when walking while talking on a cellphone, this population exhibits reduced speed and cadence, shorter step length, and increased single and double support times. Individuals with PD, beyond the motor deficits caused by the disease, also experience cognitive impairments (Foltynie *et al*., 2004; Muslimovic *et al*., 2005), which are closely related to locomotor difficulties in PD patients (e.g., increased gait variability and reduced stability; Brauer *et al*., 2011).

Performing these simultaneous tasks can involve either parallel or competing cognitive processes. In the case of walking while performing a cognitive task, this process occurs concurrently, leading to competition for cognitive resources. This competition results in reduced automatization and increased reliance on cortical resources through attentional processes (Wu; Hallett; Chan, 2015), ultimately impairing walking performance (Yogev *et al*., 2007). Consequently, cortical resources necessary for gait adjustments are not optimized efficiently or in parallel (Clark, 2015; Gilat *et al*.,

2017). PD patients, in addition to motor deficits related to walking, often face significant cognitive impairments (e.g., executive function, memory, and attention). Notably, executive function and attention play crucial roles in gait regulation (Maruyama; Yanagisawa, 2006; Amboni *et al*., 2008). This combination of factors leads to considerable walking disabilities (Amboni; Barone; Hausdorff, 2013), which are further exacerbated in PD due to motor control asymmetry. Hence, gait asymmetry could be a potential impairment in dual-task scenarios (Plotnik *et al*., 2009).

Although the knowledge surrounding gait deficits in PD patients during DT scenarios is extensive (Kelly; Eusterbrock; Shumway-Cook, 2012), the effects of DT on gait asymmetry still require further investigation. Additionally, the relationship between gait symmetry and cognitive function needs to be better understood. The necessity to allocate sufficient cognitive resources simultaneously for walking and a DT (motor or cognitive) could explain the observed impairments in gait symmetry. According to the capacity-sharing theory (Tombu; Jolicoeur, 2003), when two functions requiring the same resources are performed simultaneously, the performance of one or both functions may be compromised. This cognitive resource competition may well exceed the available resources, increasing gait asymmetry. Some studies (Yogev *et al*., 2007; Plotnik *et al*., 2005; Plotnik *et al*., 2009) have demonstrated that DT negatively affects gait symmetry parameters in PD patients.

Yogev *et al*. (2007) investigated the effects of DT on PD patients, elderly fallers, and healthy older adults. Participants performed habitual walking and walking with a cognitive DT (arithmetic calculations – subtracting 7). In normal walking conditions, swing time asymmetry was significantly greater in both patient groups compared to controls. Furthermore, for both patient groups (PD and fallers), asymmetry increased under DT conditions compared to habitual walking, suggesting a relationship between asymmetry regulation and cognitive function. Cognitive abilities were mildly impaired in both PD patients and idiopathic elderly fallers. Based on this and the observation that gait deteriorates when these individuals are exposed to cognitive loads, it can be suggested that older adults with motor deficits, cognitive deficits, or both may struggle to regulate gait rhythm and coordinate symmetric leg movements while walking. In such scenarios, where cognitive demand increases, walking becomes less automatic and more asymmetrical, indicating that gait symmetry is sensitive to cognitive load.

According to Yang *et al*. (2006), gait symmetry in healthy individuals was not affected by DT, contrary to findings in neurologically impaired patients (post-stroke). The suggestion is that individuals with more automated gait are not sensitive to the cognitive load of DT, thus maintaining symmetric gait under lower-level control. However, when gait becomes less automated (as in PD), sensitivity to cognitive load increases, manifesting as asymmetrical walking and requiring additional cognitive input. Nonetheless, there is still a lack of information regarding the point at which cognitive DT begins to impair walking and whether the level of task difficulty reaches a threshold in cognitive processing capacity, "exhausting" cognitive reserves and consequently impairing gait. It is hypothesized that DT effects are difficulty-dependent. Previous studies have indicated that locomotion was more affected in situations involving more complex cognitive tasks performed concurrently with walking (Holtzer *et al*., 2011) compared to simpler dual tasks (Galletly; Brauer, 2005; Strouwen *et al*., 2016). However, despite previous studies providing relevant insights into the effect of cognitive DT difficulty on the locomotion of elderly individuals with PD, it remains controversial whether any cognitive DT affects locomotion or if there is a difficulty threshold for task limitations.

One potential method of analysis that could advance the discussion of the effect of cognitive TD on gait asymmetry in pwPD is inter-limb coordination. Asymmetry is a metric used to check the level of difference between sides, hemibodies or limbs. While intersegmental coordination can verify the association between segments, joints and limbs during a movement. Reduced asymmetry and coordination during gait have been described as contributing to episodes of gait freezing, especially in conditions of DT (Plotnik *et al*., 2005; Plotnik; Giladi; Hausdorff, 2008). In addition, coordination between the hemibodies during gait seems to be affected by cognitive attentional demand. In healthy individuals, gait coordination occurs automatically, but in PD this task may require greater control, reducing its automaticity and impairing task performance (Wu, Hallett, 2009).

1.2 Objectives and design

The general aim of this study is to investigate asymmetry in the gait of pwPD and to analyze the effect of PD on asymmetry in spatial-temporal parameters, intersegmental coordination and neural activity. In order to respond to the gaps in the

literature and advance knowledge on the topics covered, a sequence of three studies (one review and two experimental) is proposed.

The first study aims to systematically investigate the main deficits that asymmetry causes in the locomotion of individuals with PD. Since asymmetry is a limiting symptom in the gait of pwPD, the way in which asymmetry affects the parameters linked to locomotion (kinetic, kinematic, muscular and cortical) is extremely important for understanding the consequences of this motor manifestation.

The second study aimed to determine whether individuals exhibiting asymmetrical gait during a dual-task scenario involving obstacle avoidance also demonstrate poorer intersegmental coordination, depending on the side of the circumvention. Both variables may be affected by the reduced automaticity of movement observed during dual-tasking. However, the existing literature has yet to establish a direct relationship between these two factors. Identifying a common underlying mechanism could offer new approaches to mitigate the negative effects on locomotion.

The third study sought to explore how the difficulty of a concurrent cognitive dual task during walking influences spatial-temporal asymmetry and cortical activity in individuals with Parkinson's disease (PD). More complex cognitive tasks are likely to impose greater challenges on gait in individuals with PD compared to simpler tasks. Nonetheless, the wide variability in protocols across the literature makes it difficult to ascertain the specific impact of cognitive task difficulty on walking performance, particularly whether a plateau effect may occur at higher levels of task complexity.

1.3 Hypotheses

Based on the general objectives of the project, three main hypotheses were proposed:

i) The confirmation, through articles already available in the literature, of deficits caused by the presence of asymmetry in the locomotion of individuals with Parkinson's disease (PD). These deficits are expected to manifest as greater asymmetry in kinematic, kinetic, electromyographic, and/or cortical variables, with a more pronounced asymmetry observed in individuals with PD compared to their healthy pairs;

ii) Gait asymmetry during a cognitive DT with obstacle circumvention will be accompanied by changes in intersegmental coordination between the lower limbs,

characterized by more in-phase movements and a predominant contribution of the “less affected” limb. Although Plotnik, Giladi, and Hausdorff (2008) associate poorer bilateral gait coordination with the presence of freezing of gait, we hypothesize that such impaired coordination will also be observed in participants without freezing due to the inherently challenging nature of the task. Regarding axial coordination, it is expected that a more in-phase movement pattern will emerge when performing obstacle circumvention combined with a DT, especially toward the side most affected by the disease, as obstacle crossing in this direction presents a greater challenge.

iii) There will be a threshold of difficulty beyond which asymmetry begins to manifest in spatial-temporal parameters and cortical activity in individuals with PD. Additionally, greater cortical asymmetry is expected in the prefrontal and sensorimotor regions when compared to individuals without the disease.

REFERENCES

ALAM, M. N. et al. Vertical ground reaction force marker for Parkinson's disease. **PLoS ONE**, v. 12, n. 5, p. e0175951, 2017.

AMBONI, M. et al. Freezing of gait and executive functions in patients with Parkinson's disease. Movement Disorders, v. 23, n. 3, p. 395-400, 2008.

AMBONI, M.; BARONE, P.; HAUSDORFF, J. M. Cognitive contributions to gait and falls: Evidence and implications. **Movement Disorders**, v. 28, n. 11, p. 1520-33, 2013.

BARBIERI, F.A. et al. Obstacle circumvention and eye coordination during walking to least and most affected side in people with Parkinson's disease. **Behavioural Brain Research**, v. 346, p. 105-114, 2018[a].

BARBIERI, F. A. et al. Obstacle avoidance increases asymmetry of crossing step in individuals with Parkinson's disease and neurologically healthy individuals. **Journal of Motor Behaviour**, v. 50, n. 1, p. 17-25, 2018[b].

BERETTA, V. S. et al. Challenging Postural Tasks Increase Asymmetry in Patients with Parkinson's Disease. **PLoS One**, v. 10, n. 9, p. e0137722, 2015.

BOONSTRA, T. A. et al. Parkinson's disease patients compensate for balance control asymmetry. **Journal of Neurophysiology**, v. 112, n. 12, p. 3227-3239, 2014.

BRAUER, S. G. et al. Single and dual task gait training in people with Parkinson's Disease: A protocol for a randomised controlled trial. **BMC Neurol**, v. 11, p. 90, 2011.

BROEDER, S. et al. The effects of dual tasking on handwriting in patients with Parkinson´s disease. **Neuroscience**, v. 263, p. 193–202, 2014.

CLAASSEN, D. O. et al. Cortical asymmetry in Parkinson's disease: early susceptibility of the left hemisphere. **Brain and Behavior**, v. 6, n. 12, p. e00573, 2016.

CLARK, D. J. Automaticity of walking: functional significance, mechanisms, measurement and rehabilitation strategies. Frontiers in Human Neuroscience, v. 9, p. 246, 2015.

DE LA FUENTE-FERNÁNDEZ, R. et al. Nigrostriatal dopamine system and motor lateralization. Behavioural Brain Research, v. 112, n. 1–2, p. 63–68, 2000.

DJALDETTI, R.; ZIV, I.; MELAMED, E. The mystery of motor asymmetry in Parkinson's disease. **The Lancet Neurology**, v. 5, p. 796-802, 2006.

DORSEY, E. R. et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. **Neurology**, v. 68, n. 5, p. 384–386, 2006.l

FLING, B. W.; CURTZE, C.; HORAK, F. B. Gait asymmetry in people with Parkinson's Disease is linked to reduced integrity of callosal sensorimotor regions. **Frontiers in Neurology**, v.9, p.215, 2018.

FOLTYNIE, T. et al. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. **Brain**, v. 127, p. 550-60, 2004.

FRAZZITTA, G. et al. Asymmetry and freezing of gait in parkinsonian patients. **Journal of Neurology**, v. 260, n.1, p. 71-76, 2013.

GALLETLY, R.; BRAUER, S. G. Does the type of concurrent task affect preferred and cued gait in people with Parkinson's disease? **Australian Journal of Physiotherapy**, v. 51, n. 3, p. 175–180, 2005.

GILAT, M. et al. Dopamine depletion impairs gait automaticity by altering cortico-striatal and cerebellar processing in Parkinson's disease. Neuroimage, v. 15, n. 152, p. 207-220, 2017.

HAWKES, C. H., DEL TREDICI, K.; BRAAK, H. A timeline for Parkinson's disease. **Parkinsonism & Related Disorders**, v. 16, p. 79–84, 2010.

HEINRICHS-GRAHAM, E. et al. The cortical signature of symptom laterality in Parkinson's disease. **NeuroImage: Clinical**, v. 14, p. 433-440, 2017.

HESS, C. W.; HALLETT, M. The Phenomenology of Parkinson's Disease. **Seminars in Neurology**, v. 37, n. 2, p. 109-117, 2017.

HOLTZER, R. et al. fNIRS study of walking and walking while talking in young and old individuals. **Journals of Gerontology - Series A Biological Sciences and Medical Sciences**, v. 66 A, n. 8, p. 879–887, 2011.

HUGHES, A. J. et al. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. **Brain**, v. 125, n. Pt 4, p. 861-70, 2002.

KELLY, V. E.; EUSTERBROCK, A. J.; SHUMWAY-COOK, A. A review of dual-task walking deficits in people with Parkinson's disease: motor and cognitive contributions, mechanisms, and clinical implications. **Parkinson's Disease**, v. 2012, p. 918719, 2012.

KEMPSTER, P. A. et al. Asymmetry of substantia nigra neuronal loss in Parkinson's disease and its relevance to the mechanism of levodopa related motor fluctuations. **Journal of Neurology, Neurosurgery, and Psychiatry**, v. 52, n. 1, p. 72–76, 1989.

KWON, K. et al. Is reduced arm and leg swing in Parkinson's disease associated with rigidity or bradykinesia? **Journal of the Neurological Sciences**, v. 341, p. 32-35, 2014.

LAROCHE, D. P.; COOK, S. B.; MACKALA, K. Strength asymmetry increases gait asymmetry and variability in older women. **Medice & Science in Sports & Exercise**, v. 44, n. 11, p. 2172–2181, 2012.

LEWIS, M. M. et al. **Asymmetrical lateral ventricular enlargement in Parkinson's disease. European Journal of Neurology**, v. 16, n. 4, p. 475-481, 2009.

MAETZLER, W.; HAUSDORFF, J. M. Motor Signs in the Prodromal Phase of Parkinson's Disease. **Movement Disorders**, v. 27, n. 5, p. 627-633, 2012.

MARUYAMA, T.; YANAGISAWA, N. Cognitive impact on freezing of gait in Parkinson's disease. Parkinsonism & Related Disorders, v. 12, p. S77-S82, 2006.

MCMANUS, I. C. Symmetry and asymmetry in aesthetics and the arts. **European Review**, v. 13, n. 2, p. 157–180, 2005.

MILLER-PATTERSON, C. et al. Motor asymmetry over time in Parkinson's disease. **Journal of the Neurological Sciences**, v. 393, p. 14-17, 2018.

MIRON-SHAHAR, Y. et al. Excessive phase synchronization in cortical activation during locomotion in persons with Parkinson's disease. **Parkinsonism & Related Disorders**, v. 65, p. 210-216, 2019.

MUSLIMOVIC, D. et al .Cognitive profile of patients with newly diagnosed Parkinson disease. **Neurology**, v. 25, p. 1239-45, 2005.
PLOTNIK, M. et al. Is freezing of gait in Parkinson's disease relates to asymmetric motor function? **Annals of Neurology**, v. 57, p. 656-663, 2005.

PLOTNIK, M.; HAUSDORFF, J. M. The role of gait rhythmicity and bilateral coordination of stepping in the pathophysiology of freezing of gait in Parkinson's disease. **Movement Disorders**, v. 23, n. S2, p. S444–S450, 2008.

PLOTNIK, M.; GILADI, N.; HAUSDORFF, J. M. Bilateral coordination of walking and freezing of gait in Parkinson's disease. **The European Journal of Neuroscience**, v. 27, p. 1999–2006, 2008.

PLOTNIK, M.; GILADI, N.; HAUSDORFF, J. M. Bilateral coordination of gait and Parkinson's disease: the effects of dual tasking. **Journal of neurology, neurosurgery, and psychiatry**, v. 80, n. 3, p. 347–350, 2009.

RAFFEGEAU, T. E. et al. A meta-analysis: Parkinson's disease and dual-task walking. **Parkinsonism & Related Disorders**, v. 62, p. 28-35, 2019.

ROEMMICH, R. T. et al. Locomotor adaptation and locomotor adaptive learning in Parkinson's disease and normal aging. **Clinical Neurophysiology**, v. 125, p. 313-319, 2014.

ROGGENDORF, J. et al. Arm swing asymmetry in Parkinson's disease measured with ultrasound based motion analysis during treadmill gait. **Gait & Posture**, v. 35, p. 116-20, 2012.

SALA, S. D. et al. Dual-Task Paradigm: A Means To Examine the Central Executive. **Annals of the New York Academy of Sciences**, v. 769, p. 161–172, 1995.

SANT, C. R. et al. Abordagem fisioterapêutica na doença de Parkinson. **Revista Brasileira de Ciências do Envelhecimento Humano**, v. 5, n. 1, p. 80-89, 2008.

SEGARRA, A. B. et al. Brain asymmetry and dopamine: beyond motor implications in Parkinson's disease and experimental hemiparkinsonism. **Revista de Neurologia**, v. 63, p. 415-421, 2016.

STROUWEN, C. et al. Are factors related to dual-task performance in people with Parkinson's disease dependent on the type of dual task? **Parkinsonism & Related Disorders**, v. 23, p. 23–30, 2016.

TAKAKUSAKI, K. et al. Role of basal ganglia-brainstem pathways in the control of motor behaviors. **Neuroscience Research**, v. 50, n. 2, p. 137-151, 2004.

TOMBU, M.; JOLICOEUR, P. A central capacity sharing model of dual-task performance. **Journal of Experimental Psychology: Human Perception and Performance**, v. 29, p. 3-18, 2003.
TYSNES, O. B.; STORSTEIN, A. Epidemiology of Parkinson's disease. **Journal of Neural Transmission**, v. 124, n. 8, p. 901–905, 2017.

VERREYT, N. et al. Cognitive differences between patients with left-sided and right-sided Parkinson's disease. A review. **Neuropsychology Review**, v. 21, n.4, p. 405-424. 2011.

VITECKOVA, S. et al. Gait symmetry measures:A review of current and prospective methods. **Biomedical Signal Processing and Control**, v. 42, p. 89-100, 2018.

UITTI, R. J. et al. Parkinson disease: handeness predicts asymmetry. **Neurology**, v. 64, p. 1925-1930, 2005.

WANG, J. et al. MRI evaluation of asymmetry of nigrostriatal damage in the early stage of early-onset Parkinson's disease. **Parkinsonism and Related Disorders**, v. 21, n. 6, p. 590-596, 2015.

WU, T.; HALLETT, M. Dual task interference in Parkinson's disease. **Touch Briefings**, p. 34–37, 2009.

WU, T.; HALLETT, M.; CHAN, P. Motor automaticity in Parkinson's disease. **Neurobiology of Disease**, v. 82, p. 226-234, 2015.

YAMADA, P. A. et al. Everyday tasks impair spatiotemporal variables of gait in olderadults with Parkinson's disease. **Human Movement Science**, v. 70, 102591.

YANG, B. et al. Feature extraction for EEG-based brain-computer interfaces by wavelet packet best basis decomposition. **Journal of Neural Engineering**, v. 3, n. 4, p. 251–6, 2006.

YANG, Y. R. et al. Relationships between gait and dynamic balance in early Parkinson's disease. **Gait and Posture**, v. 24, n. 4, p. 611-615, 2008.

YOGEV, G. et al. Gait asymmetry in patients with Parkinson's disease and elderly fallers: When does the bilateral coordination of gait require attention? **Experimental Brain Research**, v. 177, n. 3, p. 336-346, 2007.

CHAPTER 2

Study 1: Gait Asymmetry in Parkinson's Disease – A systematic review and meta-analysis (AsymmGait-Parkinson study)

Submited on: "Neuroscience & Biobehavioral Reviews"

Gait Asymmetry in Parkinson's Disease – A systematic review and meta-analysis (AsymmGait-Parkinson study)

Abstract

Background/Purpose: Gait asymmetry (GA) in people with Parkinson's disease (pwPD) has been inconsistently reported, leading to uncertainty about its prevalence and clinical significance. GA may relate to motor symptoms' lateralization and the effects of dopaminergic medication. The aim of this study was to systematically summarize the current literature and perform a meta-analysis to investigate the differences between GA in pwPD compared to healthy individuals and to evaluate the effect of dopaminergic medication on GA. **Results**: The review was registered in PROSPERO database (ID: CRD42021285067). The searching was conducted in the PubMed, Cochrane Library, Lilacs, PEDro and Scopus databases. The primary search resulted in 517 studies. After removing the duplicates, 417 studies remained for the analysis. After checking the full text, 39 studies with 1988 pwPD were included in this review. The meta-analysis showed that pwPD exhibited greater asymmetry in step length, step time, and swing time, particularly in the OFF state, with moderate effect sizes. Dopaminergic medication was associated with reduced swing time asymmetry. **Discussion**: Temporal aspects of GA, particularly swing time asymmetry, was most sensitive to detect differences in GA between pwPD and healthy controls and to indicate an effect of dopaminergic medication. The inconsistent findings across studies highlight the need for standardization in GA measurement. Understanding the neural mechanisms underlying GA may improve targeted therapies. Further research should explore GA in more challenging walking conditions and in free-living environments to enhance the clinical understanding of gait disturbances in PD.

2.1 Introduction

More than 65% of individuals with Parkinson's disease (PD) show a unilateral manifestation of motor symptoms [1,2]. The asymmetrical appearance of motor signs is a hallmark of PD and considered to be a "red flag" for the diagnosis of PD according to the criteria of the Movement Disorder Society [3]. Similarly, the UK Brain Bank criteria list accentuated asymmetry as a supporting finding for PD diagnosis [4].

Several pathophysiological causes for the asymmetrical manifestations are currently discussed, including i) uneven depletion of dopamine in the substantia nigra [5,6], ii) asymmetrical deregulation of the striatum, leading to further asymmetrical dysfunction of multiple circuits involving the basal ganglia and cortical regions [7–9], and iii) reduction in the integrity of the transcallosal fiber tract of the pre-supplementary and supplementary motor areas [10]. The accentuated unilateral symptoms lead to poorer motor performance of the most affected limb [11–13], but given the role of interlimb coordination, lower performance of the most affected limb might also impair motor outcome of the least affected limb for some tasks.

Gait asymmetry (GA) is defined as a dissimilarity in the pattern of movement between the left and right upper and lower extremities during walking [14]. Marked asymmetry is indicative of a substantially debilitating gait in people with PD (pwPD). Nearly half of pwPD exhibit differences in step length between their two sides [15]. GA, along with gait variability and impaired gait adaptability, is associated with freezing of gait (FOG), a debilitating symptom which is a major cause for falls in PD [10,16–18]. Indeed, degree of GA has been shown to correlate with the severity of FOG [18]. Additionally, pwPD with a history of falls present more GA compared to pwPD without falls [19 20]. Therefore, it is clinically relevant to understand how asymmetric movements impact walking and to identify which gait parameters are asymmetrical in pwPD.

GA can have a deleterious impact on motor function, potentially leading to uncoordinated bilateral gait control and impaired stepping in both the single and double support stance phases [21]. Both gait phases are correlated with medial-lateral sway during the standing position, which may be associated with instability in pwPD [22]. To illustrate, when the most affected limb is responsible for supporting the body's weight during the single stance phase, balance becomes more challenging due to deficits in the most affected limb, leading to increased asymmetry in the swing time of the contralateral limb [23]. Moreover, extended periods of double support stance may indicate an inability

to shift weight from side to side for the subsequent step [24]. Additionally, there is a reduction in the synchronization of brain activity controlling the most affected limb when pwPD are in the single stance phase, particularly in the beta band [25], which is associated with the activation in the motor area and processing of information [26]. Indeed, pwPD display greater cortical activity asymmetry compared to neurologically healthy individuals (NHI) during gait initiation, which can be interpreted as an adaptive response aimed at reducing motor asymmetry [27].

Asymmetry has been identified as one of three independent domains of Parkinsonian gait [28]. However, conflicting results exist in the literature about the degree of asymmetry of different gait features, limiting our understanding of its underlying mechanisms and clinical relevance. While some studies have reported greater asymmetry in spatial (i.e., step length) and temporal (i.e., step time) parameters in pwPD [10], others found increased asymmetry for only one of those domains when compared to healthy controls [29–31]. Another study found that while kinematic parameters have been identified to be asymmetric, kinetic parameters like ground reaction forces remain symmetric during overground unobstructed walking in pwPD [32]. In addition, the effects of dopaminergic medication on GA in pwPD also remain unclear. Some evidence suggests that GA is reduced under dopaminergic medication effects (ON state) [33,85]. However, step length asymmetry does not appear to differ between ON and OFF states (without dopaminergic medication) [33,34]. Therefore, it is necessary to summarize the findings of the existing studies with a meta-analysis and to clarify if the different findings in these studies are due to different methodologies such as different sample sizes, different PD stages investigated, or other factors. Moreover, investigating these factors will help understand the underlying mechanism of GA which might help develop tailored interventions to reduce GA in this population.

The aim of this systematic review with meta-analysis was to i) investigate which gait features are asymmetric in pwPD compared to NHI and ii) to evaluate whether antiparkinsonian medication improves outcomes of GA. We considered kinematic, kinetic, muscular and neural gait parameters.

2.2 Method

2.2.1 Protocol and registration

The protocol of this systematic review was registered in the PROSPERO database – International Prospective Register of Systematic Reviews (ID: CRD42021285067) and is available in full through the following link: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021285067. This review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [35] and Cochrane Handbook for Systematic Reviews of Interventions [36].

2.2.2 Search strategy

Initially, a systematic literature search was conducted until August 2024 in five databases - PubMed, Cochrane Library, Lilacs, PEDro and Scopus - to identify manuscripts that investigated GA in pwPD. Additional searches were performed in Google Scholar (Google LLC) when the full text was not available, and authors of relevant studies were contacted regarding unpublished material or further information on ongoing studies. Furthermore, all the references of the identified trials, relevant review articles, and current treatment guidelines were searched for further relevant articles. The search consisted of the following terms: i) "Parkin*", ii) ("asymm*" or "symm*"), and iii) ("gait" or "walk*" or "locomotion" or "mobility"), in the title, abstract and keywords. Here is an example of the search in PubMed: "Parkin*" AND ("asymm*" OR "symm*") AND ("gait" OR "walk*" OR "locomotion" OR "mobility"). The search was conducted using the Boolean operator "and" or "or" between the categories and each category was customized for each database (see details of the search terms in the Appendix A).

2.2.3 Study selection and eligibility

A population, intervention, comparison, outcome and study designs tool (a PICOS tool[35]) was used to select the eligibility, inclusion and exclusion criteria for the studies reviewed: i) Population: pwPD, ii) Intervention: not applicable, iii) Comparison: neurologically healthy individuals (NHI), or pwPD in ON vs. OFF state, iv) Outcome: gait parameters (kinematic, kinetic muscular or neural) between the left and right sides of the body, and v) Study-randomized controlled trials, non-randomized controlled trials, and non-randomized non-controlled trials.

Studies were included if 1) GA in pwPD during continuous overground unobstructed gait (e.g., gait initiation was not included) was investigated. The studies that analyzed GA only during challenging environments such as obstacle avoidance or dual tasking were not included in this systematic review. In studies analyzing GA both during continuous overground unobstructed walking and challenging environments, only asymmetry data of unobstructed walking were extracted; 2) the performance of both body sides (i.e., lower limbs or brain) was compared in kinematic, kinetic, electromyographic and/or neural gait features; 3) a control group was included or/and a comparison between ON and OFF states for pwPD; 4) they were original peer-reviewed research articles; and 5) studies were written in English. No restrictions on the publication date of the paper were considered.

We excluded studies with 1) small sample sizes of less than 10 participants per group; 2) a specific focus on gait in virtual environments or on the effects of medication other than dopaminergic medication; 3) animal models; 4) only involved treadmill walking; 5) an investigation of a new instrument or method to calculate asymmetry; 6) no available data on GA; and 7) robotic models or only descriptive methodologies.

2.2.4 Quality assessment

We used the Mendeley software (Mendeley Ltd., NY-EUA) to manage the records and remove any duplicate entries. From the initial yield, we combined original articles from electronic databases and specific searches. Titles, abstracts, and keywords were screened by three researchers (FBS, JRC, APSC) based on the established inclusion and exclusion criteria. If there were any discrepancies among the evaluators, they were resolved through a consensus discussion. The evaluators reviewed potential articles and adhered to a set of guidelines to enhance inter-rater reliability.

The methodological quality of the studies was assessed using a quality appraisal tool [37] (see Appendix B). This tool evaluates the internal and external validity of the measurement and the generalizability of the results. Each question is rated as '1' if the criterion was met, '0.5' if the information lacks detail or clarity, and '0' if the criterion was missing. A total score higher than seven indicates a high-quality study. Articles with a total score lower than seven were excluded from this systematic review. For articles with a total score <7, a consensus discussion among evaluators was used to

resolve any discrepancies. For articles with a total score >7, the mean values of the three evaluators were calculated.

2.2.5 Data extraction and analysis

One of the authors (APSC) extracted the papers and synthesized the data in tables. Two other authors (FBS and MHF) checked the tables to detect any inconsistencies between the annotations and the information provided in the articles. The data were coded for:

1) Sample characteristics: number of participants, age, and sex;

2) Clinical characteristics: disease stage (Hoehn & Yahr scale - HY), time since diagnosis (in years), side mostly affected by PD based on the motor examination of the UPDRS or MDS-UPDRS values and UPDRS or MDS-UPDRS motor part values;

3) Experimental procedures: period of the GA was acquired – ON vs. OFF state, method to calculate GA, and gait protocol;

4) Outcomes: asymmetry on kinematic, kinetic, muscular, and neural parameters;

5) Main findings: values of GA during unobstructed walking and variables correlated with GA in pwPD.

2.2.6 Quantitative data synthesis and analysis

The meta-analysis compared GA between pwPD at different dopaminergic medication periods (ON vs. OFF state) versus NHI. In addition, compared the effect of dopaminergic medication on GA in pwPD only. Therefore, three main comparisons were considered for the meta-analysis: “PD ON vs. NHI”, “PD OFF vs. NHI” and “PD ON vs. PD OFF”.

We screened all the articles included in the systematic review to ensure that they were similar in terms of the type of task and medication period. Following this, we grouped the studies that investigated specifically overground unobstructed walking at self-selected speed and separated the data according to the ON and OFF states of dopaminergic medication. The mean value and standard deviation of asymmetry outcomes were grouped for a subsequent analysis.

The meta-analysis only included the asymmetry data for groups of pwPD and NHI. Any additional groups beyond the PD and control groups in an article were not taken into consideration. For studies comparing PD with FOG vs. PD without FOG,

only data from the non-FOG group were included. Studies that assessed only individuals with FOG were excluded from the meta-analysis. In studies involving interventions, only pre-intervention asymmetry data were extracted. One study compared the use of footwear vs. walking barefoot; variables for the "with footwear" condition were used [38]. To conduct the meta-analysis for a given asymmetry variable, at least two studies were required to present their results. After verification, the following meta-analyses were performed to compare asymmetry between pwPD and their healthy peers: step length, step time, swing time and stance time. Furthermore, an additional analysis was carried out comparing the effects of dopaminergic medication (ON vs. OFF) only in pwPD for step length, step time and swing time asymmetry.

The meta-analysis was conducted using RStudio software (R Foundation for Statistical Computing, Vienna, Austria) [39]. Due to the different indexes of asymmetry between studies, the standardized mean differences (SMDs) for random effects were calculated for the outcomes as well their 95% confidence intervals (CIs). The inverse variance method calculated the combined estimates of the effects. This method assigns a weight to each study. Studies with smaller standard errors contribute more to the overall estimate of the effect [40]. The effect size (Hedges' g) was used to correct for SMD to small sample bias. SMDs were interpreted as follows: small (≥0.2), medium (≥0.5), and large (≥0.8) [41]. To evaluate the heterogeneity between studies, the restricted maximum-likelihood estimator for τ^2, the Q-Profile method for confidence interval of τ^2 and τ, and the I^2 were used [42]. I^2 values of 25%, 50% and 75% correspond to low, moderate and high heterogeneity, respectively [43]. The level of significance was set at $p < 0.05$.

2.3 Results

2.3.1 Study selection

Figure 1 depicts the flowchart with all steps from the initial search until the studies included in this systematic review and meta-analysis. The primary search resulted in 517 studies. After removing the duplicates, 417 studies remained for the analysis. After checking the title, keywords and abstract, 365 studies were excluded. Three authors read the full text of 52 studies (APSC, FBS and MHF). According to exclusion criteria, 13 studies were not suitable for inclusion in this systematic review: i) 11 studies [44,45,54,46–53] focused on developing and explaining new measures to calculate asymmetry, ii) one article [21] was excluded for not presenting the GA values; it only

presented the relationship between asymmetry and phase coordination index variables, and iii) one study [55] had a control group composed of young adults instead of NHI. Finally, 39 studies were included in this review [10,15,60–69,30,70–79,33,80–88,34,38,56–59] of which 17 were also included in the meta-analysis. Appendix C presents basic details of the reviewed studies, such as authors, publication year, country, title, and journal.

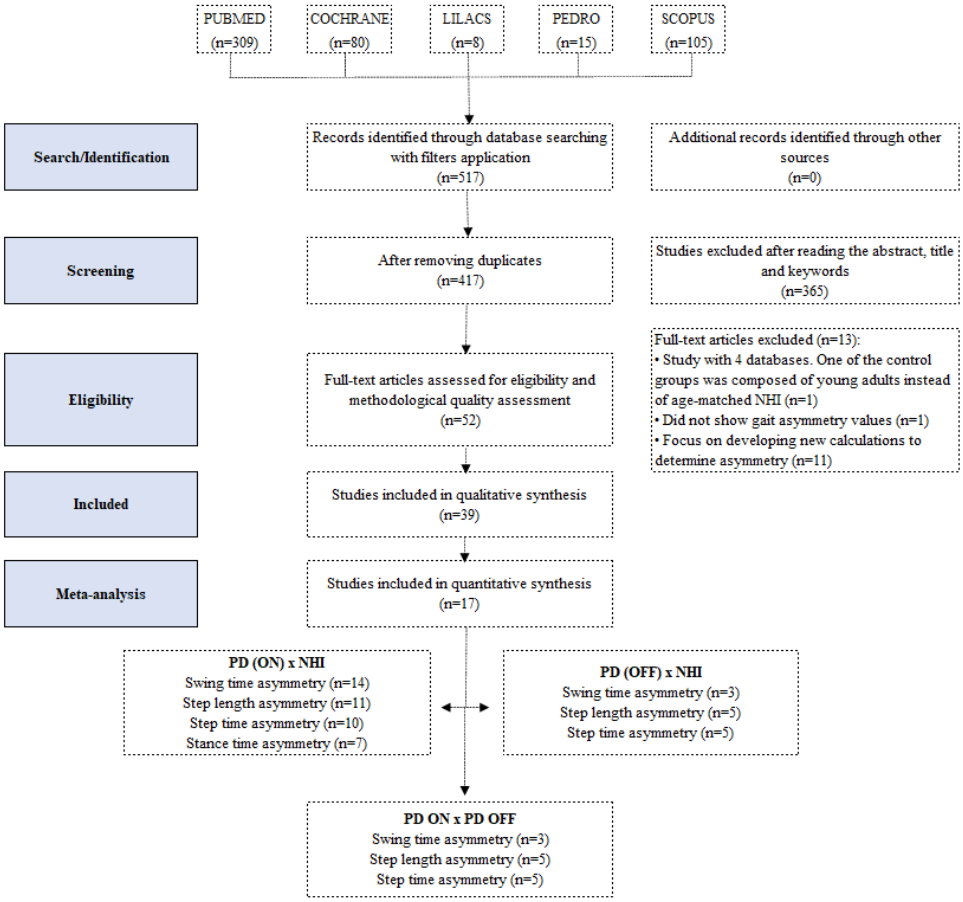


Figure 1. Flowchart including literature search and selection steps following PRISMA statement.

2.3.2 Quality assessment

The appraisal tool used to analyze the quality of the studies included in this review is presented in Appendix B. Appendix D presents the results of the methodological quality appraisal for each study, including the value for each question evaluated and the total score for each paper.

Evaluation of the 39 studies selected showed a mean ± standard deviation rating of methodological quality equal to 10 ± 1.4 points (minimum 7 points and maximum 13 points). All studies scored above 7 points in the methodological quality appraisal

analysis (out of a maximum of 14), indicating high paper quality. Over 53.8% of the papers scored above 10, surpassing 70% of the maximum score.

The questions with the lowest and highest mean scores reached were Q5 - Controlled co-variates - (mean of 0.01 ± 0.04 points) and Q1 - Research aims or questions stated clearly (1 ± 0 points), respectively. Based on the assessment of methodological quality, the studies included in this systematic review had the main risk of bias in the following areas: recruitment and sampling methods described (43.6% of papers included partially in the method); controlled covariates (95% of papers, only two studies partially included in the method); reliability of the methodology stated (84.6% of papers did not include in the method, only six studies did); internal validity of the methodology stated (79.5% of papers did not include in the method, only eight studies did); and clinical implications stated (48.7% of papers included partially or not in the method).

2.3.3 Research paradigm

a) Distribution of studies published per year

Figure 2 presents the annual distribution of publications. The earlier study included in this review was published in 1996 [63]. Only five studies were published in the first decade of the century (2001 – 2010). Almost 70% (n=27) of the studies were published in 2015 or later.

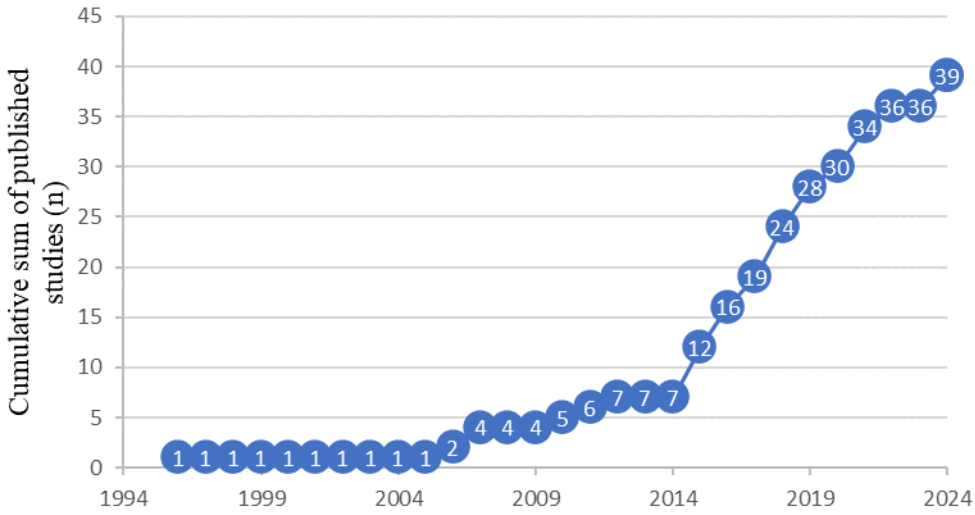


Figure 2. Cumulative amount of the included articles per year.

b) Sample characteristics

Details on demographic and clinical characteristics are presented in Table 1. In total 1988 pwPD and 1492 NHI were investigated in the 39 studies included in this review (Table 2). The average age for pwPD was 66±4 years old (minimum and maximum average: 57 – 75 years old) and for NHI was 66±5 years old. Three studies did not report the sex of participants [30,59,63], and three studies reported the number of participants in percentage (69.9% males and 30.1% females) [66,71,75]. Thus, approximately 1072 males and 638 females were assessed in the studies of this systematic review. In addition, two articles presented the same control group sample [69,70]. So, for data calculations of NHI in this review, we considered the participants' information of Vervoort et al. [69].

Motor symptoms assessed by the UPDRS or MDS-UPDRS (motor part-III) were reported in almost all studies (34/39) (Table 1). However, only a reduced number of the studies (4/39) analyzed the asymmetry of motor symptoms using UPDRS or MDS-UPDRS items [15,30,68,71]. HY stage was assessed by the majority of studies (33/39), except by six articles [33,38,62,65,72,83]. Thirteen articles [10,34,80,84,87,57,59,66,67,70,74,76,77] reported HY according to the mean value (HY= 2.2±0.6), one paper [82] according to the median (HY: 2), 10 studies [15,56,58,61,63,64,68,85,86,88] according to the number of participants at each stage (HY 0.5= 1; HY 1= 80; HY 1.5= 16; HY 2= 379; HY 2.5= 14; HY 3= 119; HY 4= 6) and nine articles [30,60,69,71,73,75,78,79,81] according to the level of disease (HY<3= 1; HY 1–3= 4; HY 2–3= 2; HY 1–4= 2).

A few articles reported the side most affected by PD (7/39) [30,62,68–70,80,82] according to the UPDRS or MDS-UPDRS scores for the right and left limbs. Despite the most affected side was most often the right side, the difference was minimal: 125 individuals with the right side as most affected vs. 111 individuals with the left side as most affected. The participants included in the studies had a disease duration of 6.1±2.9 years (minimum and maximum average: 1.3 and 12.4 years), and the effects of the dopaminergic medication on GA were investigated in 25 studies.

Table 1. Demographic and clinical characteristics of the included studies.

Authors	Age (years)	Sex (Male/Female)	MDS-UPDRS or UPDRS III (points)	UPDRS asymmetry	HY	MAS (R/L)	Disease duration (years)
Bailo et al. [#] (2024) [82]	• PD=72.5 • NHI=70.5	14/8 4/6	ON=31 (13.2; 42.9)	0.3 (0.1; 0.9) [$]	2 (1.5; 2.5)	10/12	NM
Baltadjieva et al. (2006) [56]	• PD=59.9±13.0 • NHI=62.1±11.0	24/11 13/9	NM	NM	1-2.5 (HY 1= 8; HY 1.5=4; HY 2=20; HY 2.5=3)	NM	1.5±0.9
Barbieri et al. (2018a) [30]	• PD=70.3±6.0 • NHI=70.7±7.5	NM	OFF=29.1±7.7 ON=24.1±6.2	*	< 3	3/10	NM
Barbosa et al. (2024) [34]	• PD=60.5±8.1 • NHI=60.7±8.8	10/7 20/14	21.8±8.9	NM	2.1±0.2	NM	12.1±5.1
Brodie et al. (2015) [81]	• PD=67.1±4.1 • NHI=65.9±6.9 • YC=29.6±6.6	7/3 6/5 5/4	NM	NM	1-4	NM	7.1±4.2
Buckley et al. (2019) [83]	• PD=69.2±9.9 • NHI=71.6±6.8	47/23 35/29	36.9±12.3	NM	NM	NM	NM
Danoudis et al. (2012) [84]	• PD+FOG=68.1±1.7 • PD-FOG=68.4±8.4 • NHI=69.7±5.0	14/2 9/1 9/1	23.2±5.4 15.9±3.6	NM	3.8±0.8 2.1±0.6	NM	12.4±5.0 (3-23) 2.3±2.4 (1-8)
De Bartolo et al. (2020) [72]	• DP=72.5±9.2 • NHI=72.1±5.6 • YA=32.3±5.9	14/6 8/12 8/12	35.05±16.9	NM	NM	NM	NM
Del Din et al. (2016) [86]	• PD=69.1±8.3 • NHI=69.8±7.2	34/13 27/23	32.0±10.1	NM	HY 1=5; HY 2=39; HY 3=3	NM	NM
Del Din et al. (2016) [85]	• PD=66.9±9.4 • NHI=66.6±7.7	20/10 15/15	19.5±10.7	NM	HY 1=8; HY 2=20; HY 3=2	NM	within 4 months of diagnosis

Djurić-Jovičić et al. (2017) [87]	• PD=59.8±10.5 • NHI=59.7±11.8	24/16 21/19	15.8±5.4	NM	1-1.5 (1.16±0.2)	NM	1.3±1.1
Ferreira et al. (2022) [73]	• PD(HY:1-2)=68.0±7.5 • PD(HY:2.5-3)=70.4±7.5 • NHI=68.0±6.0	21/21 13/8 18/45	24.7±10.1 32.9±9.7	NM	1-2 2.5-3	NM	5.2±3.6 5.5±3.8
Fling et al. (2018) [10]	• PD=68.7±8.0 • NHI=71.4±8.1	26/13 7/13	40.1±13.6	NM	2.4±0.6	NM	7.1±5.7
Galna et al. (2015) [88]	• PD=67.0±10.4 • NHI=69.4±7.7	81/40 78/106	25.5±10.4	NM	HY 1=28; HY 2=72; HY 3=21	NM	6.3±4.6 (months)
Gilmore et al. (2019) [33]	• PD=65.29±7.17 • NHI=63.09±8.09	41/21 7/4	OFF=29.6±9.8 ON=16.4±8.2	NM	NM	NM	8.9±4.1
Godi et al. (2021) [74]	• PD=70.0±7.8 • NHI=71.5±8.2	159/139 40/44	NM	NM	2.5±0.6 (1-4)	NM	7.6±5.4
Grajić et al. (2015) [57]	• PD=59.83±10.57 • NHI=59.79±11.85	24/16 23/20	15.8±5.4	NM	1-1.5 (1.1±0.2)	NM	1.3±1.1
Hackney, Earhart (2010) [58]	• PD=65.1±9.5 • NHI=65.0±10.0	56/22 56/17	27.5±9.2	NM	HY 0.5=1; HY 1=1; HY 1.5=11; HY 2=49; HY 2.5=8; HY 3=8	NM	8.2±5.0
Iosa et al. (2016) [75]	• PD=67.23±10.65 • NHI=61.57±12.3	58.6%/41.4% 78.6%/21.4%	30±10 (10-53)	NM	1-3	NM	7.6±4.7
Keloth et al. (2021) [76]	• PD=71.9±8.6 • NHI=67.2±3.7 • YC=27.9±2.4	17/7 17/7 18/6	25.6±10.9	NM	2.2±0.9 (1-3)	NM	4.2±3.1
Kleiner et al. (2018) [59]	• PD+FOG=64.8±8.8 • NHI=61.8±5.1	NM	21.3±7.8	NM	PD+FOG=2.7±0.76	NM	NM
Koh et al. (2019) [60]	• PD=63.1±8.1 • NHI=66.3±5.8	21/20 11/12	22.3±8.4	NM	1-3	NM	18.1±21.9 months

Leavy et al. (2018) [61]	• PD=75.0±5.9 • NHI=71.0±6.0	21/28 27/20	40.0±10.9	NM	HY 2=22; HY 3=27	NM	mean values=6.0
Lee et al. (2020) [77]	• PD=69.6±5.7 • NHI=71.4±4.9	45/29 27/25	40.9±13.3	NM	2.3±0.3 (1-3)	NM	NM
Lencioni et al. (2021) [78]	• PD=67.1 • NHI=58.1	3/7 4/6	NM	NM	2-3	NM	6.7 (1.4-12.0)
Liu et al. (2022) [79]	• PD=63.18±8.1 • NHI=61.52±6.1	40/28 22/26	PD early stage=34.5±10.6 PD advantage stage=46.6±12.8	NM	PD early stage=1-2 PD advantage stage=3-4	NM	4 (2-5.7)
Martinez et al. (2018) [62]	• PD=57±7.84 • NHI=56.5±12.4 • YC=29.5±3.63	10/1 8/4 9/7	15±4.2	NM	Mild stage (not mentioned the values of HY)	7/4	4±1.8
Miller et al. (1996) [63]	• PD=71.0±8.0 • NHI=68.0±7.0	NM	NM	NM	HY 2=15; HY 3=4	NM	7.2±4.0
Morris et al. (2017a) [64]	• PD=66.1±9.9 • NHI=68.8±7.1	79/40 78/106	24.9±10.4	NM	HY 1=28; HY 2=70; HY 3=21	NM	6.2±4.7
Morris et al. (2017b) [65]	• PD=69.8±9.7 • NHI=72.3±6.7	46/21 49/54	37.2±12.0	NM	NM	NM	Newly diagnosed idiopathic PD
Nanhoe-Mahabier et al. (2011) [66]	• PD+FOG=60.5±7.9 • PD-FOG=60.2±9.2 • NHI=57.9±7.3	71%/29% 70%/30% 60%/40%	35.4±8.9 30.6±7.0	NM	2.4±0.3 2.1±0.3	NM	9.6±3.6 7.7±4.5
Pereira et al. (2019) [38]	• PD=69.1±7.2 • NHI=70.8±5.5	7/9 6/9	28.3±7.2	NM	NM	NM	NM
Plotnik et al. (2007) [67]	• PD=71.9±1.5 • NHI=69.1±1.3 • YC=26.3±0.5	16/5 7/7 7/8	35.8±2.6	NM	2-3 (2.3±0.1)	NM	NM

Ren et al. (2015) [68]	• LPD=67.3±7.6 • RPD=66.9±5.8 • NHI=62.3±5.5	6/3 5/6 4/9	22.3±6.9 20.2±12.4	-0.3±0.3 0.3±0.4	HY 1.5=1; HY 2=5; HY 2.5=2; HY 3=1 HY 1=1; HY 2=6; HY 2.5=1; HY 3=3	0/9 11/0	3.7±2.9 5.9±4.7
Seuthe et al. (2024) [15]	• PD=66.8±10.0 • NHI=69.6±6.5	69/28 20/16	34.4±14.1	**	HY 1=1; HY 2=61; HY 3=29; HY 4=6	NM	9.8±6.8
Vervoort et al. (2015) [69]	• PIGD=61.4±10.9 • TD=57.3±8.8 • NHI=57.7±8.8	29/14 12/10 14/6	30.5±13.9 26.2±10.9	NM	1-3 1-3	26/17 14/8	7.2±4.3 4.8±2.7
Vervoort et al. (2016) [70]	• PD+FOG=65.8±9.9 • PD-FOG=58.2±9.9 • NHI=57.7±8.8	1/12 31/29 14/6	38.3±13.9 25.9±12.0	NM	2.2±0.8 2.0±0.6	6/7 36/24	7.9±5.4 5.8±3.3
Wu et al. (2021) [80]	• PD=65.6±10.1 • NHI=62.4±6.4	22/10 17/13	22.9±9.3	NM	1.73±0.44	12 (37.5%)/20 (62.5%)	2.4±1.3
Yogev et al. (2007) [71]	• PD=71.9±7.3 • NHI fallers=76.3±4.9 • NHI=67.5±3.5	81%/19% 47%/53% 55%/45%	20.4±7.9 2.9±1.9 0.2±0.6	0.2±0.1	2-3	NM	NM

NHI: control group of neurological healthy elderly individuals; MAS: most affected side (disease dominance); EF: Elderly fallers; +FOG: presence of FOG; -FOG: absence of FOG; HY: Hoehn & Yahr Scale; L: left; LFOG: predominant symptoms in the left side with FOG; LPD: predominant symptoms in the left side without FOG; NM: not mentioned; PD: Parkinson's disease group; PIGD: postural instability and gait disorder; R: right; RFOG: predominant symptoms in the right side with FOG; RPD: predominant symptoms in the right side without FOG; TD: tremor dominant; YC: young control group.

* Only informed that motor UPDRS items 20–23 and 25–26 was used to assess appendicular asymmetry.

** Motor symptom asymmetry as measured by MDS-UPDRS-III (items 3.3-3.8, 3.15-3.17); lower limb asymmetry (3.3, 3.7, 3.8, 3.17).

[#] Values are median (5th percentile; 95th percentile).

[$] Leg asymmetry index: Ratio between the difference of the worst and best leg, and the sum of the worst and best leg.

c) GA studies' comparison

With regard to the comparison of GA in pwPD vs. NHI, five studies also compared GA in pwPD vs. young adults [62,67,72,76,81], and one article compared PD vs. older fallers [71]. Furthermore, six studies considered specific PD characteristics during GA analysis: three studies compared individuals with FOG vs. non-FOG [66,70,84]; one study compared the clinical subtypes of the disease: tremor-dominant vs. postural instability and gait difficulty [69]; one study compared groups according to the disease stage (HY) [73]; and another study compared right side of symptom onset vs. left side of symptom onset [68].

Table 2 describes the walking tasks, methods to calculate GA, and the main findings of the studies included in this review. A total of 21 studies were conducted with pwPD only in the ON state [15,38,73,74,76–78,81–83,85,86,58,88,61–65,68,72]. Eight studies investigated GA in the OFF state [10,59,66,69,70,79,80,84], while four studies analyzed GA in both the ON and OFF states [30,33,34,75]. Furthermore, four studies [56,57,60,87] examined *de novo* pwPD (individuals who had not yet commenced prescribed PD-specific medications) and only two [67,71] did not mention the medication state during evaluations.

d) Walking task

The most frequently employed protocol for the assessment of gait abnormalities in pwPD was the unobstructed walking over a period of two minutes. The protocol was employed in seven studies [62,64,65,67,71,83,88]. Other studies employed between two and ten trials of varying distances - 6 to 25 m. The distances most utilized in the studies were 25 m (seven [62,64,65,67,71,83,88] studies), 10 m (seven studies [15,58,61,75,85,86]) and 8 m (five studies [10,38,60,63,66]).

e) GA index's calculation

There was a great variety of indexes used to measure GA in pwPD (Table 2). At least 20 different indexes were applied. Only one study did not describe the index used [38]. The two most used indexes for calculating GA were the asymmetry index [71] (seven studies) [56,58,62,67,71,75,77] and Lord and collaborators index [89] (five studies – factor analysis) [61,64,69,83,86]. The other indexes used to measure GA in pwPD were the symmetry angle index [60,79], symmetry index [30,73], absolute value between right and left sides [65,84,85,88], and latency corrected ensemble average (LCEAs) symmetry magnitude

[63]. In addition, three studies used conventional statistical analysis to compare the gait parameters between the most and least affected side steps [57,70,78]. The equations of indexes are provided in the Appendix E.

f) Outcomes analyzed

Table 3 outlines the gait variables investigated in each study and identifies the variables showing asymmetry during gait. All studies included in this systematic review examined at least one kinematic outcome related to GA, except for Keloth et al. [76]. The most assessed kinematic outcomes were swing time (n=23; 59%), step length (n=22; 56.4%), step time (n=20; 51.3%), stance time (n=11; 28.2%), step width (n=4; 10.3%), stride length (n=4; 10.3%), and joint angle (e.g., range of motion, and angular velocity of ankle, knee and hip – n=4; 10.3%). However, the asymmetry of kinetic (e.g., heel-strike, toe-off force, mid-stance force, time to heel-peak, time to mid-stance and time to toe-off force) [56,62] and muscular (Root mean square – RMS, magnitude and phase symmetry from the LCEA) [63,76] outcomes during walking were investigated for only four studies (10.3%). In addition, no study explored neural asymmetry during walking in pwPD, although two studies investigated the relationship of interhemispheric structural connectivity and functional connectivity with kinematic outcomes [10,70]. Other variables presented in a small number of studies were double support time, step velocity, stride time, harmonic ratio (HR) and auto symmetry.

Table 2. Gait protocols, GA index and main findings of the studies included in the review.

Authors	Number of participants	Status of medication	Gait protocol	GA index	Main findings
Bailo et al. (2024) [82]	• PD=22 • NHI=10	ON	• 6-minute walk test (6MWT) • Self-selected speed	HR and iHR	• HR and iHR in the VT Direction: correlation with MDS-UPDRS III, akinesia/bradykinesia and worst leg impairment • No correlation: best leg impairment and leg asymmetry index • The iHR in the ML direction correlated only with MDS-UPDRS III and 6MWT
Baltadjieva et al. (2006) [56]	• PD (de novo)=35 • NHI=22	de novo	• 4 x 20 m • Unobstructed walking • Self-selected speed	GI	• PD – greater asymmetry in gait temporal parameters, but not in the ground reaction forces
Barbieri et al. (2018a) [30]	• PD=13 • NHI=13	OFF/ON	• 5 x 10 m (per condition) • Unobstructed walking • Walking with obstacle avoidance • Self-selected speed	SI	• GA - no effects of groups for all GA variables
Barbosa et al. (2024) [34]	• PD=17 • NHI=34	OFF/ON	• 3 x 7 m (comprising going, turning and returning) • Self-selected speed	IA	• Asymmetry was not different across levodopa administration neither comparing PD and NHI
Brodie et al. (2015) [81]	• PD=10 • NHI=11 • YC=9	ON	• 5 x 22 m • Self-selected speed • Unobstructed walking with and without auditory cues (cued with varying paired-step asymmetries of: −10%, −5%, 0%, +5%, and +10%)	MA and AA	• Baseline: No difference in GA between PD and NHI • Symmetric cues – did not provide more symmetric gait
Buckley et al. (2019) [83]	• PD=70 • NHI=64	ON	• 2 minutes (25 m) • Self-selected speed	Based on [90] and AS	• The kinematic variables of asymmetry discriminated mildly the PD and NHI • Upper body variables should be measured with spatial-temporal

					characteristics
Danoudis et al. (2012) [84]	• PD+FOG=16 • PD-FOG=10 • NHI=10	OFF	• 4 x 8.3 m • Unobstructed walking with normalized step length: 100%, 75%, 50% and 25%	Asymmetry	• Step length affects GA and gait coordination of gait • PD+FOG-greater asymmetry vs. PD-FOG (step length and swing time) and NHI (swing and step time) • No differences between PD-FOG and NHI at preferred speed
De Bartolo et al. (2020) [72]	• PD=20 • NHI=20 • YA=20	ON	• 2 x 18 m (per condition) • Self-selected speed • 7 conditions: without music and with six different music tracks	Percentage of overlapping between curve accelerations of right and left sides	• Gait patterns (not GA) were altered by listening to music depending by the musical genre=among the three groups
Del Din et al. (2016) [86]	• PD=47 • NHI=50	ON	• Ambulatory environment: 4 x 10 m • Free-living (7 days) • Self-selected speed	Based on [90]	• PD and NHI – greater GA in unobstructed walking vs ambulatory environment • PD – greater GA in both conditions vs. NHI
Del Din et al. (2016) [85]	• PD=30 • NHI=30	ON	• 4 x 10 m • Unobstructed walking • Self-selected speed	Asymmetry	• Body-worn monitor is more sensitive data for asymmetry features
Djurić-Jovičić et al. (2017) [87]	• PD=40 • NHI=40	de novo	• 6 x 8 – 9 m (per condition) Self-selected speed • Unobstructed walking • Unobstructed walking + motor DT (carrying a glass of water) • Unobstructed walking + cognitive DT (serial 7 subtraction)	Asymmetry	• Asymmetry of step time – an indicator to classify the disease in early stages
Ferreira et al. (2022) [73]	• PD(HY:1-2)=42 • PD(HY:2.5-3)=21 • NHI=63	ON	• 3 x 8.5 m • Self-selected speed	SI	• ML algorithms have potential both to PD diagnosis and stage identification • Less importance weight to the asymmetry parameters

Fling et al. (2018) [10]	• PD=39 • NHI=20	OFF	• 3 x 8 m • Unobstructed walking • Self-selected speed	RI	• PD – greater asymmetry in step time and length vs. NHI • PD-lower transcallosal fiber tract integrity of the pre-SMA and S1 associated with greater asymmetry in step length asymmetry
Galna et al. (2015) [88]	• PD=121 • NHI=184	ON	• 2 minutes (25 m) • Unobstructed walking • Self-selected speed	Asymmetry	• PD – greater asymmetry in step time, swing time and stance time vs. NHI
Gilmore et al. (2019) [33]	• PD=62 • NHI=11	OFF/ON	• Self-selected speed • Forward (5 x 18 m) and backward (4 x 10 m) unobstructed walking	"PKMAS" Software	• Forward walking: a) ON – lower step time asymmetry vs OFF b) PD – greater asymmetry in step length and swing time vs. NHI (both in ON and OFF) • backwards walking: PD-greater asymmetry in step time and swing time vs. NHI (both in ON and OFF)
Godi et al. (2021) [74]	• PD=298 • NHI=84	ON	• 4 x 8.6 m • Barefoot walking • Self-selected speed	Asymmetry=|ln(left/right)| * 100	• Step and swing time asymmetry: greater in PD than NHI • Asymmetry variables have low discriminative accuracy to discriminate between PD and NHI compared to the other variables
Grajić et al. (2015) [57]	• PD=40 • NHI=43	de novo	• 6 x 8-9 m • Unobstructed walking • Self-selected speed	Side of disease onset vs. contralateral leg	• Gait symmetry in PD remained preserved • PD (side onset) x NHI (left side): PD is more asymmetric
Hackney, Earhart (2010) [58]	• PD=78 (FOG and Non-FOG) • NHI=74	ON	• 3 x 10 m (per condition) • Self-selected speed • Unobstructed forward and backward walking with and without DT (counting backward)	GI	• Freezers – greater GA vs. non-freezers • Greater asymmetry in swing time during all challenging conditions (backward and DT)

Iosa et al. (2016) [75]	• PD=70 • NHI=NM	ON (all) OFF (n=15)	• 5 x 10 m • Self-selected speed	SRI and GI	• GI was higher in PD vs. NHI. However, SRI was small for PD vs. NHI
Keloth et al. (2021) [76]	• PD=24 • NHI=24 • YC=24	ON	• Self-selected speed • Straight-line walking (greater than 2 m)	AI	• AI-PD was higher than NHI • PwPD-AI value was higher according to the sub-phases of gait cycler
Kleiner et al. (2018) [59]	• PD+FOG=33 • NHI=14	OFF	• 6 x 9 m (per condition) • Self-selected speed • Unobstructed walking with and without cognitive DT	Step length asymmetry	• PD+FOG – greater asymmetry in step length during unobstructed walking + cognitive DT
Koh et al. (2019) [60]	• PD=41 • NHI=23	de novo	• 2 x 8 m (per condition) • Self-selected speed • Unobstructed walking	SA	• PD – no difference between NHI for swing time and step length asymmetry • PD-shoulder and elbow asymmetries affects arm swing asymmetry • Asymmetries in spatial and temporal parameters – no predicted arm swing asymmetry
Leavy et al. (2018) [61]	• PD=49 • NHI=47	ON	• 6 x 10 m • Unobstructed walking • Self-selected speed	Based on [90]	• No correlation between perceived walking difficulties and GA parameters
Lee et al. (2020) [77]	• PD=74 • NHI=52	ON	• 3 x 15 m (per condition) • Walking in self-selected speed, 20% slower and 20% faster than self-selected speed	GI	• PD patients demonstrated higher GA at slower and preferred speeds than controls
Lencioni et al. (2021) [78]	• PD=10 • NHI=10	ON	• 5 x • Self-selected speed • Controls performed additional trials at slower velocities	More vs. less affected side	• No effects of lower limb were found on spatial-temporal parameters • PD-symmetry in gait stability, although both limbs showed larger MoS values compared to NHI

Liu et al. (2022) [79]	• PD=68 • NHI=48	OFF	• 3 x 5 m • Self-selected speed	SA	• PD – greater step length asymmetry, asymmetry of arm-swing angle and asymmetry of arm-swing velocity than NHI
Martinez et al. (2018) [62]	• PD=11 • NHI=12 • YC=16	ON	• 5 minutes (25 m) • Self-selected speed	GI	• PD – greater GA vs. NHI and YC • No difference between groups for kinematic and kinetic variables in both legs • GA – predicted by the affected side related to clinical onset, cognitive status and motor scale
Miller et al. (1996) [63]	• PD=19 • NHI=18	ON	• 2 x 8 m walks (speed not mentioned)	LCEAs	• The PD group had a significantly lower shape symmetry in the MG and TA muscles • The VL symmetry was similar in the PD and NHI groups • After a gait training program involving RAS, PD group had improvements in TA symmetry
Morris et al. (2017a) [64]	• PD=119 • NHI=184	ON	• 2 minutes (25 m) – per condition • Self-selected speed • Unobstructed walking with and without cognitive DT (digit span)	Based on [90]	• GA is unable to predict cognitive decline
Morris et al. (2017b) [65]	• PD=67 • NHI= 103	ON	• 2 minutes (25 m) • Self-selected speed • Free-living walking assessment continuously for 7 days	Asymmetry	• Free-living – greater asymmetry in step length vs. laboratory in both groups • Body worn monitors are more sensitive in detecting asymmetry features
Nanhoe-Mahabier et al. (2011) [66]	• PD+FOG=12 • PD-FOG=15 • NHI=15	OFF	• 6 x 8 m • Unobstructed walking • Self-selected speed	Step length and swing asymmetry	• No spatial stepping asymmetry among groups • No temporal stepping asymmetry freezers vs. non-freezers • Freezers and non-freezers – greater asymmetry in temporal stepping parameters vs. NHI • Correlation between UPDRS score and spatial stepping asymmetry

Pereira et al. (2019) [38]	• PD=16 • NHI=15	ON	• 3 x 8 m (per condition) • Self-selected speed • Walking barefoot and with habitual footwear	NM	• Walking with habitual footwear-greater GA in NHI, but not in PD
Plotnik et al. (2007) [67]	• PD=21 • NHI=14 • YC=15	NM	• 2 minutes (25 m) • Self-selected speed	GI	• PD – higher GA than NHI • PCI was moderately correlated with GA
Ren et al. (2015) [68]	• LPD=9 • RD=11 • NHI=13	ON	• 3 x condition • Self-selected speed • Unobstructed walking with eyes-open, egocentric reference point (walk toward a subjectively perceived center of a target) and vision-occluded	Asymmetry	• PD – direction of veering depends on the side of PD onset • LPD and RPD – no GA compared to NHI • LPD – lower GA in egocentric reference point vs. eyes-open
Seuthe et al. (2024) [15]	• PD= 97 • NHI=36	ON	• 10 x 10m • Unobstructed walking • Self-selected speed	IA	• Step length, swing time and stance time asymmetry was greater in PD than NHI • PD had higher asymmetry during gait, but not during turning • No correlations between symptom laterality and GA or turning asymmetry
Vervoort et al. (2015) [69]	• PIGD=43 • TD=22 • NHI=20	OFF	• At least 40 steps • Unobstructed walking • Self-selected speed	Based on [90]	• No differences in GA between PIGD and TD • No differences in GA between NHI and PD (PIGD and TD)
Vervoort et al. (2016) [70]	• PD+FOG=13 • PD-FOG=60 • NHI=20	OFF	• 10 x 6 m • Self-selected speed • Unobstructed walking with and without DT (auditory version of Stroop task)	Dominant x non-dominant leg	• PD – greater asymmetry in step length during DT vs. NHI (no significant) • PD-hypo- and hyper-brain connectivity vs. controls in DT-related neural networks

Wu et al. (2021) [80]	• PD =32 • NHI=30	OFF	• 7 m • Self-selected speed • Unobstructed walking with 180° turning and returned to their initial place	Same index as "step time or length or swing asymmetry"	• PD and NHI - no difference in any of the assessed gait parameters • Early-stage PD: presented increased variability but still symmetrical gait pattern
Yogev et al. (2007) [71]	• PD=21 • EF=15 • NHI=11	NM	• 2 minutes (25 m) – per condition • unobstructed walking without and with DT (serial 7 subtractions out loud)	GI	• PD and NHI fallers-greater GA vs. healthy controls • PD and NHI fallers – increased GA in DT condition • GA-associated with gait speed and gait variability in DT walking; no correlation with asymmetry of PD classic motor symptoms

NHI: control group of neurological healthy elderly individuals; DT: dual task; EF: Elderly fallers; +FOG: presence of FOG;-FOG: absence of FOG; LCEA: latency corrected ensemble average; LFG: predominant symptoms in the left side with FOG; LPD: predominant symptoms in the left side without FOG; LSWT: leg with the long swing time; MA: mean asymmetry – Brodie et al. (2015); MG: medial gastrocnemius; PD: Parkinson's disease group; PIGD: postural instability and gait disorder; RFOG: predominant symptoms in the right side with FOG; RPD: predominant symptoms in the right side without FOG; SSWT: leg with the short swing time; TA: tibialis anterior; TD: tremor dominant; VL: vastus lateralis; SMA: supplementary motor areas; S1: primary somatosensory cortice; YC: young control group; NM: not mentioned; de novo: without medication (de novo patients); Asymmetry=|right measure-left measure|; AI-Asymmetry index=100-([higher value of sEMG RMS/lower value of sEMG RMS] * 100); AS: auto symmetry-Moe-Nilssen & Helbostad (2004); GA – GA-Plotnik et al. (2005); GI – GA=|ln(SSWT/LSWT)|; HR= Harmonic ratio-Lowry et al. (2009); iHR= Improved harmonic ratio – Pasciuto et al. (2017); IA – Index of Asymmetry=(right side – left side)/(right side + left side); LCEA – latency corrected ensemble average-Miller et al. (1996); RI – ratio index=1-|left/right| * 100; SA – Symmetry angle-Zifchock et al. (2008); SI – Symmetry index-Robinson, Herzog, Nigg (1987); SIratio – Maximum angular velocity ratio-Zampieri et al. (2010); SRI-Symmetry ratio index=ratio between longer step and shorter step within 1 stride; Step time or length or swing asymmetry=([max time-min time] / max time) * 100%; Symmetric index=[(value of LASL-value of MASL)/(value of LASL+value of MASL)] * 100.

Table 3. Gait variables investigated in each study according to kinematic, kinetic, muscular (EMG) and/or neural gait feature. The third column shows the results presented only for GA values when comparing NHI and pwPD or GA with correlate variables.

Authors	Asymmetry variables investigated	Results
Bailo et al. (2024) [82]	Kinematic • HR • IHR both metrics for trunk acceleration in AP, ML and VT directions	PD: ↓ Harmonic Ratio and Improved Harmonic Ratio vertical asymmetry compared to NHI
Baltadjieva et al. (2006) [56]	Kinematic • Swing time asymmetry Kinectic • Heel strike force asymmetry • Toe-off force asymmetry	PD: ↑ swing time asymmetry compared to NHI PD = NHI: Heel-strike force asymmetry and Toe-off force asymmetry
Barbieri et al. (2018) [30]	Kinematic • Step length asymmetry • Step time asymmetry • Step width asymmetry • Step velocity asymmetry • Double support asymmetry	PD = NHI
Barbosa et al. (2024) [34]	Kinematic • Step length asymmetry • Step time asymmetry • Stance Time asymmetry • Swing Time asymmetry	PD = NHI
Brodie et al. (2015) [81]	Kinematic Mean asymmetry (MA) Absolute paired-step asymmetry (AA) both metrics applied for in step time	PD = NHI

Buckley et al. (2019) [83]	Kinematic • Step length asymmetry • Step time asymmetry • Swing time asymmetry • Stance time asymmetry Head and pelvis acceleration • Auto symmetry (AP, ML, VT) • HR (AP, ML, VT)	The kinematic variables of asymmetry discriminated mildly the PD and NHI Similar coupling between upper body accelerations and lower body spatial-temporal characteristics in both groups.
Danoudis et al. (2012) [84]	Kinematic • Step length asymmetry • Step time asymmetry • Swing time asymmetry	PD+FOG: ↑ step length asymmetry compared to NHI ↑ swing time asymmetry compared to NHI ↑ step time asymmetry compared to NHI PD-FOG = NHI
De Bartolo et al. (2020) [72]	Kinematic • Pelvis ROM asymmetry: Sagittal angles (tilt) Frontal angles (obliquity) Transversal angles (rotation)	Rotation and Obliquity asymmetry: different between groups
Del Din et al. (2016) [86]	Kinematic • Step length asymmetry • Step time asymmetry • Swing time asymmetry • Stance time asymmetry	PD: ↑ swing time and step length asymmetry compared to NHI
Del Din et al. (2016) [85]	Kinematic • Step length asymmetry • Step time asymmetry • Swing time asymmetry • Stance time asymmetry	PD: ↑ step length asymmetry compared to NHI
Djurić-Jovičić et al. (2017) [87]	Kinematic • Step length asymmetry • Step time asymmetry • Stride time asymmetry	Step time asymmetry: an indicator to classify PD in early stages

Ferreira et al. (2022) [73]	Kinematic • Step length asymmetry • Step width asymmetry • Step time asymmetry • Step velocity asymmetry • Step double support asymmetry • Step single support asymmetry	Asymmetry parameters had less importance to classify and rate PD
Fling et al. (2018) [10]	Kinematic • Step length asymmetry • Step time asymmetry	PD: ↑ step time and step length asymmetry compared to NHI
Galna et al. (2015) [88]	Kinematic • Step length asymmetry • Step time asymmetry • Swing time asymmetry • Stance time asymmetry	PD: ↑ step time, swing time and stance time asymmetry compared to NHI
Gilmore et al. (2019) [33]	Kinematic • Step length asymmetry • Step time asymmetry • Swing time asymmetry	PD: ↑ step length and swing time asymmetry compared to NHI ON: ↓ step time asymmetry compared to OFF
Godi et al. (2021) [74]	Kinematic • Step time asymmetry • Swing time asymmetry	PD: ↑ step time and swing time asymmetry compared to NHI
Grajić et al. (2015) [57]	Kinematic • Cyclo time • Stride length • Swing time • Coefficient of variation (CT, SL, ST) Right x Left side for all variables	PD: ↑ CT, ST and CV-SL (PD onset x NHI left side) NHI: ↑ CV-ST (PD other x NHI right side)
Hackney, Earhart (2010) [58]	Kinematic • Swing time asymmetry	PD: ↑ swing time asymmetry compared to NHI

Iosa et al. (2016) [75]	Kinematic • Step length asymmetry (SRI) • Swing time asymmetry (GI)	PD: ↑ swing time asymmetry compared to NHI
Keloth et al. (2021) [76]	EMG bilateral muscle asymmetry of RMS - TA bilateral muscle asymmetry of RMS - MG	PD: ↑ MG and TA asymmetry compared to NHI for total gait cycle
Kleiner et al. (2018) [59]	Kinematic • Step length asymmetry	PD: ↑ step length asymmetry compared to NHI
Koh et al. (2019) [60]	Kinematic • Step length asymmetry • Swing time asymmetry • Symmetry angle of shoulder • Symmetry angle of elbow	PD = NHI for swing time and step length
Leavy et al. (2018) [61]	Kinematic • Step length asymmetry • Step time asymmetry • Swing time asymmetry	The asymmetry parameters were not good at differentiating the groups.
Lee et al. (2020) [77]	Kinematic • Swing time asymmetry	PD: ↑ swing time asymmetry compared to NHI
Lencioni et al. (2021) [78]	Kinematic • Spatial-temporal (gait speed, stride length, cadence and step width) • Margin of Stability (MoS - AP and ML) for all variables according to lower limb (more and less affected)	PD = NHI
Liu et al. (2022) [79]	Kinematic • Step length asymmetry • Arm-swing angle asymmetry • Arm-swing velocity asymmetry	PD: ↑ step length, arm swing angle and arm swing velocity asymmetry compared to NHI

Martinez et al. (2018) [62]	Kinematic • Swing time asymmetry • Variables below were presented according to R and L sides: Stride time Stance time Swing time CV of stride, stance and swing time Percentage of stance time Percentage of swing time Kinetic • Variables below were presented according to R and L sides: Heel-peak force Mid-stance force Toe-off force Time to heel peak Time to mid-stance force Time to toe-off force	PD = NHI for all parameters PD: ↑ swing time asymmetry compared to young adults
Miller et al. (1996) [63]	Kinematic • Single-limb support symmetry EMG • Magnitude (shape) and phase (timing) symmetry from LCEA of MG, TA and VL muscles	PD = NHI - single-limb support asymmetry PD: ↓MG and TA asymmetry compared to NHI
Morris et al. (2017a) [64]	Kinematic • Step length asymmetry • Step time asymmetry • Swing time asymmetry • Stance time asymmetry	PD: asymmetry parameters were unable to predict cognitive decline in early PD
Morris et al. (2017b) [65]	Kinematic • Step length asymmetry • Step time asymmetry • Swing time asymmetry • Stance time asymmetry	Temporal asymmetry parameters were strongly associated with asymmetry domain for laboratory and free-living conditions for both groups.

Nanhoe-Mahabier et al. (2011) [66]	Kinematic • Step length asymmetry • Step time asymmetry	PD: ↑ step time asymmetry compared to NHI
Pereira et al. (2019) [38]	Kinematic • Step length asymmetry • Step time asymmetry • Swing phase asymmetry • Stance phase asymmetry • Step velocity asymmetry • Step width asymmetry	Habitual footwear: PD less asymmetric than NHI for step velocity.
Plotnik et al. (2007) [67]	Kinematic • Swing time asymmetry	PD: ↑ swing time asymmetry compared to NHI and young adults
Ren et al. (2015) [68]	Kinematic • Stride length asymmetry	PD = NHI
Seuthe et al. (2024) [15]	Kinematic • Step length asymmetry • Swing time asymmetry • Stance time asymmetry • Turning time asymmetry • Number of steps asymmetry	PD: ↑ step length, swing time and stance time asymmetry compared to NHI
Vervoort et al. (2015) [69]	Kinematic • Step length asymmetry • Step time asymmetry • Swing time asymmetry • Stance time asymmetry	PD = NHI

Vervoort et al. (2016) [70]	Kinematic • Step length asymmetry • Step time asymmetry • Stance time asymmetry • Swing time asymmetry • Double support time asymmetry	PD = NHI
Wu et al. (2021) [80]	Kinematic • Stride length asymmetry • Stride time asymmetry • Stance phase time asymmetry • Swing phase time asymmetry • Heel strike angle asymmetry • Toe-off angle asymmetry • ROM asymmetry - ankle joint, knee joint and hip joint	PD = NHI
Yogev et al. (2007) [71]	Kinematic • Swing time asymmetry	PD: ↑ swing time asymmetry compared to NHI

HR: Harmonic Ratio; IHR: Improved Hamonic Ratio; AP: anteroposterior; ML: mediolateral; VT: vertical; CT: cyclo time; SL: stride length; ST: swing time; MG: medial gastrocnemius; TA: tibialis anterior; VL: vastus lateralis; RMS: root mean square; ROM: Range of Motion.

2.3.4 Overview of main findings of the systematic review

A summary of the main findings in the studies included in this systematic review is described in Figure 3.

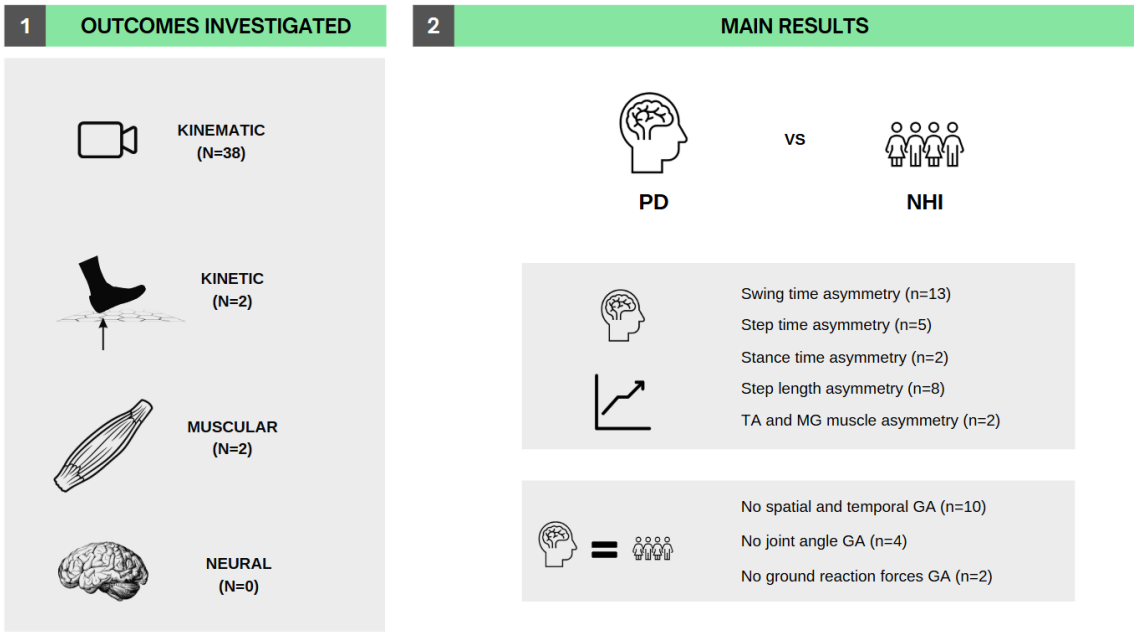


Figure 3. On the left there are the type of outcomes and the respective number of studies that investigated each one. On the right, the number of studies showing significant (or non-significant) results in GA when comparing pwPD vs NHI. The arrow graphic represents significant greater asymmetry in pwPD compared to NHI.

a) kinematic outcomes

The majority studies reported greater GA for temporal and spatial gait parameters during walking in pwPD compared to NHI. However, an important finding of this systematic review is that 10 studies reported no differences in GA between pwPD and NHI [30,34,60,62,68–70,78,80,81].

With regard to temporal parameters, the studies placed particular emphasis on the investigation of swing time and step time. A greater degree of swing [15,33,84,86,88,56–58,67,71,74,75,77] and step time [10,66,74,84,88] asymmetry was observed in pwPD compared to NHI during unobstructed walking. Only two studies reported greater stance time asymmetry in pwPD [15,88]. Moreover, the investigation of step length asymmetry was a consistent spatial parameter analyzed by the studies included in this systematic review. The findings indicated that step length asymmetry was greater in pwPD compared to

NHI [10,15,33,59,68,84–86]. Additionally, only one study reported greater step velocity asymmetry in pwPD compared to NHI [38]. Furthermore, Barbieri et al. [30] found that NHI had greater step velocity than PD in both limbs (the most and least affected limbs). No study reported asymmetry for double support time and step width.

Four studies investigated joint angle (range of motion) asymmetry during walking [60,72,79,80], but none of them found greater asymmetry in lower limb joint angles. Specifically, they reported differences in asymmetry for arm swing and trunk movement. PwPD showed less trunk rotation and obliquity asymmetry [72], and greater arm-swing angle [79] asymmetry compared to NHI. According to Koh and collaborators [60], shoulder and elbow asymmetries affected arm swing asymmetry in early PD

Few studies compared the effects of dopaminergic medication on spatial and temporal GA in pwPD (OFF vs. ON comparison) [30,33,34]. When it comes to temporal parameters, pwPD exhibited significantly lower asymmetry of step time under the influence of dopaminergic medication compared to OFF state [33,85]. In addition, in OFF state, step time was increased for the least affected limb compared to the most affected limb [30]. Despite the important role of dopaminergic medication in regulating kinematic parameters, not all studies have found dopaminergic effects on asymmetry in spatial and temporal stepping parameters. Some studies did not report reduction on asymmetry in step time [34], stance time [34] and swing time [33,34] between OFF and ON states. The only spatial parameter that was compared between the OFF and ON states was step length asymmetry. This spatial parameter was not affected by dopaminergic medication in two studies [33,34].

b) kinetic outcomes

Although only two studies investigated the asymmetry in kinetic outcomes [56,62] during walking, the results were consistent: no differences in the GA between pwPD and NHI. Baltadjieva and collaborators [56] found no significant group differences (*de novo* PD patients vs. NHI) in the asymmetry of the forces at heel-strike or of toe-off between the longer swing time and shorter swing time foot [56]. Martinez and collaborators [62] observed similar peak forces between groups at heel-peak, mid-stance and toe-off for right and left foot, as well for time to heel-peak, time to mid-stance and time to toe-off force.

c) muscular outcomes

Muscular asymmetry during walking was measured in two studies of this systematic review [63,76]. Miller and collaborators [63] investigated bilateral asymmetry in the medial gastrocnemius, tibialis anterior and vastus lateralis by latency-corrected ensemble average. The symmetry was greater in the medial gastrocnemius and tibial anterior in NHI compared to the pwPD. Corroborating these findings, Keloth and collaborators [76] reported that pwPD had significantly higher average asymmetry index (medial gastrocnemius and tibial anterior muscles) than NHI for the total gait cycle.

d) neural outcomes

No study investigated neural asymmetry during walking in pwPD. Two studies [10,70] investigated the relationship between asymmetry in kinematic (spatial and temporal stepping parameters) and neural outcomes investigated by Magnetic Resonance Imaging. On one hand, Fling and collaborators [10] reported that reduced transcallosal fiber tract integrity of the pre-supplementary motor area and primary somatosensory was associated with greater step length asymmetry in pwPD. In contrast, Vervoort and collaborators [70] found no relationship between kinematic outcomes and neural connectivity.

2.3.5 Meta-analysis

a) PD OFF vs. controls

Swing time, step time and step length asymmetry were assessed in three [30,33,34], five [10,30,33,34,66] and five [10,30,33,34,66] studies accessed, respectively (Figure 4). PwPD without dopaminergic medication showed significantly greater swing time and step time asymmetry, with a moderate effect size and no heterogeneity, compared to NHI. No significant effect was found for step length asymmetry.

b) PD ON vs. controls

Under the effect of dopaminergic medication, 11 [15,30,88,33,34,38,73,75,83,85,86], 14 [15,30,83,85,86,88,33,34,38,58,62,74,75,77], 10 [30,33,34,38,73,74,83,85,86,88] and 7 [15,34,38,83,85,86,88] studies analyzed step length, swing time, step time and stance time asymmetry, respectively (Figure 5). PwPD showed significantly greater asymmetry in step length, swing time, step time and stance time compared to NHI, all with a small effect size. There was high heterogeneity between studies for step length, swing time and stance time asymmetry, and moderate heterogeneity for step time asymmetry. The funnel plot asymmetry only

presented significant risk of publication bias for stance time asymmetry (p<0.02; t: -3,29; see Appendix F).

c) PD ON vs. PD OFF

Three studies compared pwPD in ON vs OFF medication states [30,33,34] (Figure 6). PD OFF exhibited significantly greater swing time asymmetry compared to PD ON, without heterogeneity. No significant effects of medication status were identified for step length and step time asymmetry.

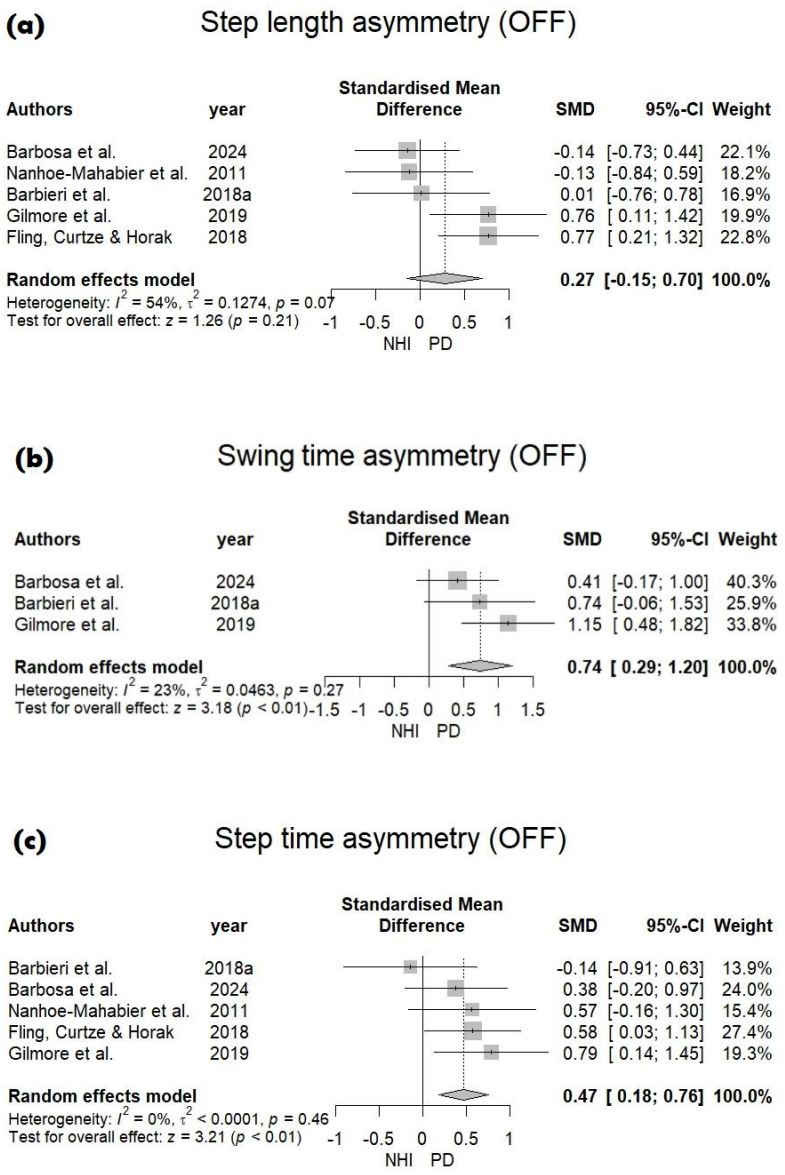


Figure 4. Forest plots of GA for (a) step length asymmetry, (b) swing time asymmetry, and (c) step time asymmetry for the comparison between pwPD at OFF state vs. NHI. PD: people with Parkinson's disease; NHI: neurologically age-matched healthy individuals; SMD: Standardized mean difference; CI: Confidence interval.

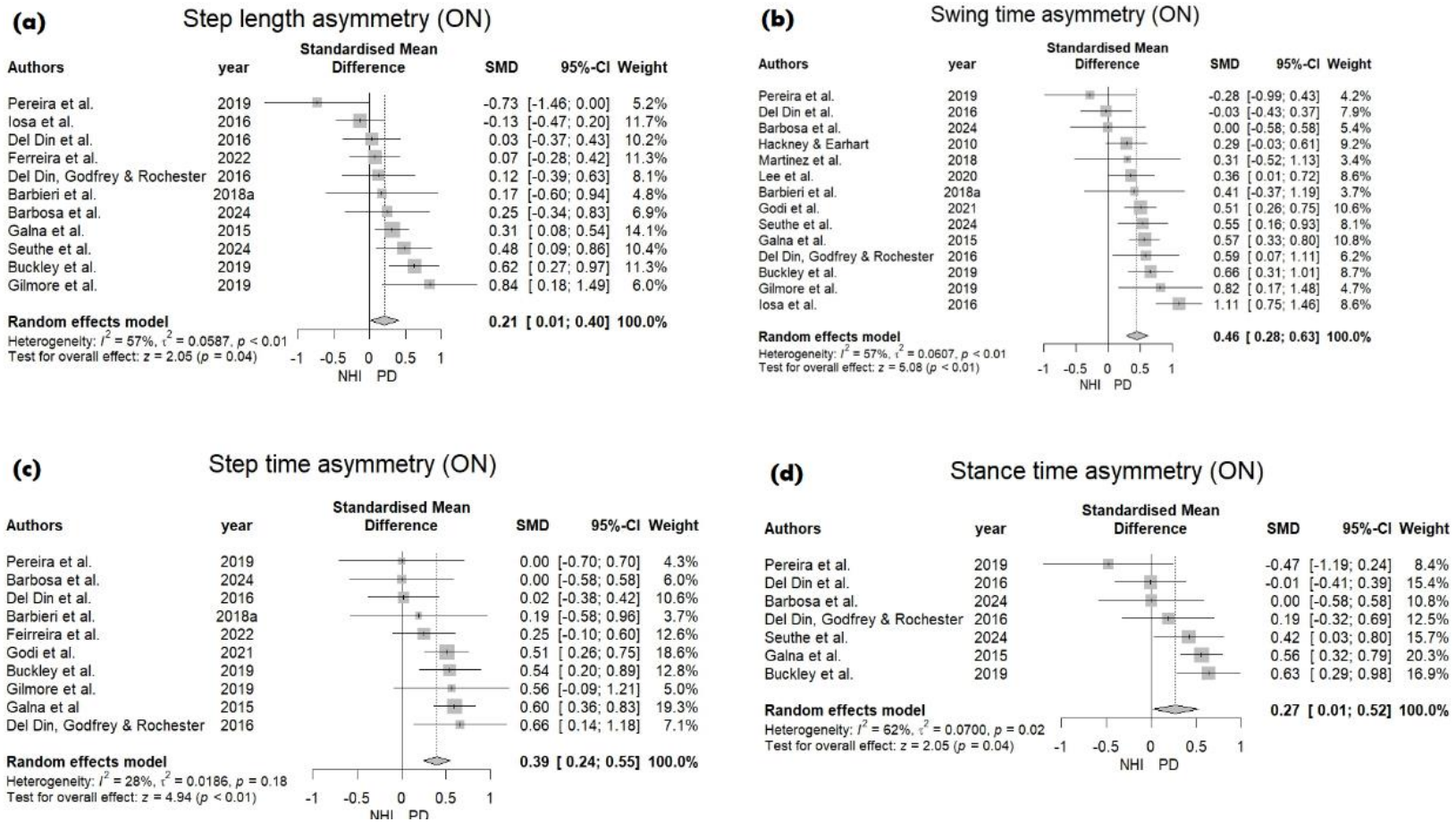


Figure 5. Forest plots of GA for (a) step length asymmetry, (b) swing time asymmetry, (c) step time asymmetry, and (d) stance time asymmetry for the comparison between pwPD at ON state vs. NHI. PD: people with Parkinson's disease; NHI: neurologically age-matched healthy individuals; SMD: Standardized mean difference; CI: Confidence interval.

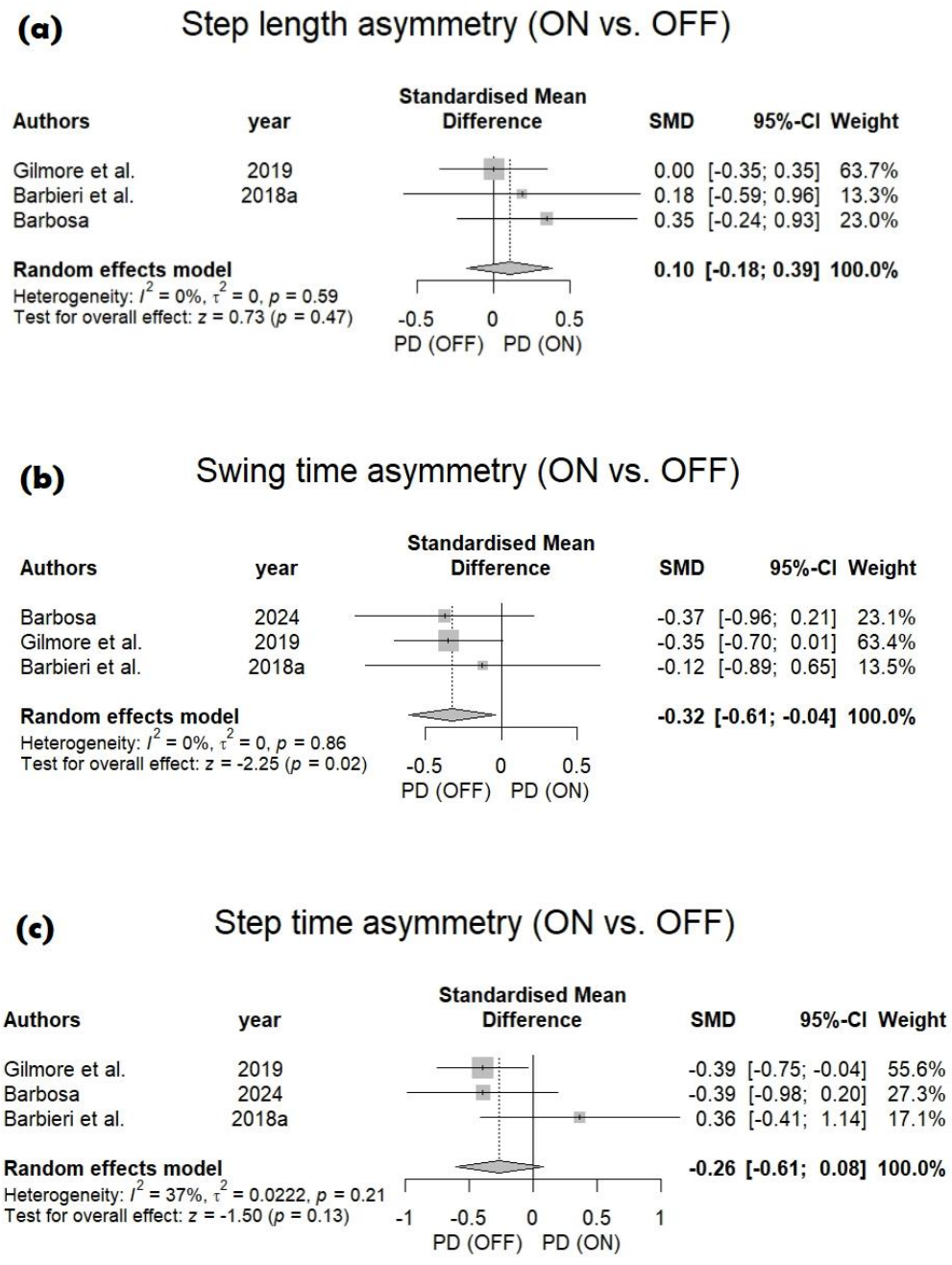


Figure 6. Forest plots of GA for (a) step length asymmetry, (b) swing time asymmetry, and (c) and step time asymmetry for the comparison between PD at ON vs. OFF state of dopaminergic medication. PD: people with Parkinson's disease; SMD: Standardized mean difference; CI: Confidence interval.

2.4 Discussion

This systematic review with meta-analysis included 39 studies that compared kinematic, kinetic, muscular and neural asymmetry during overground unobstructed walking between pwPD and NHI. Additionally, the effect of dopaminergic medication on GA was investigated. The interest from the scientific community in GA in pwPD notably increased after 2015 with the publication of almost 30 scientific articles on the topic. All papers, except one [76], investigated at least one kinematic parameter regarding GA, while only very few papers examined kinetic and muscular parameters and no study investigated neural asymmetries.

We have shown that pwPD increased asymmetries for all temporal gait parameters, namely swing-, step- and stance time asymmetries compared to NHI for both, ON and OFF state of medication. For step length asymmetry as a measure for spatial asymmetry, only significant results were found for the ON state of medication but not for the OFF state of medication. Moderate heterogeneity and a relatively small number of studies may have led to the non-significant result for the OFF state condition. No meta-analysis could be conducted for the kinetic and muscular results given the very small number of studies. However, the studies investigating muscular activity reported greater muscle activation asymmetry of the medial gastrocnemius and tibialis anterior compared to NHI [76]. PwPD exhibit higher values in asymmetry index during the swing phase for tibialis anterior muscle and during single support and swing phases for the medial gastrocnemius muscle [76] which may explain differences in asymmetry between pwPD and NHI. Further explanations are multivariate.

Seuthe et al. [15] suggest that GA is most likely caused by complex mechanisms, which include but are not limited to symptom distribution in the limbs. Also, they speculate that the degree of deterioration of postural control may also contribute to the asymmetry incongruences. In a general view, GA can be explained by an uneven deficiency of dopamine in the striatum, possibly on top of an uneven number of dopaminergic cells in each hemisphere at birth [91]. Moreover, degeneration of nigral dopaminergic neurons in basal ganglia is associated with motor (e.g., balance and sequential and rhythmic movements) and sensory (e.g., visuospatial processing) deficits in PD [5,6,92]. Particularly, Fling et al. [10] explained reduced symmetric control of gait by changes in the transcallosal connections between the pre-supplementary motor areas and the primary somatosensory cortices in PD. Specifically, they showed that greater temporal and spatial GA between the two legs was associated with decreased microstructural integrity of callosal white matter tracts connecting the pre-SMA and SMAs. Furthermore, strong associations were observed between the callosal

integrity of fiber tracts connecting pre-supplementary motor areas and primary somatosensory cortical regions and step length asymmetries in pwPD. In addition, asymmetrical degeneration of both the dopaminergic and non-dopaminergic neural systems [1,7] and asymmetrical activity in the motor cortex [93] can explain GA in pwPD. PD increases left hemisphere susceptibility, in the left nigrostriatal pathway, which is more affected than the right, irrespective of handedness, commonly seen in the early stage of PD [7]. This can cause lower muscle activity in the right lower extremity [76]. However, none of these studies have compared the neural activity when the step is performed with the least vs. most affected limb. This represents a significant gap in the existing literature that should be addressed in future studies. By understanding the asymmetry of neural activity during the step performed with the least and most affected limb, it may be possible to develop more accurate and detailed explanations of the GA mechanisms.

The consistently greater asymmetry in temporal parameters in pwPD can be explained by the deficit in temporal processing [94] and disrupted internal rhythmic timing [95] due to the reduced ability of basal ganglia to generate repetitive movements [96], or other factors such as modified spinal cord pathways [76], in pwPD. It has been proposed that internal timing is dependent on striatal dopaminergic degeneration levels, and that timing problems may be a potential marker for frontal and striatal dysfunctions in PD [97]. Another possible explanation is that bradykinesia features, which primarily affect the lower limbs, are typically asymmetrical, affecting temporal gait parameters asymmetrically [98–100]. Bradykinesia feature asymmetry is believed to be a result of the unbalanced involvement of the basal ganglia circuits and their projections to the primary motor cortex [99,100]. Accordingly, previous neurophysiological studies exploring primary motor cortex activity in pwPD have revealed distinct cortical activity patterns between the most affected and least affected hemispheres [99].

Although our study demonstrated that pwPD exhibited greater asymmetry in kinematic parameters, especially for temporal parameters, compared to NHI, several findings prompted us to question whether this greater GA is always exhibited in pwPD. The meta-analysis indicated a modest (small) effect with considerable (moderate to high) heterogeneity for the GA in pwPD in ON state vs. NHI. Around 26% (ten studies) of studies reported the absence of GA for kinematics and two studies did not find asymmetry in kinetic parameters between pwPD and NHI. Moreover, no study identified significant asymmetry in step width, double support time, or joint angle analysis in pwPD. The wide variability in the experimental protocols shown above may be a potential explanation for some controversial findings. Also, some gait features can progress similarly (or very similar) between the sides, without

detecting significant asymmetry. Maybe due to these controversial findings, asymmetry variables are not the best predictors for disease diagnosis and discriminate pwPD from NHI [73,74]. Therefore, although GA in pwPD should be assessed in different environments and contexts, it is recommended that future studies should seek to exert greater control over the factors that may influence GA responses, with the aim to report more conclusive findings.

2.4.1 Dopaminergic medication partly improves gait asymmetry

With regard to our second study aim, we found that dopaminergic medication improved swing time asymmetry, but not step length- or step time asymmetry. These results need to be interpreted cautiously given the very few numbers of studies (n=3) for each domain. Levodopa intake leads to a compensatory neural "re-wiring" minimizing asymmetrical neurodegeneration and loss of dopamine in the basal ganglia [7]. The over-activation of right and left brain cortices in PD is higher without medication (OFF state) [101]. In addition, Santos et al. [102] found that dopaminergic medication intake strengthened cortico-muscular coherence in the alpha bands accompanied by a decrease in PD-typical-related impairments in gait outcomes, i.e., increases in stride length and speed and improvements in step-timing coordination, making PD (ON) walk more similarly to NHI. The authors suggest that dopaminergic medication improves the strength of the oscillatory coupling between the motor cortex and muscles. The overall increase in cortico-muscular coherence in the alpha band after medication may indicate that dopamine improves the processing of sensory feedback information due to its positive effects on the basal ganglia and its connections with related brain areas, thus facilitating sensory-motor integration. The effect of medication intake on GA is consistent with its effect on gait rhythmicity [103], which suggests that dopamine levels in pwPD directly influence GA. This is supported by the finding that dopaminergic medication replacement therapy reduces the timing deficits in PD [104]. These results suggest that dopaminergic medication may be an effective strategy for reducing GA in pwPD, providing novel insights into the potential benefits of gait interventions for pwPD.

2.4.2 Methodological quality

Overall, the identified research articles presented high methodological quality ratings. The research aims were clearly stated, key outcome variables were clearly described, the methodology was chosen adequately to answer the research question and described sufficiently to be repeated, and key findings were supported by the results. In contrast, the description of recruitment and sampling methods was frequently omitted or insufficient. In

addition, only two studies in this systematic review controlled for covariates, and most studies poorly accounted for the reliability and internal validity of their methods. Finally, clinical implications were not stated for more than half of the studies. These sources of bias are limitations to the current evidence, thereby implying caution when interpreting and/or applying the findings collated here.

Wide variability among experimental protocols to assess GA in pwPD

The experimental protocols used to investigate GA in PD exhibited considerable heterogeneity across the studies included in this systematic review, particularly regarding sample characteristics, walking tasks and indexes for GA calculation. Studies on GA in pwPD have included almost twice as many men as women at different disease stages. This is a potentially important factor to consider in gait studies, given that women with HY stage I have reduced gait speed compared to men in the same stage, but while the women's gait speed stabilizes throughout the disease course, men worsens as the disease progresses [105].

Although the majority of studies included individuals with mild to moderate levels of the disease (HY stages I to III), a notable number of studies [15,74,79,81] also included participants with advanced disease (HY stage IV). Notwithstanding the tendency for motor symptoms in pwPD to remain asymmetric [105,106], the deterioration in gait performance (e.g., reduction in gait velocity) [105] is linearly correlated with the staging of PD [107]. In addition, individuals with HY stage IV frequently experience severe disability [105,106], which can manifest as freezing of gait, increased gait variability, postural instability, and balance problems. These impairments can ultimately result in a loss of independent gait ability and the necessity for assistive devices [108]. While including individuals with HY stage IV can provide valuable insights into how GA progresses, it may not be suitable to analyze mild to moderate levels of disease together with those in advanced stages, as this could potentially bias the findings.

The studies included in this systematic review employed overground unobstructed walking at self-selected speed. However, there was considerable variation in the distance (or time of the trial) of walking tested (6 m to 25 m; 2 minutes to 5 minutes), the local data collection (e.g., free-living walking, laboratory, hospital/clinic corridor) and the number of trials (2 to 10). Moreover, six studies incorporated an analysis of turning into their unobstructed walking analysis [33,34,65,80,82,86] . The lack of standardization of gait protocols may render comparison of the studies' results challenging. This is evidenced by the reduced number of studies included in the meta-analysis (up to a maximum of 14 studies for swing time). Potentially, some non-significant results in certain meta-analyses occurred due to the

low number of included studies included. It would be beneficial for future studies to determine guidelines for more standardized gait tasks and protocols to investigate GA in pwPD.

A minimum of 20 distinct indexes were employed in the studies included in this systematic review. It is evident that there is no consensus regarding the selection of symmetry indexes for the assessment of GA in PD. One crucial aspect is that the indexes are based on the selection of a single side as the reference point (the one most affected by disease) [109]. However, there is a striking mismatch between the side with the larger step length during walking and the side with greater motor symptoms, as assessed by MDS-UPDRS-III [15]. In this systematic review, only seven studies determined the body side most affected by PD using UPDRS or MDS-UPDRS-III items. Consequently, the utilization of disparate reference values (right vs. left side, or most vs. least affected side) for identical dataset results in disparate outcomes, impedes the comparison of results from disparate studies and samples, and may disguise the asymmetry by reducing the index value [110]. Determining an optimal asymmetry index for analyzing the level of GA in PD could improve clinical monitoring and treatment of PD.

2.4.3 Clinical implications, study limitations and future directions

Temporal aspects of asymmetry, particularly swing time asymmetry, was most sensitive to detect GA between pwPD and NHI and to indicate a treatment effect of dopaminergic medication. We therefore suggest including these measures in future studies.

Over the course of this review, some limitations were identified. These include i) due to the different indices used to determine asymmetry, the studies in the meta-analysis were grouped not by these methods, but by the asymmetry variable analyzed; ii) despite performing a methodological quality assessment, we did not analyze the risk of bias; iii) ON vs. OFF states was only tested within the included studies, but an inclusion criterion in this systematic review was that the studies should include NHI. So, there might be more literature available having an ON vs OFF comparison not included here; iv) meta-analysis for some variables only included a low number of studies, which can reduce the probability of significant results; and v) the systematic review and meta-analysis did not address the impact of the level of disease on GA, preventing discussion about the GA progression in PD.

Finally, some aspects need to be better explored in future studies. The influence of the environment seems to be an important component of GA. Challenging walking tasks, such as obstacle environmental and dual-tasking paradigm, also cause GA in pwPD [30,58,111–113].

Indeed, challenging tasks seem to increase GA in pwPD [58]. Challenging walking requires rapid planning and execution of adaptive movements, and increasing motor demands [114], which seem to exacerbate GA. Also, increased sensorimotor integration is required, which leads to reduced automatic control due to the absence of cognitive compensatory options [115] and may well outweigh the available resources, consequently increasing GA in PD. One possible explanation is that the basal ganglia is important for set-dependent adaptation of movement patterns for changes in conditions, indicating that pwPD have inflexible control [116]. However, little is known about GA during challenging walking in pwPD, which seems to be an interesting direction for future studies. In addition, the free-living environment seems to be more sensitive to detecting asymmetry than the laboratory environment [86]. However, there is little information on GA in pwPD in free-living environments, which should be explored for future studies.

2.5 Conclusions

This systematic review with meta-analysis has shown that pwPD have higher GA than NHI. Temporal aspects of GA, particularly swing time asymmetry, were most sensitive. Dopaminergic medication partly improved GA.

References

1. Riederer P, Sian-Hülsmann J. The significance of neuronal lateralisation in Parkinson's disease. *J Neural Transm*. 2012;119(8):953-962. doi:10.1007/S00702-012-0775-1

2. Hipp G. Das Luxemburger Parkinson-Kohortenprogramm: Neue Strategien für eine umfassende Studie zur Erfassung von Biodaten und klinischen Daten. *Basal Ganglia*. 2015;5(1):XVI. doi:10.1016/J.BAGA.2015.02.246

3. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. 2015;30(12):1591-1601. doi:10.1002/MDS.26424

4. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry*. 1992;55(3):181-184. doi:10.1136/JNNP.55.3.181

5. Booij J, Tissingh G, Boer GJ, et al. [123I]FP-CIT SPECT shows a pronounced decline of striatal dopamine transporter labelling in early and advanced Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1997;62(2):133-140. doi:10.1136/JNNP.62.2.133

6. Kaasinen V, Nurmi E, Bergman J, et al. Personality traits and brain dopaminergic function in Parkinson's disease. *Proc Natl Acad Sci U S A*. 2001;98(23):13272. doi:10.1073/PNAS.231313198

7. Claassen DO, McDonell KE, Donahue M, et al. Cortical asymmetry in Parkinson's

disease: early susceptibility of the left hemisphere. *Brain Behav*. 2016;6(12). doi:10.1002/brb3.573

8. Clower DM, Dum RP, Strick PL. Basal ganglia and cerebellar inputs to "AIP." *Cereb Cortex*. 2005;15(7):913-920. doi:10.1093/CERCOR/BHH190

9. Middleton FA, Strick PL. Basal ganglia and cerebellar loops: Motor and cognitive circuits. *Brain Res Rev*. 2000;31(2-3):236-250. doi:10.1016/S0165-0173(99)00040-5

10. Fling BW, Curtze C, Horak FB. Gait asymmetry in people with Parkinson's disease is linked to reduced integrity of callosal sensorimotor regions. *Front Neurol*. 2018;9(APR):215. doi:10.3389/fneur.2018.00215

11. Lafargue G, D'Amico A, Thobois S, Broussolle E, Sirigu A. The ability to assess muscular force in asymmetrical Parkinson's disease. *Cortex*. 2008;44(1):82-89. doi:10.1016/J.CORTEX.2005.11.001

12. Penko AL, Hirsch JR, Voelcker-Rehage C, Martin PE, Blackburn G, Alberts JL. Asymmetrical pedaling patterns in Parkinson's disease patients. *Clin Biomech*. 2014;29(10):1089-1094. doi:10.1016/j.clinbiomech.2014.10.006

13. Spagnolo F, Rini AM, Guida P, Longobardi S, Battista P, Passarella B. The Choice of Leg During Pull Test in Parkinson's Disease: Not Mere Chance. *Front Neurol*. 2020;11. doi:10.3389/FNEUR.2020.00302

14. Plotnik M, Hausdorff JM. The role of gait rhythmicity and bilateral coordination of stepping in the pathophysiology of freezing of gait in Parkinson's disease. *Mov Disord*. 2008;23 Suppl 2:S444-50. doi:10.1002/mds.21984

15. Seuthe J, Hermanns H, Hulzinga F, et al. Gait asymmetry and symptom laterality in Parkinson's disease: two of a kind? *J Neurol*. 2024;271(7):4373-4382. doi:10.1007/S00415-024-12379-0

16. Plotnik M, Giladi N, Balash Y, Peretz C, Hausdorff JM. Is freezing of gait in Parkinson's disease related to asymmetric motor function? *Ann Neurol*. 2005;57(5):656-663. doi:10.1002/ANA.20452

17. Smulders K, Esselink RA, Bloem BR, Cools R. Freezing of gait in Parkinson's disease is related to impaired motor switching during stepping. *Mov Disord*. 2015;30(8):1090-1097. doi:10.1002/MDS.26133

18. Frazzitta G, Pezzoli G, Bertotti G, Maestri R. Asymmetry and freezing of gait in parkinsonian patients. *J Neurol*. 2013;260(1):71-76. doi:10.1007/s00415-012-6585-4

19. Lord S, Galna B, Yarnall AJ, Coleman S, Burn D, Rochester L. Predicting first fall in newly diagnosed Parkinson's disease: Insights from a fall-naïve cohort. *Mov Disord*. 2016;31(12):1829-1836. doi:10.1002/mds.26742

20. Wood BH, Bilclough JA, Bowron A, Walker RW. Incidence and prediction of falls in Parkinson's disease: a prospective multidisciplinary study. *J Neurol Neurosurg Psychiatry*. 2002;72(6):721-725. doi:10.1136/JNNP.72.6.721

21. Plotnik M, Giladi N, Hausdorff JM. Bilateral coordination of walking and freezing of gait in Parkinson's disease. *Eur J Neurosci*. 2008;27(8):1999-2006.

doi:10.1111/j.1460-9568.2008.06167.x

22. Costa TM, Simieli L, Bersotti FM, Mochizuki L, Barbieri FA, Coelho DB. Gait and posture are correlated domains in Parkinson's disease. *Neurosci Lett*. 2022;775:136537. doi:10.1016/J.NEULET.2022.136537

23. Guadagnin EC, Barbieri FA, Simieli L, Carpes FP. IS MUSCULAR AND FUNCTIONAL PERFORMANCE RELATED TO GAIT SYMMETRY IN OLDER ADULTS? A SYSTEMATIC REVIEW. *Arch Gerontol Geriatr*. 2019;84. doi:10.1016/J.ARCHGER.2019.103899

24. Nieuwboer A, Dom R, De Weerdt W, Desloovere K, Fieuws S, Broens-Kaucsik E. Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. *Mov Disord*. 2001;16(6):1066-1075. doi:10.1002/MDS.1206

25. Tamás G, Pálvölgyi L, Takáts A, Szirmai I, Kamondi A. Delayed beta synchronization after movement of the more affected hand in essential tremor. *Neurosci Lett*. 2006;405(3):246-251. doi:10.1016/J.NEULET.2006.07.001

26. Chung JW, Ofori E, Misra G, Hess CW, Vaillancourt DE. Beta-band activity and connectivity in sensorimotor and parietal cortex are important for accurate motor performance. *Neuroimage*. 2017;144(Pt A):164-173. doi:10.1016/J.NEUROIMAGE.2016.10.008

27. Faria MH, Simieli L, Rietdyk S, Penedo T, Santinelli FB, Barbieri FA. (A)symmetry during gait initiation in people with Parkinson's disease: A motor and cortical activity exploratory study. *Front Aging Neurosci*. 2023;15. doi:10.3389/FNAGI.2023.1142540/FULL

28. Arcolin I, Corna S, Giardini M, Giordano A, Nardone A, Godi M. Proposal of a new conceptual gait model for patients with Parkinson's disease based on factor analysis. *Biomed Eng Online*. 2019;18(1):70. doi:10.1186/s12938-019-0689-3

29. Roemmich RT, Nocera JR, Stegemöller EL, Hassan A, Okun MS, Hass CJ. Locomotor adaptation and locomotor adaptive learning in Parkinson's disease and normal aging. *Clin Neurophysiol*. 2014;125(2):313-319. doi:10.1016/j.clinph.2013.07.003

30. Barbieri FA, Simieli L, Orcioli-Silva D, et al. Obstacle Avoidance Increases Asymmetry of Crossing Step in Individuals With Parkinson's Disease and Neurologically Healthy Individuals. *J Mot Behav*. 2018;50(1):17-25. doi:10.1080/00222895.2016.1271303

31. Ravi DK, Baumann CR, Bernasconi E, et al. Does Subthalamic Deep Brain Stimulation Impact Asymmetry and Dyscoordination of Gait in Parkinson's Disease? *Neurorehabil Neural Repair*. 2021;35(11):1020-1029. doi:10.1177/15459683211041309

32. Nanhoe-Mahabier W, Snijders AH, Delval A, et al. Split-belt locomotion in Parkinson's disease with and without freezing of gait. *Neuroscience*. 2013;236. doi:10.1016/j.neuroscience.2013.01.038

33. Gilmore G, Gouelle A, Adamson MB, Pieterman M, Jog M. Forward and backward walking in Parkinson disease: A factor analysis. 2019;74:14-19. doi:10.1016/j.gaitpost.2019.08.005

34. Barbosa R, Mendonça M, Bastos P, et al. 3D Kinematics Quantifies Gait Response to Levodopa earlier and to a more Comprehensive Extent than the MDS-Unified Parkinson's Disease Rating Scale in Patients with Motor Complications. *Mov Disord Clin Pract*. 2024;11(7):795-807. doi:10.1002/MDC3.14016

35. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097

36. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training. Accessed August 15, 2024. https://training.cochrane.org/handbook/archive/v6.3

37. Galna B, Peters A, Murphy AT, Morris ME. Obstacle crossing deficits in older adults: a systematic review. *Gait Posture*. 2009;30(3):270-275. doi:10.1016/J.GAITPOST.2009.05.022

38. Pereira MP, Orcioli-Silva D, de Sousa PN, Beretta VS, Gobbi LTB. The effects of habitual footwear in gait outcomes in people with Parkinson's disease. *Gait Posture*. 2019;68:111-114. doi:10.1016/j.gaitpost.2018.11.013

39. R Core Team. R: The R Project for Statistical Computing. Published online 2023. Accessed September 9, 2024. https://www.r-project.org/

40. Higgins JPT, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect [last updated August 2023]. Cochrane Handbook for Systematic Reviews of Interventions version 6.5. doi:10.1002/9781119536604.ch6

41. Cohen J. Statistical Power Analysis for the Behavioral Sciences. *Stat Power Anal Behav Sci*. Published online May 13, 2013. doi:10.4324/9780203771587

42. Borenstein M, Hedges L V., Higgins JPT, Rothstein HR. *Introduction to Meta-Analysis*. John Wiley & Sons, Ltd Registered; 2009. doi:10.1007/978-3-319-52636-2_287

43. Higgins JPT. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557

44. Liao F, Wang J, He P. Multi-resolution entropy analysis of gait symmetry in neurological degenerative diseases and amyotrophic lateral sclerosis. *Med Eng Phys*. 2008;30(3):299-310. doi:10.1016/j.medengphy.2007.04.014

45. Ren P, Karahan E, Chen C, et al. Gait Influence Diagrams in Parkinson's Disease. *IEEE Trans Neural Syst Rehabil Eng*. 2017;25(8):1257-1267. doi:10.1109/TNSRE.2016.2622285

46. Marino R, Verrelli CM, Gnucci M. Synchronicity Rectangle for temporal gait analysis: Application to Parkinson's Disease. *Biomed Signal Process Control*. 2020;62:102156. doi:10.1016/J.BSPC.2020.102156

47. Santanna A, Salarian A, Wickstrom N. A new measure of movement symmetry in early Parkinson's disease patients using symbolic processing of inertial sensor data. *IEEE Trans Biomed Eng*. 2011;58(7):2127-2135. doi:10.1109/TBME.2011.2149521

48. Su BL, Song R, Guo LY, Yen CW. Characterizing gait asymmetry via frequency sub-band components of the ground reaction force. *Biomed Signal Process Control*. 2015;18:56-60. doi:10.1016/J.BSPC.2014.11.008

49. Broom L, Worley A, Gao F, et al. Translational methods to detect asymmetries in temporal and spatial walking metrics in parkinsonian mouse models and human subjects with Parkinson's disease. *Sci Rep*. 2019;9(1). doi:10.1038/s41598-019-38623-6

50. Demonceau M, Donneau AF, Croisier JL, et al. Contribution of a Trunk Accelerometer System to the Characterization of Gait in Patients With Mild-to-Moderate Parkinson's Disease. *IEEE J Biomed Heal informatics*. 2015;19(6):1803-1808. doi:10.1109/JBHI.2015.2469540

51. Flood MW, O'Callaghan BPF, Diamond P, Liegey J, Hughes G, Lowery MM. Quantitative clinical assessment of motor function during and following LSVT-BIG® therapy. *J Neuroeng Rehabil*. 2020;17(1). doi:10.1186/s12984-020-00729-8

52. Ghaderyan P, Ghoreshi Beyrami SM. Neurodegenerative diseases detection using distance metrics and sparse coding: A new perspective on gait symmetric features. *Comput Biol Med*. 2020;120. doi:10.1016/j.compbiomed.2020.103736

53. Xia Y, Ye Q, Gao Q, Lu Y, Zhang D. Symmetry Analysis of Gait between Left and Right Limb Using Cross-Fuzzy Entropy. *Comput Math Methods Med*. 2016;2016:1737953. doi:10.1155/2016/1737953

54. Zhao H, Cao J, Wang R, Lei Y, Liao WH, Cao H. Accurate identification of Parkinson's disease by distinctive features and ensemble decision trees. *Biomed Signal Process Control*. 2021;69:102860. doi:10.1016/J.BSPC.2021.102860

55. di Biase L, Raiano L, Caminiti ML, Pecoraro PM, Di Lazzaro V. Parkinson's Disease Wearable Gait Analysis: Kinematic and Dynamic Markers for Diagnosis. *Sensors*. 2022;22(22). doi:10.3390/s22228773

56. Baltadjieva R, Giladi N, Gruendlinger L, Peretz C, Hausdorff JM. Marked alterations in the gait timing and rhythmicity of patients with de novo Parkinson's disease. *Eur J Neurosci*. 2006;24(6):1815-1820. doi:10.1111/j.1460-9568.2006.05033.x

57. Grajić M, Stanković I, Radovanović S, Kostić V. Gait in drug naïve patients with de novo Parkinson's disease--altered but symmetric. *Neurol Res*. 2015;37(8):712-716. doi:10.1179/1743132815Y.0000000043

58. Hackney ME, Earhart GM. The effects of a secondary task on forward and backward walking in Parkinson's disease. *Neurorehabil Neural Repair*. 2010;24(1):97-106. doi:10.1177/1545968309341061

59. Kleiner AFR, Pagnussat AS, Prisco G di, et al. Analyzing gait variability and dual-task interference in patients with Parkinson's disease and freezing by means of the word-color Stroop test. *Aging Clin Exp Res*. 2018;30(9):1137-1142. doi:10.1007/s40520-017-0862-0

60. Koh SB, Park YM, Kim MJ, Kim WS. Influences of elbow, shoulder, trunk motion and temporospatial parameters on arm swing asymmetry of Parkinson's disease during

walking. *Hum Mov Sci*. 2019;68:102527. doi:10.1016/j.humov.2019.102527

61. Leavy B, Löfgren N, Nilsson M, Franzén E. Patient-reported and performance-based measures of walking in mild-moderate Parkinson's disease. *Brain Behav*. 2018;8(9):e01081. doi:10.1002/brb3.1081

62. Martínez M, Villagra F, Castellote JM, Pastor MA. Kinematic and kinetic patterns related to free-walking in parkinson's disease. *Sensors (Switzerland)*. 2018;18(12). doi:10.3390/s18124224

63. Miller RA, Thaut MH, McIntosh GC, Rice RR. Components of EMG symmetry and variability in parkinsonian and healthy elderly gait. 1996;101(1):1-7. Accessed March 30, 2020. http://www.ncbi.nlm.nih.gov/pubmed/8625872

64. Morris R, Lord S, Lawson RA, et al. Gait Rather Than Cognition Predicts Decline in Specific Cognitive Domains in Early Parkinson's Disease. *J Gerontol A Biol Sci Med Sci*. 2017;72(12):1656-1662. doi:10.1093/gerona/glx071

65. Morris R, Hickey A, Del Din S, Godfrey A, Lord S, Rochester L. A model of free-living gait: A factor analysis in Parkinson's disease. *Gait Posture*. 2017;52:68-71. doi:10.1016/j.gaitpost.2016.11.024

66. Nanhoe-Mahabier W, Snijders AH, Delval A, et al. Walking patterns in Parkinson's disease with and without freezing of gait. *Neuroscience*. 2011;182:217-224. doi:10.1016/j.neuroscience.2011.02.061

67. Plotnik M, Giladi N, Hausdorff JM. A new measure for quantifying the bilateral coordination of human gait: effects of aging and Parkinson's disease. *Exp brain Res*. 2007;181(4):561-570. doi:10.1007/S00221-007-0955-7

68. Ren X, Salazar R, Neargarder S, et al. Veering in hemi-Parkinson's disease: Primacy of visual over motor contributions. *Vision Res*. 2015;115(Pt A):119-127. doi:10.1016/j.visres.2015.08.011

69. Vervoort G, Bengevoord A, Nackaerts E, Heremans E, Vandenberghe W, Nieuwboer A. Distal motor deficit contributions to postural instability and gait disorder in Parkinson's disease. *Behav Brain Res*. 2015;287:1-7. doi:10.1016/j.bbr.2015.03.026

70. Vervoort G, Heremans E, Bengevoord A, et al. Dual-task-related neural connectivity changes in patients with Parkinson' disease. *Neuroscience*. 2016;317:36-46. doi:10.1016/j.neuroscience.2015.12.056

71. Yogev G, Plotnik M, Peretz C, Giladi N, Hausdorff JM. Gait asymmetry in patients with Parkinson's disease and elderly fallers: When does the bilateral coordination of gait require attention? *Exp Brain Res*. 2007;177(3):336-346. doi:10.1007/s00221-006-0676-3

72. De Bartolo D, Morone G, Giordani G, et al. Effect of different music genres on gait patterns in Parkinson's disease. *Neurol Sci*. 2020;41(3):575-582. doi:10.1007/S10072-019-04127-4

73. Ferreira MIASN, Barbieri FA, Moreno VC, Penedo T, Tavares JMRS. Machine learning models for Parkinson's disease detection and stage classification based on spatial-temporal gait parameters. *Gait Posture*. 2022;98:49-55.

doi:10.1016/J.GAITPOST.2022.08.014

74. Godi M, Arcolin I, Giardini M, Corna S, Schieppati M. A pathophysiological model of gait captures the details of the impairment of pace/rhythm, variability and asymmetry in Parkinsonian patients at distinct stages of the disease. *Sci Rep*. 2021;11(1):21143. doi:10.1038/s41598-021-00543-9

75. Iosa M, Morone G, Fusco A, et al. Loss of fractal gait harmony in Parkinson's Disease. *Clin Neurophysiol*. 2016;127(2):1540-1546. doi:10.1016/j.clinph.2015.11.016

76. Keloth SM, Arjunan SP, Raghav S, Kumar DK. Muscle activation strategies of people with early-stage Parkinson's during walking. *J Neuroeng Rehabil*. 2021;18(1). doi:10.1186/s12984-021-00932-1

77. Lee M, Youm C, Noh B, Park H, Cheon SM. Gait characteristics under imposed challenge speed conditions in patients with parkinson's disease during overground walking. *Sensors (Switzerland)*. 2020;20(7). doi:10.3390/s20072132

78. Lencioni T, Anastasi D, Carpinella I, et al. Strategies for maintaining dynamic balance in persons with neurological disorders during overground walking. *Proc Inst Mech Eng H*. 2021;235(9):1079-1087. doi:10.1177/09544119211023624

79. Liu P, Yu N, Yang Y, et al. Quantitative assessment of gait characteristics in patients with Parkinson's disease using 2D video. *Park Relat Disord*. 2022;101:49-56. doi:10.1016/j.parkreldis.2022.06.012

80. Wu Z, Jiang X, Zhong M, et al. Mild Gait Impairment and Its Potential Diagnostic Value in Patients with Early-Stage Parkinson's Disease. *Behav Neurol*. 2021;2021:6696454. doi:10.1155/2021/6696454

81. Brodie MAD, Dean RT, Beijer TR, et al. Symmetry matched auditory cues improve gait steadiness in most people with Parkinson's disease but not in healthy older people. *J Parkinsons Dis*. 2015;5(1):105-116. doi:10.3233/JPD-140430

82. Bailo G, Saibene FL, Bandini V, et al. Characterization of Walking in Mild Parkinson's Disease: Reliability, Validity and Discriminant Ability of the Six-Minute Walk Test Instrumented with a Single Inertial Sensor. *Sensors*. 2024;24(2). doi:10.3390/s24020662

83. Buckley C, Galna B, Rochester L, Mazzà C. Upper body accelerations as a biomarker of gait impairment in the early stages of Parkinson's disease. *Gait Posture*. 2019;71:289-295. doi:10.1016/j.gaitpost.2018.06.166

84. Danoudis M, Iansek R, Simpson P. Freezing of gait in Parkinson's disease: Further insights into pathophysiological mechanisms. *Park Relat Disord*. 2012;18(5):543-547. doi:10.1016/j.parkreldis.2012.02.005

85. Del Din S, Godfrey A, Rochester L. Validation of an Accelerometer to Quantify a Comprehensive Battery of Gait Characteristics in Healthy Older Adults and Parkinson's Disease: Toward Clinical and at Home Use. *IEEE J Biomed Heal Informatics*. 2016;20(3):838-847. doi:10.1109/JBHI.2015.2419317

86. Del Din S, Godfrey A, Galna B, Lord S, Rochester L. Free-living gait characteristics in ageing and Parkinson's disease: impact of environment and ambulatory bout length. *J*

Neuroeng Rehabil. 2016;13(1):46. doi:10.1186/s12984-016-0154-5

87. Djurić-Jovičić M, Belić M, Stanković I, Radovanović S, Kostić VS. Selection of gait parameters for differential diagnostics of patients with de novo Parkinson's disease. *Neurol Res*. 2017;39(10):853-861. doi:10.1080/01616412.2017.1348690

88. Galna B, Lord S, Burn DJ, Rochester L. Progression of gait dysfunction in incident Parkinson's disease: Impact of medication and phenotype. *Mov Disord*. 2015;30(3):359-367. doi:10.1002/mds.26110

89. Lord S, Galna B, Verghese J, Coleman S, Burn D, Rochester L. Independent domains of gait in older adults and associated motor and nonmotor attributes: validation of a factor analysis approach. *J Gerontol A Biol Sci Med Sci*. 2013;68(7):820-827. doi:10.1093/GERONA/GLS255

90. Lord S, Galna B, Verghese J, Coleman S, Burn D, Rochester L. Independent Domains of Gait in Older Adults and Associated Motor and Nonmotor Attributes : Validation of a Factor Analysis Approach. 2013;68(7):820-827. doi:10.1093/gerona/gls255

91. Djaldetti R, Ziv I, Melamed E. The mystery of motor asymmetry in Parkinson's disease. *Lancet Neurol*. 2006;5(9):796-802. doi:10.1016/S1474-4422(06)70549-X

92. Magrinelli F, Picelli A, Tocco P, et al. Pathophysiology of Motor Dysfunction in Parkinson's Disease as the Rationale for Drug Treatment and Rehabilitation. *Parkinsons Dis*. 2016;2016. doi:10.1155/2016/9832839

93. Heinrichs-Graham E, Santamaria PM, Gendelman HE, Wilson TW. The cortical signature of symptom laterality in Parkinson's disease. *Neuroimage (Amst)*. 2017;14:433. doi:10.1016/J.NICL.2017.02.010

94. Jones CRG, Jahanshahi M. Motor and perceptual timing in Parkinson's disease. *Adv Exp Med Biol*. 2014;829:265-290. doi:10.1007/978-1-4939-1782-2_14

95. Tolleson CM, Dobolyi DG, Roman OC, et al. Dysrhythmia of Timed Movements in Parkinson's disease and Freezing of Gait. *Brain Res*. 2015;1624:222. doi:10.1016/J.BRAINRES.2015.07.041

96. Debaere F, Wenderoth N, Sunaert S, Van Hecke P, Swinnen SP. Cerebellar and premotor function in bimanual coordination: parametric neural responses to spatiotemporal complexity and cycling frequency. *Neuroimage*. 2004;21(4):1416-1427. doi:10.1016/J.NEUROIMAGE.2003.12.011

97. Ashoori A, Eagleman DM, Jankovic J. Effects of Auditory Rhythm and Music on Gait Disturbances in Parkinson's Disease. *Front Neurol*. 2015;6(NOV):234. doi:10.3389/FNEUR.2015.00234

98. Paparella G, De Riggi M, Cannavacciuolo A, et al. Interhemispheric imbalance and bradykinesia features in Parkinson's disease. *Brain Commun*. 2023;6(1). doi:10.1093/BRAINCOMMS/FCAE020

99. Bologna M, Paparella G, Fasano A, Hallett M, Berardelli A. Evolving concepts on bradykinesia. *Brain*. 2020;143(3):727-750. doi:10.1093/BRAIN/AWZ344

100. Monje MHG, Sánchez-Ferro Á, Pineda-Pardo JA, Vela-Desojo L, Alonso-Frech F,

Obeso JA. Motor Onset Topography and Progression in Parkinson's Disease: the Upper Limb Is First. *Mov Disord*. 2021;36(4):905-915. doi:10.1002/MDS.28462

101. Koren O, Bartsch RP, Katzir Z, et al. Dopaminergic medication reduces interhemispheric hyper-synchronization in Parkinson's disease. *Parkinsonism Relat Disord*. 2022;97:39-46. doi:10.1016/J.PARKRELDIS.2022.02.009

102. Santos PCR dos, Heimler B, Koren O, Flash T, Plotnik M. Dopamine improves defective cortical and muscular connectivity during bilateral control of gait in Parkinson's disease. *Commun Biol 2024 71*. 2024;7(1):1-15. doi:10.1038/s42003-024-06195-5

103. Hausdorff JM, Balash J, Giladi N. Effects of cognitive challenge on gait variability in patients with Parkinson's disease. *J Geriatr Psychiatry Neurol*. 2003;16(1):53-58. doi:10.1177/0891988702250580

104. Malapani C, Rakitin B, Levy R, et al. Coupled temporal memories in Parkinson's disease: a dopamine-related dysfunction. *J Cogn Neurosci*. 1998;10(3):316-331. doi:10.1162/089892998562762

105. Vila MH, Pérez R, Mollinedo I, Cancela JM. Analysis of Gait for Disease Stage in Patients with Parkinson's Disease. *Int J Environ Res Public Health*. 2021;18(2):720. doi:10.3390/IJERPH18020720

106. Miller-Patterson C, Buesa R, McLaughlin N, Jones R, Akbar U, Friedman JH. Motor asymmetry over time in Parkinson's disease. *J Neurol Sci*. 2018;393:14-17. doi:10.1016/j.jns.2018.08.001

107. Corrêa PS, Pagnussat AS, Cabeleira MEP, et al. Is the dopaminergic loss associated with gait and postural impairments in subjects with Parkinson's disease at different motor stages? *Eur J Neurosci*. 2019;50(12):3889-3895. doi:10.1111/EJN.14522

108. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology*. 1967;17(5):427-442. doi:10.1212/WNL.17.5.427

109. Cabral S, Resende RA, Clansey AC, Deluzio KJ, Selbie WS, Veloso AP. A Global Gait Asymmetry Index. *J Appl Biomech*. 2016;32(2):171-177. doi:10.1123/JAB.2015-0114

110. Zifchock RA, Davis I, Higginson J, Royer T. The symmetry angle: a novel, robust method of quantifying asymmetry. *Gait Posture*. 2008;27(4):622-627. doi:10.1016/J.GAITPOST.2007.08.006

111. Orcioli-Silva D, Barbieri FA, dos Santos PCR, et al. Double obstacles increase gait asymmetry during obstacle crossing in people with Parkinson's disease and healthy older adults: A pilot study. *Sci Rep*. 2020;10(1). doi:10.1038/s41598-020-59266-y

112. Barbieri FA, Polastri PF, Gobbi LTB, et al. Obstacle circumvention and eye coordination during walking to least and most affected side in people with Parkinson's disease. *Behav Brain Res*. 2018;346:105-114. doi:10.1016/j.bbr.2017.11.032

113. Corradini JR, Silveira-Ciola AP, Pereira VAI, et al. Dual tasking reduces gait asymmetry of trajectory deviation during obstacle circumvention in people with Parkinson's disease. *Hum Mov Sci*. 2022;83. doi:10.1016/j.humov.2022.102938

114. Snijders AH, Weerdesteyn V, Hagen YJ, Duysens J, Giladi N, Bloem BR. Obstacle avoidance to elicit freezing of gait during treadmill walking. *Mov Disord*. 2010;25(1):57-63. doi:10.1002/MDS.22894

115. Vitório R, Lirani-Silva E, Orcioli-Silva D, Beretta VS, Gobbi ASOTB. Electrocortical dynamics of usual walking and the planning to step over obstacles in Parkinson's disease. *Sensors*. 2023;23(10):1-13.

116. Cools R, Barker RA, Sahakian BJ, Robbins TW. L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia*. 2003;41(11):1431-1441. doi:10.1016/S0028-3932(03)00117-9

CHAPTER 3

Study 2: Intersegmental coordination during a obstacle circumvention is not affected by side of symptoms and a dual task in people with Parkinson's disease

Intersegmental coordination during a obstacle circumvention is not affected by side of symptoms and a dual task in people with Parkinson's disease

ABSTRACT

Gait asymmetry, a key characteristic Parkinson's disease (PD), is linked to gait impairments and manifests in tasks like obstacle circumvention, particularly on the more affected side. These deficits differ from those seen in neurologically healthy individuals (NHI) and may indicate PD progression. Asymmetry and coordination impairments become more pronounced under dual-task conditions. To investigate the intersegmental coordination patterns during walking while circumventing an obstacle to the more or less affected side in pwPD under a cognitive dual-task, and to compare these patterns with NHI. Seventeen individuals with PD (PG) and 17 age matched NHI (CG) were evaluated during obstacle circumvention (OC) and OC with a dual task (OC+DT). The axial and lower interlimb coordination of head-pelvis, head-trunk, trunk-pelvis and the bilateral coupling of thighs, legs and feet were analyzed. Group effects were shown for head-pelvis (PG> pelvis phase, CG> head phase), head-trunk (CG> head phase), trunk-pelvis (CG> out-of-phase) and foot-foot (CG> out-of-phase). Small effects of task (OC > in-phase pattern for femur-femur and head-pelvis) and interaction between side*group (foot-foot) and side*group*task (leg-leg and head-trunk) were also found. Circumvention obstacles, whether to the more or less affected side, did not substantially impairs intersegmental coordination in individuals with PD. Similarly, adding a dual cognitive task did not significantly impair axial or inter-limb coordination, suggesting the task did not fully tax cognitive resources. However, group differences were evident, highlighting intersegmental coordination as a potential marker to distinguish individuals with PD from healthy controls.

Keywords: challenge; motor control; neurological diseases; biomechanics; cognition

3.1 Introduction

Individuals with PD present gait impairments (Mirelman *et al.*, 2019). In situations of obstacle avoidance, deficits can manifest asymmetrically (Barbieri *et al.*, 2018; Simieli *et al.*, 2017). When avoiding an obstacle on the less affected side compared to the more affected side, there is a greater mediolateral and horizontal distance between the body and the obstacle, use of the "lead-out" strategy and a greater number and time of fixations on the obstacle (Barbieri *et al.*, 2018). Therefore, avoiding an obstacle from the side most affected by PD is a riskier task.

In contrast to their peers without the disease, who make adjustments close to the deviation, individuals with PD start adapting their spatial-temporal parameters when they are still far from the obstacle - the approach stage (3-5 steps before the obstacle) - and during the deviation (2 steps - immediately before and during the deviation)(Simieli *et al.*, 2017). However, when considering the axial intersegmental coordination pattern, adjustments are made close to the obstacle: with greater head movement in the step before the obstacle and greater trunk rotation during the circumvention step. Furthermore, the distance from the start to the obstacle does not seem to interfere with the pattern of axial intersegmental coordination in the deviation task (Silveira-Ciola *et al.*, 2021).

When performing dual tasks (DT), in which cognitive abilities are even more required, the walking performance of pwPD is severely affected (Raffegeau *et al.*, 2019a), as there is a loss of automaticity which can impair the performance of one or both tasks (Wu; Hallett, 2008). These tasks involve cortical and subcortical areas common to cognitive processes, which are used in a deficient way by individuals with PD (Szameitat *et al.*, 2002). With this in mind, performing a risky task while walking (such as avoiding an obstacle) in combination with a cognitive task (such as talking on a cell phone, counting or having a conversation) can compromise the performance of these tasks, since in studies that examined changes in dual tasks in both walking and simultaneous tasks, the majority showed impairments in both (Kelly; Eusterbrock; Shumway-Cook, 2012a). Based on this, two possible motor impairments due to performing a DT while walking are changes in gait symmetry and bilateral coordination, suggesting that elderly people suffering from motor deficits, cognitive deficits or both may have difficulties regulating gait rhythm and coordinating symmetrical leg movements while walking (Yogev *et al.*, 2007).

It is important to investigate this relationship, since impairments in asymmetry and coordination during walking seem to indicate possible deficits resulting from the progression of PD, such as the occurrence of freezing during walking (FOG). Individuals with FOG have a less symmetrical and less coordinated gait compared to those without FOG (Plotnik; Giladi; Hausdorff, 2008b). However, it is still debated whether these factors predispose to FOG or whether they are intrinsic characteristics of it. In the literature, a gap needs to be answered: do these changes deteriorate even before FOG? And are there situations that worsen symmetry and coordination during walking, such as dual-task situations or more challenging tasks? However, the relationship between coordination and symmetry is still questioned, suggesting that the mechanisms behind asymmetry and worse coordination are different (Plotnik; Giladi; Hausdorff, 2009a).

Therefore, the objective of the study is to verify the intersegmental coordination pattern during walking with obstacle circumvention to the side more or less affected by PD concomitant with a cognitive dual task. The secondary objective is to compare coordination and asymmetry between individuals with PD and their neurologically healthy peers. Three hypotheses were raised: i) poorer axial and trunk intersegmental coordination (higher frequency of occurrence "in phase") during circumvention to the side most affected by the disease (Barbieri *et al.*, 2018; Cano-De-La-Cuerda *et al.*, 2017); ii) individuals with PD will have a more asymmetrical gait (swing time, step length and step time) and poorer bilateral lower limbs (with a predominant contribution of the "less affected" limb) and axial intersegmental coordination (higher frequency of occurrence "in phase") compared to the CG; and iii) control subjects may have asymmetrical symptoms, but to a lesser extent than those with PD, but will not have coordination deficits (Bonacina *et al.*, 2024).

3.2 Methods

3.2.1 Participants

Seventeen individuals with idiopathic Parkinson's disease (PG) and 17 neurologically healthy elderly (control group – CG) participated in the study. They were matched according to age and gender. Individual of PG were recruited through the "Ativa Parkinson" Extension Project offered by the São Paulo State University "Júlio de Mesquita Filho" (UNESP) - Bauru Campus. While individuals of CG were recruited through a convenience sample (elderly participants of other UNESP projects and friends or family members of individuals with PD).

All those with PD should have their medical diagnosis confirmed by a private neurologist according to the UK Brain Bank (Hughes *et al.*, 1992). In addition, being classified in stages 1 to 3 on the modified Hoehn & Yahr Scale, not being in the pharmacological adaptation phase (being at least three months taking the same medication) and being under drug treatment with levodopa. The following exclusion criteria were established (for both groups): age below 60 years; presence of other neurological disorders, cardiac problems (i.e., arrhythmias, indication of myocardial ischemia), musculoskeletal disorders (Alcock; O'Brien; Vanicek, 2018); cognitive deficits (verified by the Mini Mental State Examination - MMSE) and brain surgery or deep brain stimulation (DBS) for the treatment of PD (Bryant *et al.*, 2016). The study was approved by the Local Research Ethics Committee (CAAE: 45435615.7.1001.5398). All participants were informed about the study procedures and invited to sign the Informed Consent Form.

3.2.2 Experimental design

All procedures were performed at the Human Movement Research Laboratory (MOVI-LAB) - UNESP - Campus de Bauru. Each participant made a visit to the laboratory in which the assessments (clinical and floor) were made. The participants of the PG were instructed to take the dopaminergic medication 1 hour before the evaluations so that they could perform all the evaluations in the "ON" period.

3.2.3 Clinical evaluations

An experienced examiner performed the assessments described below. To characterize the sample, personal data (name, age, sex and education), anthropometric measurements (body mass, height, body mass index [BMI]), clinical, cognitive and medication history were acquired. All information was collected in as much detail as possible to obtain information about the origin of PD and to eliminate the influence of other diseases that may confuse the diagnosis of idiopathic PD.

To verify the degree of motor impairment, the Unified Parkinson's Disease Rating Scale (UPDRS - Part III) was applied to all individuals in the PG. Higher values indicate a greater degree of motor impairment (Martínez-Martín *et al.*, 1994). Based on the score obtained in some of those items in the UPDRS - Part III, the evolutionary stage of PD was determined using the modified Hoehn & Yarh Scale (H&Y - Goetz et al., 2004). Furthermore,

it was determined, through the UPDRS (items 20, 21, 22, 23, 25 and 26), the symmetry index between the members. The value of the right member was subtracted from the value of the left member. Positive values indicate the right limb as the most affected, while negative values indicate greater involvement of the left limb. In the case of the CG, the manual and pedal preference of the participants was determined. To determine manual preference, the hand with which the participants wrote was considered; to determine the pedal preference, they performed three kicks in a ball; the dominant limb was the one used at least twice.

To assess possible cognitive impairment and, consequently, inability to understand the tests, the Mini Mental State Examination (MMSE) was applied. The score was adjusted according to the education level of each individual (Brucki *et al.*, 2003).

3.2.4 Gait evaluation

The gait assessment occurred under four different conditions: i) circumvention an obstacle to the right (OC_R); ii) circumvention an obstacle to the left (OC_L); iii) circumvention the obstacle to the right performing a cognitive dual task (OC_R + DT) and iv) to the left (OC_L + DT). In all conditions the participants walked at they preferred speed on a 8.5m long and 3.5m wide walkway. In all attempts, a cylindrical obstacle (0.35m in diameter and 1.3m in height) was positioned in the middle of the walkway and in the center of it. The participants were instructed to walk towards the obstacle, circumvention it (avoiding contact) and return to the same direction that they were before the circumvention. The participants' initial position was always the same and aligned with the obstacle. The participants were not instructed to which side to make the circumvention, being at their own criteria. However, to count the five attempts for each side, the evaluators "obstructed" the passage of one side when this number was reached (placing a chair on that side), with the intention of the participant make the circumvention to the side that was still missing. In total, each participant made 20 attempts, five for each condition. The order of the attempts was randomly defined. For security purposes, an evaluator accompanied the participant during the execution of the task in all attempts.

During the circumvention with a cognitive dual task concomitant, an audio (recorded in advance) was played together while walking. The audio presented a random sequence of numbers containing a wildcard number (indicated in bold in the following example: 2,**3**,8,**3**,4,7,1,**3**,**3**,5); in all attempts the sequence of numbers and the wildcard number were

modified. The individuals were instructed to count how many times a given number (wildcard number) was spoken in the audio. The wildcard number was provided to the participant before starting the attempt, with the following instruction: "You will count how many times the number "x" is spoken in the audio". In addition, all participants were instructed not to count out loud and not to use their hands to help quantify the numbers. At the end of each attempt, participants were asked how many times the wildcard number was spoken to account for mistakes and successes. A familiarization attempt was granted before each condition.

The collection of kinematic data was carried out using the three-dimensional data acquisition system from Vicon® 3D (Vicon Motion Systems Ltd. UK). Eight cameras (Bonita System Cameras), with a sampling frequency of 100 Hz, distributed throughout the room made it possible to analyze the gait during the entire route. Thirty-nine photo reflexive markers were positioned at the participant's anatomical points following the model "Plug-in Gait Full Body" (Vicon®), in addition to five on the obstacle. The data were filtered through a 5th order low-pass Butterworth filter (zero-lag) and a cutoff frequency of 6 Hz.

3.2.5 Data analysis

In all conditions, the gait analysis was carried out in two phases: the approach phase - two steps before the obstacle; and the circumvention phase - two steps during the obstacle circumvention (Figure 7). Nexus software (Vicon®) was used to calculate the spatial-temporal parameters of gait and determine the segments of the head, trunk, pelvis, thigh, leg and foot. The segments were determined based on the anatomical coordinates of the local system (medial-lateral [x], anteroposterior [y], transverse [z]). The vertical plane [z] was used to analyze the displacement of the head, trunk and hip segments, since the aim was to verify the rotation of the segments. For the measurement of lower limb segments, the anteroposterior plane [y] was used to obtain flexion and extension information. After exporting this data, the analyses were carried out using routines developed in the Matlab® environment (2024 version, MathWorks, MA, USA). Based on the phases of approaching and deviating from the obstacle, the values for step length, width, duration and speed and percentage in double support were determined. The symmetry index (Dingwell; Davis; Frazier, 1996), a modified version of Herzog (Herzog *et al.*, 1989), was then applied to each of the variables in order to verify the presence of asymmetry in the spatial-temporal parameters of the PD group.

$$\text{Symmetry index} = \frac{(\text{right or less affected limb} - \text{left or more affected limb})}{(\text{right or less affected limb} + \text{left or more affected limb})} \times 100\%$$

Once the presence of asymmetry was confirmed in the PD group (appendix G), the vector coding technique was used to determine axial intersegmental coordination (head/trunk, head/hip and trunk/hip) and lower limb coordination (thigh, leg and foot). Associations between thigh, leg and foot will be compared bilaterally (e.g. right thigh/left thigh). More information on this technique is given in the paragraph below.

With this technique, it is possible to establish the relative movement and coupling (association) between two joints or segments (Chang; Van Emmerik; Hamill, 2008). Rinaldi et al. (2017) explain the procedures for this analysis (Rinaldi; Emmerik; Moraes, 2017). The transverse plane was used to verify the rotational movements of the head, trunk and hips, while the sagittal plane was used for the movement of the lower limb segments. For each coupling, the frequency of occurrence (%) of four coordination patterns was determined: (a) in phase - both segments move in the same direction, (b) out of phase - the segments move in opposite directions, (c) phase of segment 1 and (d) phase of segment 2. The coordination patterns of 'c' and 'd' are defined by the predominance of the movement of one segment over the other, so that while one segment is moving, the other is not. In this study, vector coding analysis was used to verify the coupling between the segments during the entire phase of the obstacle circumvention: approach phase + circumvention phase. Afterwards, both phases were summed for each coordination pattern.

3.2.6 Statistical analysis

The SPSS 22.0 program (SPSS, Inc.) was used for statistical treatment. The Student's t-test for independent samples was used to compare anthropometric measurements (age, height, body mass and BMI) and cognitive status (MMSE) between the groups. The Shapiro-Wilk and Levene tests were used to check the normality of the data distribution and the homogeneity of the variances, respectively. The significance level was set at $p < 0.05$. The data on intersegmental coordination during walking was analyzed using ANOVAs for each association; the following factors were considered: (group [PG and CG] x task [OC and OC+DT] x side [more and less affected side, i.e., non-dominant and dominant]) with repeated measures for the frequency of occurrence (%) of each coordination pattern. The sphericity

criteria were met (Mauchly test: $p > 0.05$). Finally, the Bonferroni post hoc test was used to indicate the main and interaction effects ($p<0.05$).

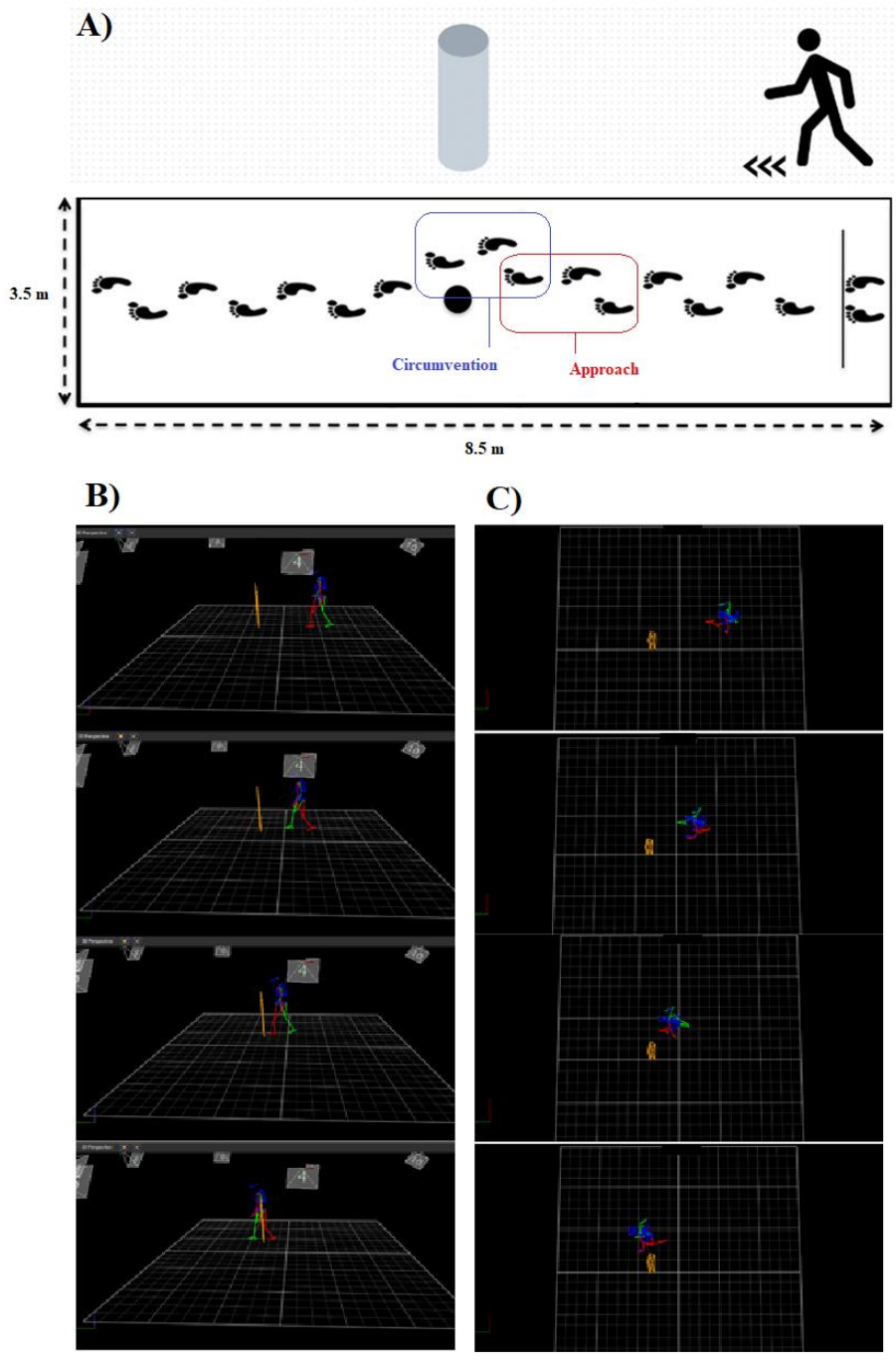


Figure 7. A) illustration of the task performed by the individuals (two steps of aprroach and two steps of circumvention phases). B) and C) displays data captured by VICON cameras using Nexus software. The left panels (B) provide a lateral view, while the right panels (C) present a top-down view, illustrating the individual, the obstacle, and the walkway.

3.3 Results

3.3.1 Sample characteristics and clinical parameters

The characteristics of the participants included in the study can be seen in Table 4. There were no statistical differences for any of the variables compared ($p>0.05$), indicating homogeneity between the groups. It is worth noting the predominance of right-handed individuals in the study, and there were no left-handed individuals in the PDG. Furthermore, the side most affected by Parkinson's disease was the right.

Table 4. Table 4 shows the scores for the participants' anthropometric characteristics and clinical assessments.

	CG	**PG**	**p-value**
Sex (M/F)	9M/8F	7M/10F	-
Age (years)	66.24 ± 5.49	64.88 ± 8.00	0.569
Body mass (kg)	72.63 ± 11.55	70.90 ± 14.68	0.706
Height (m)	1.64 ± 0.09	1.61 ± 0.09	0.328
BMI (kg/m^2)	26.92 ± 3.04	27.40 ± 5.67	0.758
MMSE (points)	27.59 ± 1.54	27.94 ± 1.82	0.546
UPDRS - III	-	22.94 ± 7.83	-
Modified HY	-	2.03 ± 0.60	-
Most affected side (R/L)	-	11 / 6	-
Manual dominance (R/L)	15 / 2	17 / 0	-

Values are presented by mean ± standard deviation. CG: control group; PG: Parkinson's disease group; M: masculine; F: feminine; BMI: Body Mass Index; MMSE: Mini Mental State Examination; UPDRS: Unified Parkinson's Disease Rating Scale; H&Y: modified Hoehn & Yahr Scale; R: right; L: left.

3.2 Intersegmental coordination during OC to the most and least affected side with or without a DT

Coupling between left x right thigh

ANOVA showed only one main task effect (in phase: $F_{1,31} = 5.254$, $p=0.029$, $\eta^2 = 0.145$). The in-phase pattern between right and left thighs was greater at OC compared to OC+DT (Figure 8 - 1a).

Coupling between left x right leg

ANOVA showed an interaction effect between group*task*side (right leg: $F_{1,31} = 5.646$, $p=0.024$, $\eta^2 = 0.154$). In the OC condition, during circumvention to the less

affected/dominant side, the CG showed greater coordination of the right leg compared to the PG (p=0.034). In addition, the CG in the OC condition showed greater coordination of the right leg when circumventing to the dominant side compared to when circumvention the obstacle to the non-dominant side (p=0.011). Those results can be seen in Figure 8 – 2c.

Coupling between left x right foot

ANOVA showed a main effect of group (out of phase: $F_{1,31}$ = 3.426, p=0.043, η^2 = 0.250; Figure 8 – 3b). The PG presented a greater out phase pattern of coordination compared to the CG. In addition, a group*side interaction effect was found (out-phase: $F_{1,31}$ = 5.997, p=0.020, η^2 = 0.162; Figure 8 – 3b); when circumvention to the less affected side, the PG showed a greater out of phase pattern of coordination between the feet compared to the CG (p=0.007).

Coupling between head/pelvis

There was a group (head: $F_{1,31}$ = 7.183, p=0.012, η^2 = 0.188; pelvis: $F_{1,31}$ = 8.738, p=0.006, η^2 = 0.220) and task effect (in phase: $F_{1,31}$ = 6.100, p=0.019, η^2 = 0.164). When comparing the coupling between head and pelvis, the PG showed greater pelvis coordination (Figure 9 – 1d), while the CG showed a predominance of head coordination (Figure 9 – 1c). In addition, the in-phase pattern was greater during the OC compared to the OC+DT (Figure 9 – 1a).

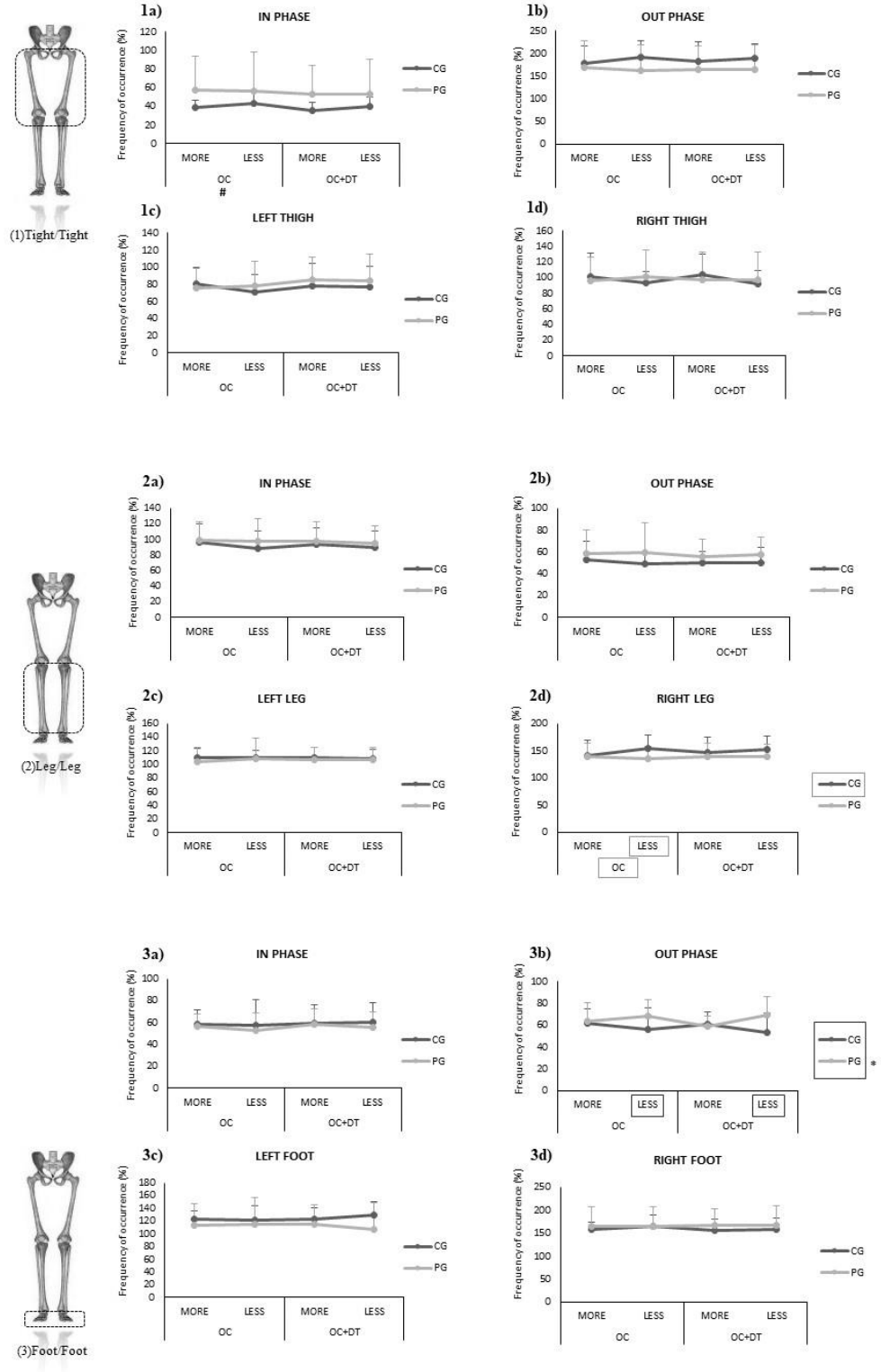
Coupling between head/trunk

ANOVA found a group effect (head: $F_{1,31}$ = 5.967, p=0.020, η^2 = 0.161). The CG showed greater head coordination compared to PG (Figure 9 – 2c). In addition, an interaction effect between group*task*side was reported (in phase: $F_{1,31}$ = 5.386, p=0.027, η^2 = 0.148; Figure 9 – 2a). However, the pairwise comparisons did not present a p-value <0.05.

Coupling between trunk/pelvis

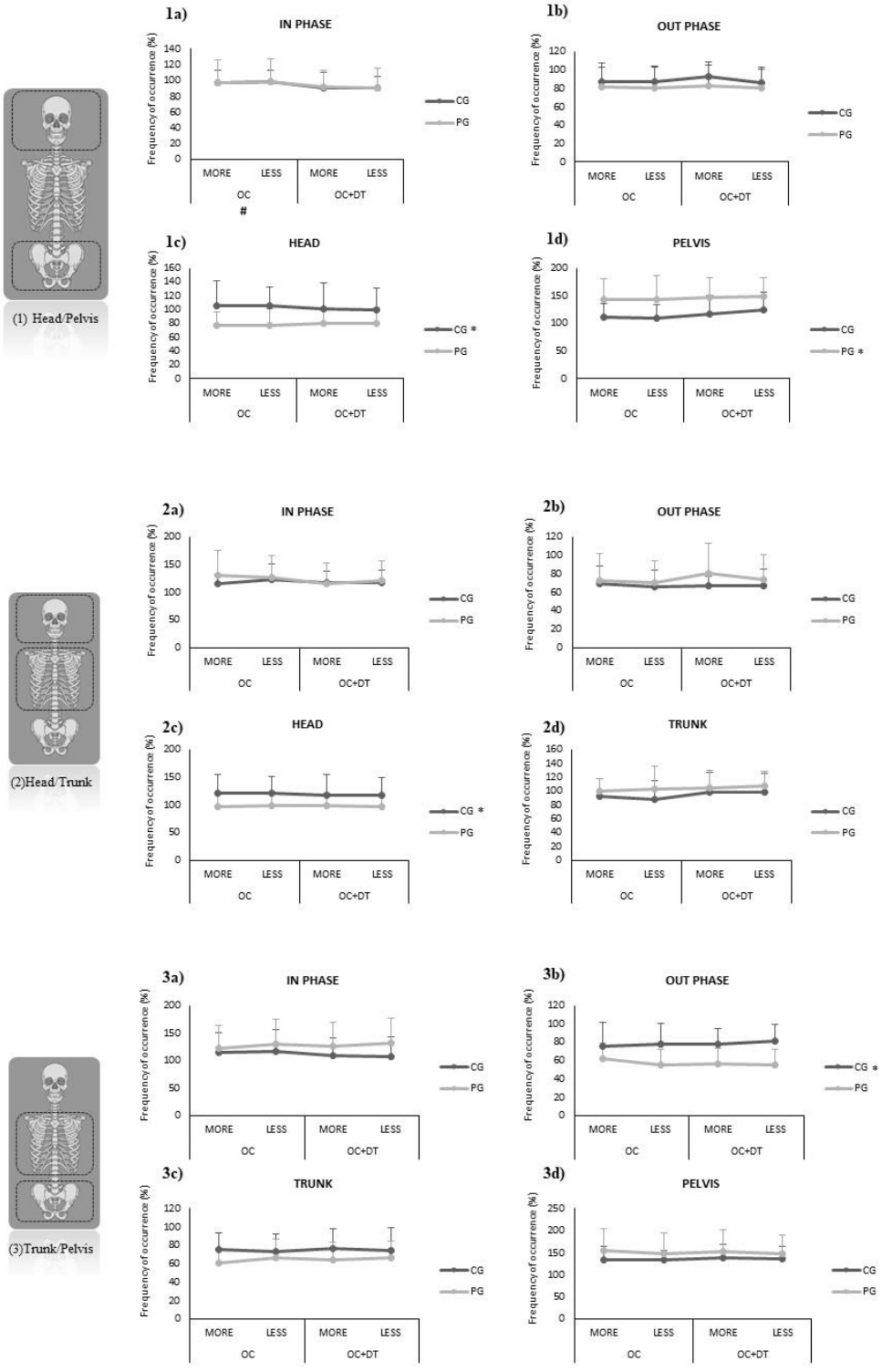
Only a group effect was found for the coupling between trunk and pelvis (out of phase: $F_{1,31}$ = 11.840, p=0.002, η^2=0.276). The CG had a greater out-of-phase pattern between trunk and pelvis compared to the PG (Figure 9 – 3b).

Figure 8. Intersegmental coordination between thighs, legs and feet during an obstacle cirvumvention with and without a dual task to the more and less affected side.



*: indicates main effects of group; #: # Indicates main effects of task; Combination of continuous rectangles indicates interaction effects between Group x side.

Figure 9. Intersegmental coordination between head-pelvis (1), head-trunk (2) and trunk-pelvis (3) during an obstacle cirvumvention with and without a dual task to the more and less affected side.



*: indicates main effects of group; #: # Indicates main effects of task.

3.4 Discussion

This study aimed to investigate whether circumventing an obstacle to the side more or less affected by PD during a dual task compromises the intersegmental coordination pattern between the lower limbs and the axial segment. The initial hypothesis was that the axial coordination pattern would be more in phase when performing the deviation to the side more affected by the disease. In addition, it was expected that performing a dual task would increase the in-phase pattern between the segments. Finally, it was assumed that pwPD would have a greater pattern of coordination in phase of the axial segments and between the limbs. Contrary to the predicted hypotheses, in general, the side to which the circumvention was performed did not interfere with the intersegmental coordination pattern, nor did the concomitant performance of a dual cognitive task, except for some specific observations that will be discussed in the following paragraphs. The main result identified was the differences between the groups, showing that pwPD and neurologically healthy individuals adopt different coordination patterns, with these differences being even more marked in axial coordination.

The main finding of this study is the difference in the pattern of axial coordination between the groups. In the coordination between head-pelvis and head-trunk, individuals with PD had less coordination of the head compared to the control group. This finding is in line with Silveira-Ciola et al. (2021), who reported less head coordination in individuals with PD during obstacle circumvention. Thus, the results reinforce the lower pattern of head coordination in individuals with PD, possibly reflecting limitations associated with axial rigidity, a typical characteristic of the disease (Franzén *et al.,* 2009). Delayed head rotation, frequently observed in individuals with PD and freezing, also corroborates these findings (Spildooren *et al.*, 2013).

Although they presented less coordination of the head, individuals with PD showed greater coordination of the pelvis compared to the control group in the head-pelvis pattern. Vaugoyeau et al. (2006) reported that individuals with PD show a delay in axial movement during the start of diagonal walking, following the sequence: head, shoulders and pelvis (Vaugoyeau *et al.,* 2006). In the present study, the lower predominance of the head coordination pattern may indicate greater dependence on the pelvis strategy to compensate for limitations in the other segments. Finally, the control group showed greater out-of-phase coordination between the trunk and pelvis compared to individuals with PD. Previous studies

(Huxham *et al.*, 2008; Silveira-Ciola *et al.*, 2021) have already highlighted that neurologically healthy older people show greater dissociation between trunk and pelvis during obstacle deviations/turning, reflecting greater segmental independence. Thus, measures that assess trunk coordination and axial stiffness can be useful for the initial diagnosis of PD (Van Emmerik *et al.*, 1999). Individuals with PD, even in the early stages, can show symptoms that differentiate them from healthy elderly people (Bonacina *et al.*, 2024), which can help with early diagnosis (Baltadjieva *et al.*, 2006; Wu *et al.*, 2021). As the disease progresses, these differences in gait become even more evident (Vila *et al.*, 2021). In the present study, individuals in the moderate stage of PD were assessed, and the results show distinct patterns of intersegmental coordination between the groups, helping to differentiate between this population.

In the coordination pattern between the lower limbs, some notable differences were identified between the groups. Firstly, the control group (CG), when performing the circumvention to the dominant side, showed greater coordination of the right leg compared to the Parkinson's group (PD) when performing the circumvention to the less affected side. Although all 17 individuals with PD were right-handed, 11 of them had the right side as the most affected by the disease. Possibly, the motor symptoms of Parkinson's on the right side may have favored a lower coordination pattern in this leg compared to the healthy elderly. In addition, the CG showed greater coordination of the right leg when performing the deviation to the dominant side compared to the non-dominant side, which reflects the predominance of laterality among the group's participants (15 right-handed and only 2 left-handed).

The PD showed an unexpected pattern, with greater “out of phase” coordination between the feet, especially when deviating to the less affected side. This finding contradicts the initial hypotheses since it was expected to observe a less rhythmic movement (more in phase) in this population, regardless of the side of the circumvention. Studies suggest that interlimb coordination is more adaptable than intralimb coordination during gait (Haddad *et al.*, 2006; Whitall; Caldwell, 1992) allowing the locomotor system to employ compensatory strategies to deal with the demands of the task and environmental restrictions. Despite the motor asymmetry characteristic of PD, both limbs seem to contribute to the necessary adjustments in coordination during walking. The locomotor system can adjust coordination between the limbs individually as a way of adapting to changes caused by injury or dysfunction (Haddad *et al.*, 2006). In this context, there is evidence that separate functional

networks control the circuits of the right and left limbs (Lopes, 2010), indicating the possibility of training them individually. This approach could offer a new therapeutic perspective for correcting gait asymmetries, especially in individuals with PD (Choi; Bastian, 2007).

The dual task did not negatively influence the coordination of most of the couplings, to the extent that was expected. Except when checking the head-pelvis and thigh-thigh patterns, in which “in-phase” coordination was greater in the obstacle circumvention task compared to the dual-task condition. This finding is significant, considering that dual-task situations often amplify motor deficits in individuals with PD (Kelly; Eusterbrock; Shumway-Cook, 2012a; Raffegeau *et al.*, 2019a), especially during challenging tasks (Koçer *et al.*, 2023). Furthermore, walking is particularly vulnerable to cognitive load due to the unique sensitivity of bilateral limb coordination to dual-task effects (Yogev-Seligmann; Hausdorff; Giladi, 2008).

The literature shows that dual-tasking impairs motor performance in pwPD, compromising bilateral coordination, symmetry and increasing gait variability (Plotnik; Giladi; Hausdorff, 2009a; Yogev *et al.*, 2005; 2007). This impact occurs due to the attentional overload caused by the simultaneous execution of tasks, resulting in an increased risk of falls, especially in elderly fallers and pwPD (Plotnik; Giladi; Hausdorff, 2009a). Evidence also indicates that tasks involving internal factors of cognitive interference, such as mental calculations, tend to impair gait control more than external factors (Al-Yahya *et al.*, 2011a). Thus, the use of DT walking tests is a useful tool for the early identification of executive and motor deficits in PD. Unexpectedly, our study was not in line with the results reported in the literature.

In the present study, the greater “in-phase” coordination observed during OC (without dual-tasking) may reflect a functional adaptation during obstacle avoidance. In this condition, the head and pelvis operated in a more synchronized way, possibly facilitating changes in direction and the motor adaptations needed to avoid the obstacle. This pattern suggests that, in the absence of cognitive interference, these segments perform their functions more efficiently. In addition, dual-task training has been proposed as an effective rehabilitative strategy with the potential to automate movements and reduce secondary interference in PD (Tan *et al.*, 2024). It is important to consider that, in everyday life, the situations faced by individuals with PD often involve challenges closer to the conditions evaluated here, such as avoiding

obstacles (a table, irregularities in the ground, avoiding contact with a person on the street, etc). This gap between simple gait tasks and more complex situations, such as 360° turns, still requires greater understanding in order to better guide interventions and rehabilitation strategies that reflect situations with environmental demands that represent everyday life.

Some limitations should be considered in future studies to answer the gaps that remain: i) the participants were not instructed to choose a single strategy to perform the circumvention (lead-in or lead-out). This is a fact that should be taken into account, since approaching the obstacle with the leg closest to it or furthest from it could influence the pattern of the other segments; ii) the initial distance of the obstacle for all individuals was standardized, however, the moment at which individuals actually started the detour was not controlled; iii) errors in the cognitive task were counted, however, we did not ask participants whether they prioritized the walking task or the cognitive task, as well as whether they found this task easy, moderate or difficult.

3.5 Conclusion

Turning away from an obstacle, whether to the more or less affected side in individuals with PD, did not compromise the intersegmental coordination pattern as extensively as anticipated. Similarly, the addition of a dual cognitive task during walking under environmental demands (presence of an obstacle) did not significantly affect the axial and inter-limb coordination patterns in individuals with PD. This suggests that the cognitive task may not have fully engaged the patients' cognitive resources to the extent necessary to impair gait performance. Nonetheless, differences between the groups were evident, reinforcing the potential of intersegmental coordination as a measure to distinguish individuals with PD from neurologically healthy controls.

REFERENCES

AL-YAHYA, E. *et al.* Cognitive motor interference while walking: a systematic review and meta-analysis. **Neuroscience and biobehavioral reviews**, [*s. l.*], v. 35, n. 3, p. 715–728, 2011. Available at: https://pubmed.ncbi.nlm.nih.gov/20833198/. Accessed at: 22 Nov. 2024.

ALCOCK, L.; O'BRIEN, T. D.; VANICEK, N. Association between somatosensory, visual and vestibular contributions to postural control, reactive balance capacity and healthy ageing in older women. **Health care for women international**, [*s. l.*], v. 39, n. 12, p. 1366–1380, 2018. Available at: https://pubmed.ncbi.nlm.nih.gov/30395787/. Accessed at: 22 Nov. 2024.

BALTADJIEVA, R. *et al.* Marked alterations in the gait timing and rhythmicity of patients with de novo Parkinson's disease. **European Journal of Neuroscience**, [*s. l.*], v. 24, n. 6, p. 1815–1820, 2006.

BARBIERI, F. A. *et al.* Obstacle Avoidance Increases Asymmetry of Crossing Step in Individuals With Parkinson's Disease and Neurologically Healthy Individuals. **Journal of Motor Behavior**, [*s. l.*], v. 50, n. 1, p. 17–25, 2018.

BONACINA, D. *et al.* Spatiotemporal, kinematic and kinetic gait characteristics in Parkinson's disease compared to healthy individuals: A systematic review with meta-analysis. **Clinical biomechanics (Bristol, Avon)**, [*s. l.*], v. 120, 2024. Available at: https://pubmed.ncbi.nlm.nih.gov/39426345/. Accessed at: 22 Nov. 2024.

BRUCKI, S. M. D. *et al.* Sugestões para o uso do mini-exame do estado mental no Brasil. **Arquivos de Neuro-Psiquiatria**, [*s. l.*], v. 61, n. 3 B, p. 777–781, 2003. Available at: https://www.scielo.br/j/anp/a/YgRksxZVZ4b9j3gS4gw97NN/?lang=pt. Accessed at: 22 Nov. 2024.

BRYANT, M. S. *et al.* Acute and Long-Term Effects of Multidirectional Treadmill Training on Gait and Balance in Parkinson Disease. **PM & R : the journal of injury, function, and rehabilitation**, [*s. l.*], v. 8, n. 12, p. 1151–1158, 2016. Available at: https://pubmed.ncbi.nlm.nih.gov/27178378/. Accessed at: 22 Nov. 2024.

CANO-DE-LA-CUERDA, R. *et al.* Axial rigidity is related to the risk of falls in patients with Parkinson's disease. **NeuroRehabilitation**, [*s. l.*], v. 40, n. 4, p. 569–577, 2017. Available at: https://pubmed.ncbi.nlm.nih.gov/28211826/. Accessed at: 22 Nov. 2024.

CHANG, R.; VAN EMMERIK, R.; HAMILL, J. Quantifying rearfoot–forefoot coordination in human walking. **Journal of Biomechanics**, [*s. l.*], v. 41, n. 14, p. 3101–3105, 2008.

CHOI, J. T.; BASTIAN, A. J. Adaptation reveals independent control networks for human walking. **Nature neuroscience**, [*s. l.*], v. 10, n. 8, p. 1055–1062, 2007. Available at: https://pubmed.ncbi.nlm.nih.gov/17603479/. Accessed at: 22 Nov. 2024.

DINGWELL, J. B.; DAVIS, B. L.; FRAZIER, D. M. Use of an instrumented treadmill for real-time gait symmetry evaluation and feedback in normal and trans-tibial amputee subjects.

Prosthetics and orthotics international, [*s. l.*], v. 20, n. 2, p. 101–110, 1996. Available at: https://pubmed.ncbi.nlm.nih.gov/8876003/. Accessed at: 22 Nov. 2024.

FRANZÉN, E. *et al.* Reduced Performance in Balance, Walking and Turning Tasks is Associated with Increased Neck Tone in Parkinson's Disease. **Experimental neurology**, [*s. l.*], v. 219, n. 2, p. 430, 2009. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC2775914/. Accessed at: 22 Nov. 2024.

GOETZ, C. G. *et al.* Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. **Movement disorders : official journal of the Movement Disorder Society**, [*s. l.*], v. 19, n. 9, p. 1020–1028, 2004. Available at: https://pubmed.ncbi.nlm.nih.gov/15372591/. Accessed at: 22 Nov. 2024.

HADDAD, J. M. *et al.* Adaptations in interlimb and intralimb coordination to asymmetrical loading in human walking. **Gait & posture**, [*s. l.*], v. 23, n. 4, p. 429–434, 2006. Available at: https://pubmed.ncbi.nlm.nih.gov/16099160/. Accessed at: 22 Nov. 2024.

HERZOG, W. *et al.* Asymmetries in ground reaction force patterns in normal human gait. **Medicine and science in sports and exercise**, [*s. l.*], v. 21, n. 1, p. 110–114, 1989. Available at: https://pubmed.ncbi.nlm.nih.gov/2927295/. Accessed at: 22 Nov. 2024.

HUGHES, A. J. *et al.* Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. **Journal of neurology, neurosurgery, and psychiatry**, [*s. l.*], v. 55, n. 3, p. 181–184, 1992. Available at: https://pubmed.ncbi.nlm.nih.gov/1564476/. Accessed at: 22 Nov. 2024.

HUXHAM, F. *et al.* Head and trunk rotation during walking turns in Parkinson's disease. **Movement disorders : official journal of the Movement Disorder Society**, [*s. l.*], v. 23, n. 10, p. 1391–1397, 2008. Available at: https://pubmed.ncbi.nlm.nih.gov/18528897/. Accessed at: 22 Nov. 2024.

KELLY, V. E.; EUSTERBROCK, A. J.; SHUMWAY-COOK, A. A review of dual-task walking deficits in people with Parkinson's disease: motor and cognitive contributions, mechanisms, and clinical implications. **Parkinson's disease**, [*s. l.*], v. 2012, 2012. Available at: https://pubmed.ncbi.nlm.nih.gov/22135764/. Accessed at: 22 Nov. 2024.

KOÇER, B. *et al.* Comparison of dual-task costs during different types of walking in people with Parkinson's disease: a controlled study. **Acta neurologica Belgica**, [*s. l.*], v. 123, n. 6, p. 2221–2227, 2023. Available at: https://pubmed.ncbi.nlm.nih.gov/37036604/. Accessed at: 22 Nov. 2024.

LOPES, A. A. A Marcha: a influência do Gerador de Padrão Central. [*s. l.*], p. 1–14, 2010. Available at: http://recipp.ipp.pt/bitstream/10400.22/1307/1/COM_AlexandreLopes_2010.pdf%0Ahttps://academic.oup.com/ptj/article/2837028/Central%0Ahttp://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11784280%0Ahttp://recipp.ipp.p.

MARTÍNEZ-MARTÍN, P. *et al.* Unified Parkinson's Disease Rating Scale characteristics and

structure. The Cooperative Multicentric Group. **Movement disorders : official journal of the Movement Disorder Society**, [*s. l.*], v. 9, n. 1, p. 76–83, 1994. Available at: https://pubmed.ncbi.nlm.nih.gov/8139608/. Accessed at: 22 Nov. 2024.

MIRELMAN, A. *et al.* Gait impairments in Parkinson's disease. **The Lancet Neurology**, [*s. l.*], v. 18, n. 7, p. 697–708, 2019.

PLOTNIK, M.; GILADI, N.; HAUSDORFF, J. M. Bilateral coordination of gait and Parkinson's disease: the effects of dual tasking. **Journal of neurology, neurosurgery, and psychiatry**, [*s. l.*], v. 80, n. 3, p. 347–350, 2009. Available at: https://pubmed.ncbi.nlm.nih.gov/19228674/. Accessed at: 22 Nov. 2024.

RAFFEGEAU, T. E. *et al.* A meta-analysis: Parkinson's disease and dual-task walking. **Parkinsonism & related disorders**, [*s. l.*], v. 62, p. 28–35, 2019. Available at: https://pubmed.ncbi.nlm.nih.gov/30594454/. Accessed at: 22 Nov. 2024.

RINALDI, N. M.; EMMERIK, R. van; MORAES, R. Changes in interlimb coordination during walking and grasping task in older adult fallers and non-fallers. **Human movement science**, [*s. l.*], v. 55, p. 121–137, 2017. Available at: https://pubmed.ncbi.nlm.nih.gov/28810172/. Accessed at: 22 Nov. 2024.

SILVEIRA-CIOLA, A. P. *et al.* The starting distance of obstacle circumvention did not affect intersegmental coordination in individuals with Parkinson's disease. **Human Movement Science**, [*s. l.*], v. 80, n. August, p. 1–9, 2021.

SIMIELI, L. *et al.* Gaze and motor behavior of people with PD during obstacle circumvention. **Gait & posture**, [*s. l.*], v. 58, p. 504–509, 2017. Available at: https://pubmed.ncbi.nlm.nih.gov/28950250/. Accessed at: 22 Nov. 2024.

SPILDOOREN, J. *et al.* Head-pelvis coupling is increased during turning in patients with Parkinson's disease and freezing of gait. **Movement disorders : official journal of the Movement Disorder Society**, [*s. l.*], v. 28, n. 5, p. 619–625, 2013. Available at: https://pubmed.ncbi.nlm.nih.gov/23408374/. Accessed at: 22 Nov. 2024.

SZAMEITAT, A. J. *et al.* Localization of executive functions in dual-task performance with fMRI. **Journal of cognitive neuroscience**, [*s. l.*], v. 14, n. 8, p. 1184–1199, 2002. Available at: https://pubmed.ncbi.nlm.nih.gov/12495525/. Accessed at: 22 Nov. 2024.

TAN, X. *et al.* A Review of Recent Advances in Cognitive-Motor Dual-Tasking for Parkinson's Disease Rehabilitation. **Sensors (Basel, Switzerland)**, [*s. l.*], v. 24, n. 19, 2024. Available at: https://pubmed.ncbi.nlm.nih.gov/39409390/. Accessed at: 22 Nov. 2024.

VAN EMMERIK, R. E. A. *et al.* Identification of axial rigidity during locomotion in Parkinson disease. **Archives of physical medicine and rehabilitation**, [*s. l.*], v. 80, n. 2, p. 186–191, 1999. Available at: https://pubmed.ncbi.nlm.nih.gov/10025495/. Accessed at: 22 Nov. 2024.

VAUGOYEAU, M. *et al.* Axial rotation in Parkinson's disease. **Journal of Neurology,**

Neurosurgery, and Psychiatry, [*s. l.*], v. 77, n. 7, p. 815, 2006. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC2117490/. Accessed at: 22 Nov. 2024.

VILA, M. H. *et al.* Analysis of Gait for Disease Stage in Patients with Parkinson's Disease. **International Journal of Environmental Research and Public Health**, [*s. l.*], v. 18, n. 2, p. 720, 2021. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC7830506/. Accessed at: 17 Oct. 2024.

WHITALL, J.; CALDWELL, G. E. Coordination of symmetrical and asymmetrical human gait. **Journal of motor behavior**, [*s. l.*], v. 24, n. 4, p. 339–353, 1992. Available at: https://pubmed.ncbi.nlm.nih.gov/14769563/. Accessed at: 22 Nov. 2024.

WU, Z. *et al.* Mild Gait Impairment and Its Potential Diagnostic Value in Patients with Early-Stage Parkinson's Disease. **Behavioural Neurology**, Wu Z; Department of Geriatric Neurology, Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China., v. 2021, p. 6696454, 2021. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8041560. Accessed at: 21 Sep. 2023.

WU, T.; HALLETT, M. Neural correlates of dual task performance in patients with Parkinson's disease. **Journal of neurology, neurosurgery, and psychiatry**, [*s. l.*], v. 79, n. 7, p. 760–766, 2008. Available at: https://pubmed.ncbi.nlm.nih.gov/18006652/. Accessed at: 22 Nov. 2024.

YOGEV-SELIGMANN, G.; HAUSDORFF, J. M.; GILADI, N. The role of executive function and attention in gait. **Movement disorders : official journal of the Movement Disorder Society**, [*s. l.*], v. 23, n. 3, p. 329–342, 2008. Available at: https://pubmed.ncbi.nlm.nih.gov/18058946/. Accessed at: 22 Nov. 2024.

YOGEV, G. *et al.* Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? **The European journal of neuroscience**, [*s. l.*], v. 22, n. 5, p. 1248–1256, 2005. Available at: https://pubmed.ncbi.nlm.nih.gov/16176368/. Accessed at: 22 Nov. 2024.

YOGEV, G. *et al.* Gait asymmetry in patients with Parkinson's disease and elderly fallers: when does the bilateral coordination of gait require attention? **Experimental brain research**, [*s. l.*], v. 177, n. 3, p. 336–346, 2007. Available at: https://pubmed.ncbi.nlm.nih.gov/16972073/. Accessed at: 22 Nov. 2024.

CHAPTER 4

Study 3: Influence of the difficulty of the cognitive task during walking on the asymmetry of spatial-temporal parameters and cortical activity in individuals with Parkinson's disease

Influence of the difficulty of the cognitive task during walking on the asymmetry of spatial-temporal parameters and cortical activity in individuals with Parkinson's disease

ABSTRACT

Background: Dual tasking (DT) during gait competes for cognitive resources, which can impair performance, especially in people with Parkinson's disease (pwPD), due to decreased movement automaticity and basal ganglia dysfunction. The interaction between cognitive dual tasks and gait asymmetry, especially using real-time neural assessments, remains limited. **Aim:** To investigate how the level of difficulty in cognitive DT during gait impacts symmetry of spatial-temporal parameters and cortical activity in pwPD. **Methods:** 15 individuals diagnosed with PD and 15 age-matched neurologically healthy individuals (NHI) were evaluated. Gait was assessed (ON state) in situations with and without (ST) a cognitive DT. Participants walked for 25 seconds, uninterruptedly, at their preferred speed on an 8.5m long walkway. The degree of difficulty of the DT was categorized into five conditions: i) very easy (VE); ii) easy (E); iii) moderate (M); iv) reasonably difficult (RD); and v) difficult task (D). They were instructed to count “how many times the number ‘x’ is spoken in the audio”. At the end of each attempt, participants were asked how many times the wildcard number was spoken. In total, the participants performed 18 trials, three per condition. Spatial-temporal parameters were collected, alongside cortical activity in the prefrontal, sensorimotor, and occipital regions. Symmetry indices were calculated for both metrics. The Mann-Whitney test was used to assess group differences, while Friedman test evaluated the effects of DT difficulty. Statistical significance was set at $p < 0.05$. **Results:** pwPD exhibit greater asymmetry in spatial-temporal parameters (step speed, double support and swing time) and cortical activity (pré-frontal, sensoriomotora and occipital) compared to NHI. The task difficulty increased the asymmetry of step speed and swing time exclusively in individuals with PD. Asymmetry of the gamma band in the occipital region was greater in VE task compared to the ST. **Conclusion:** When walking with different cognitive DT difficulties, pwPD exhibit greater asymmetry in spatial-temporal parameters and cortical activity compared to NHI. The effects of task difficulty on asymmetry were exclusively in individuals with PD.

Keywords: cortex; symmetry; gait; neurodegenerative disorders; neuroscience

4.1 INTRODUCTION

When performing two tasks simultaneously, there is competition for cognitive resources that, when limited, can cause worse performance in one or both tasks (Woollacott; Shumway-Cook, 2002), especially if these tasks compete for the same processing resources (Ruthruff; Pashler; Klaassen, 2001). Performing a dual task can impair walking performance, especially in the elderly population and individuals with neurodegenerative diseases (Kahya *et al.*, 2019), such as Parkinson's disease (PD). Some reasons related to PD itself may contribute to poorer walking performance in PD (Kelly; Eusterbrock; Shumway-Cook, 2012), including: i) decreased movement automaticity due to changes in the circuitry of the basal ganglia and, consequently, greater dependence on cognitive resources to control movements (Takakusaki *et al.*, 2004); ii) dysfunction of the basal ganglia mediated by dopamine, contributing to executive function deficits (Zgaljardic *et al.*, 2006); and iii) alterations in non-dopaminergic pathways measured by other neurotransmitters such as serotonin (Barone, 2010).

The combination of these factors compromises the performance of DT during walking, resulting in lower speed and step length (Raffegeau *et al.*, 2019; Rochester *et al.*, 2004), worse bilateral coordination between the lower limbs (Plotnik; Giladi; Hausdorff, 2008), less flexion-extension of the hip, knee and ankle joints (Pinto *et al.*, 2020) and increased variability (Plotnik *et al.*, 2011). Furthermore, in situations where tasks are concomitant with walking, the asymmetry seems to intensify even more (Kleiner *et al.*, 2017; Plotnik *et al.*, 2005; Plotnik; Giladi; Hausdorff, 2009; Yogev *et al.*, 2007).

Asymmetry in PD is a characteristic present from the beginning of the disease - manifested by the classic motor signs - and persists throughout its progression, causing changes in locomotor activities (Barbieri *et al.*, 2018; Boonstra *et al.*, 2014; Djaldetti; Ziv; Melamed, 2006; Miller-Patterson *et al.*, 2018; Verreyt *et al.*, 2011), in addition to generating functional and structural changes in the cerebral cortex (Claassen *et al.*, 2016). In addition, motor asymmetry in PD seems to influence cognitive function (Coloman; Chimagomedova, 2020). However, only two studies have investigated the effects of cognitive dual-tasking and its implications for gait asymmetry and neural connectivity (Peterson *et al.*, 2015; Vervoort *et al.*, 2016); however, in both studies, neural assessment was not carried out concurrently with walking, which limits the extrapolation of these findings to situations in which information is obtained in real time (for example, using an electroencephalogram - EEG).

Aging and age-related neurodegenerative conditions results in increased brain activity specifically in the PFC while walking with a DT (Kahya *et al.*, 2019). When considering the unique findings of DT in PD gait there is greater cortical activation of the prefrontal cortex [PFC] and motor cortex [M1] (Al-Yahya *et al.*, 2011). In addition, a lower response in the theta bands has been found in cognitive tasks (Ozdemir *et al.*, 2016). More complex tasks can further compromise walking (Lapointe; Stierwalt; Maitland, 2010), as the brain may have limited cognitive reserve (Stern, 2009). However, little is known about the effect of the level of difficulty of cognitive DT or which cognitive skill "depletes" this cognitive processing capacity, impairing the spatial-temporal parameters of walking in people with PD (pwPD).

These factors make us wonder: is any cognitive task detrimental? If deficits occur due to increased cognitive load and difficulty in prioritizing the most important task, is there a cut-off line to define how much difficulty is needed to initiate deficits? Furthermore, what are the neural mechanisms behind the interaction between walking and cognition? In a recent systematic review, this gap was made clear, emphasizing that the mechanism of the interrelation between gait and cognitive is still nuclear (Wang *et al.*, 2020).

Thus, the aim of the study is to investigate the effect of the level of difficulty of the cognitive dual task during walking on spatial-temporal parameters symmetry and cortical activity in individuals with Parkinson's disease. Three hypotheses were raised: i) PD will present asymmetry of spatial-temporal parameters (step length, duration and speed); ii) lower activation of the theta band with high asymmetry in the prefrontal cortex during DT as a way of compensating for deficits during this activity (Kahya *et al.*, 2019); iii) the difficulty of the dual task will modulate the intensity of these impairments, and the more difficult the task, the greater these asymmetries.

4.2 METHODS

4.2.1 Participants and experimental design

The study included 15 individuals diagnosed with PD (PG) and 15 NHI (CG) matched for age and gender. The groups were matched according to age and gender. Individuals of PG were recruited through the "Ativa Parkinson" Extension Project offered by the São Paulo State University "Júlio de Mesquita Filho" (UNESP) - Bauru Campus. While CG individuals were composed by friends or family members of individuals with PD, university employees or elderly participants of other UNESP projects. The minimum number of participants for the

study was determined using the “G power” software based on the article by Bond et al (2000), indicating nine participants per group. This number of participants per group represents a probability index of finding a significant difference of 0.95 and an α value of 0.05.

As inclusion criteria, pwPD should have their medical diagnosis confirmed by a neurologist according to the UK Brain Bank (Hughes *et al.*, 1992), being classified in stages 1 to 3 on the modified Hoehn & Yahr Scale, and being under drug treatment with levodopa. They could be excluded if presented one of the following items (for both groups): age below 60 years; presence of other neurological disorders, cardiac problems (i.e., arrhythmias, indication of myocardial ischemia), musculoskeletal disorders (Alcock; O’Brien; Vanicek, 2018); cognitive deficits (verified by the Mini Mental State Examination - MMSE) and brain surgery or deep brain stimulation (DBS) for the treatment of PD (Bryant *et al.*, 2016). The study was approved by the Local Research Ethics Committee (CAAE: 78660517.2.0000.5398). All participants were informed about the study procedures and invited to sign the Informed Consent Form.

The assessments (clinical and gait evaluation) were performed in one visit to the Human Movement Research Laboratory (MOVI-LAB) - UNESP - Campus de Bauru. All participants of the PG were instructed to take the dopaminergic medication 1 hour before the evaluations.

4.2.2 Clinical assessments

The characteristics of the sample (name, age, sex and education), anthropometric measurements (body mass, height and body mass index [BMI]), clinical, cognitive, and medication history were acquired. Motor impairment was assessed using the Unified Parkinson’s Disease Rating Scale (UPDRS - Part III), where higher scores indicate more severe motor symptoms (Martínez-Martín *et al.*, 1994). Additionally, the stage of disease progression was determined using the modified Hoehn & Yahr Scale (H&Y) (Goetz *et al.*, 2004). The symmetry index of motor symptoms was calculated using UPDRS items 20, 21, 22, 23, 25, and 26 by subtracting the score of the right limb from the left. Positive values indicated greater impairment in the right limb, while negative values indicated more involvement of the left limb. For the control group (CG), manual preferences were identified. Hand preference was determined by observing the hand used for writing. Cognitive functions were evaluated using both the Mini-Mental State Examination (MMSE) (Brucki *et al.*, 2003)

and Montreal Cognitive Assessment (MoCA) (Cesar *et al.*, 2019), with scores adjusted according to the participants' education level. Similarly to the MMSE, the MoCA is an instrument used to screen for cognitive decline and its maximum score is 30 points. However, it has categories that assess executive function, visuospatial ability, short-term memory, attention, concentration and working memory, language and temporal and spatial orientation.

4.2.3 Gait assessment

Gait was assessed in situations without a single task and with a concomitant cognitive dual task. Participants walked for 25 seconds, uninterruptedly, at their preferred speed on an 8.5m long and 3.5m wide walkway. The subjects were instructed to walk in a straight line to the end of the walkway, change direction while standing still (180°) and return along the same straight line. An evaluator accompanied the participants throughout the walkway for safety purposes. In the cognitive dual task trials, the degree of difficulty of the task was categorized into five conditions: i) very easy task (VE); ii) easy task (E); iii) moderate task (M); iv) reasonably difficult task (RD); and v) difficult task (D). Twenty-five-second audios (25 s) were used, recorded in advance, which presented a sequence of twelve different numbers (from 0 to 9). The following instruction was given before each task: “You will count how many times the number ‘x’ is spoken in the audio”. The wildcard number was provided to the participant before starting the attempt. The individuals were not allowed to count out loud and to use their hands to help quantify the numbers. At the end of each attempt, participants were asked how many times the wildcard number was spoken to account for mistakes and successes. A familiarization attempt was granted before each condition.

For example, the participant was instructed to count how many times the number 2 appeared in the audio during the walking task (e.g. 0 **2** **2** 4 1 1 5 6 **2** 1 **2** 5). At the end of the attempt, they were asked how many times the number 2 appeared in the audio. The sucesses (correct indication of the number of times the requested number was spoken, in this example, 4 times) or mistakes (incorrect indication of the number of times the requested number was spoken, in this example, 2 times) of the cognitive task were counted to calculate the absolute error (difference between the correct answer and the answer given by the participant - in this example, if the participant spoke “2”, the amplitude of the error would be: 4-2 = 2). The numbers spoken through the audio did not have a constant frequency to prevent the participant from using it as an auditory cue while walking. In order to gradually increase the

difficulty in the study conditions, more than a single wildcard number was spoken in the sequence: i) VE: sequence with only one number (which will also be the wildcard; e.g.: **1 1 1 1 1 1 1 1 1 1 1**); ii) E: sequence with six numbers and one wildcard (e.g. 0 2 2 4 **1 1** 5 6 2 **1** 2 5); iii) M: sequence with six numbers and two wildcards (e.g. 0 **2** 4 **2 1 2** 5 6 **2 1 2** 5); iv) RD: sequence with six numbers and three wildcards (e.g.: 0 **2 2 4 1 1** 5 6 **2 1** 5); and v) D: sequence with six numbers and four wildcards (e.g.: 0 **2 2 4 1 1 5** 6 **2 1 5**). The number of times a given number appeared in the sequence was randomized. The participants' gait was also assessed without the effect of a DT (named the “single task” condition). The order of the conditions was randomized among the participants. In total, the participants performed 18 trials, three per condition. Every six trials there was a one-minute rest period to avoid the effects of tiredness and/or fatigue.

Kinematic data was carried out using the three-dimensional data acquisition system from Vicon® 3D (Vicon Motion Systems Ltd. UK). Eight cameras (Bonita System Cameras), with a sampling frequency of 200 Hz, record all attempts. Thirty-nine photo reflexive markers were positioned at the participant's anatomical points following the model "Plug-in Gait Full Body" (Vicon®). The data were filtered through a 5th order low-pass Butterworth filter (zero-lag) and a cutoff frequency of 6 Hz.

4.2.4 Data analysis

Spatial-temporal data

The spatial-temporal parameters of gait were determined based on photo-reflective markers placed on the participants' feet (dorsum of the foot between the second and third metatarsals and the posterior region of the calcaneus). The acceleration and deceleration phases (start and end of the walkway, respectively) were excluded from the analysis of spatial-temporal parameters. Therefore, the five central steps were analyzed for each trial, totaling 10 steps. Based on the 10 steps, the average of each leg was calculated for the parameters of interest. Next, the average of the 3 trials was calculated for each parameter: step length, width, duration and speed, double support time and swing time. Finally, the symmetry index was applied to all the spatial-temporal gait parameters (Dingwell; Davis; Frazier, 1996; Herzog *et al.*, 1989):

$$\text{Symmetry index} = \frac{\text{(less affected side – more affected side)}}{\text{(less affected side + more affected side)}} \times 100\%$$

The same formula was applied to the CG. However, “least affected member” was replaced by preferred member and “most affected member” by non-preferred member. The most affected/non-preferred member was considered to be the one with the lowest swing time value. A value of zero in the symmetry index indicates that there is no difference between the sides. The higher the value, the greater the asymmetry between the sides.

Cortical activity data

Cerebral cortex activity was recorded throughout the gait assessment. The procedures described in analysis were the same used by Araújo-Silva (Araújo-Silva *et al.*, 2022). The procedures suggested by the manufacturers of the portable EEG system (eego^{TM}sports, ANT Neuro, Enschede, Netherlands) with a sampling frequency of 1024 Hz were used to collect the signal. A cap with 64 active electrodes connected to an amplifier was used to record and send the signal in real time via Wi-Fi to the control computer. The positioning of the cap followed the norms of the international electrode positioning system (standard 10/10 positioning (Oostenveld; Praamstra, 2001). An electrode was also used to detect eye movements. Data on the electrical activity of the cerebral cortex was recorded using EEGO^{TM} software (ANT Neuro, Enschede, Netherlands). The signal analysis procedures were carried out in the open source software EEGLAB (sccn.ucsd.edu/eeglab; (Delorme *et al.*, 2011)). The raw signal was filtered with a 4th order 0.5-50 Hz Buttherworth band-pass filter. Visual inspection to identify large artefact periods (Whittier *et al.*, 2020). Channels with a standard deviation (SD) higher than 400 μV and > 5SD from the mean were removed (https://sccn.ucsd.edu/wiki/EEGLAB_Wiki) (Gwin *et al.*, 2010). A down-sample was performed to 512 Hz and the data was re-referenced to the common average (Whittier *et al.*, 2020). The Independent Component Analysis (ICA - Runica) was performed to remove artifacts such as blinking and eye movement, muscle componente and other potential artifacts (Radüntz *et al.*, 2015). Artefatos remanescentes foram identificados por meio de inspeção visual e removidos (Faria *et al.*, 2023; Santinelli *et al.*, 2021). The average power spectral density analysis (PSD) (Yuvaraj *et al.*, 2014) was then performed in the following frequency bands: right (Fp2, F8 and F4) and left (Fp1, F7 and F3) prefrontal cortex, right (T8, C4, P8, P4) and left (T7, C3, P7, P3) sensorimotor cortex and right (O2) and left (O1) occipital cortex (Tropini *et al.*, 2011). In addition, the following frequency bands were considered for the

analysis and calculation of the variables: theta (θ): 4-7 Hz; alpha (α): 8-12 Hz; beta (β): 13-30 Hz; gamma (γ): 31-50 Hz.

The EEG signal of all participants was recorded at rest and during walking. In the resting trials, the participant remained seated while performing the same dual tasks as during walking. In this way, PSD during walking was normalized by the value of PSD at rest:

$$\Delta PSD = PSD\ walking/PSD\ resting$$

For the analysis of the EEG signal, only the 15 seconds of the walking attempt were considered (eliminating the initial 5 seconds and the final 5 seconds).

4.2.5 Statistical analysis

Statistical analysis were conducted at the SPSS 22.0 program (SPSS, Inc.). The Shapiro-Wilk and Levene tests were used to check the normality of the data distribution and the homogeneity of the variances, respectively. Age values and anthropometric variables were compared using the Student's t-test for independent samples. The principles of normality and homogeneity were not met for the other study variables, so non-parametric tests were applied. The cognitive scales were compared between the groups using the Mann-Whitney test. The same test was applied to verify the difference between the groups (PD vs. CG) in the symmetry indexes of the gait spatial-temporal and cortical activity. To check the effects of the level of difficulty of the task (no dual task, very easy, easy, moderate, reasonably difficult and difficult), the Friedman test (X^2) was applied with the Wilcoxon post hoc test. The significance level was set at $p < 0.05$.

4.3 RESULTS

4.3.1 Clinical evaluation and performance in the cognitive dual task

The data for the sample included in the study can be seen in Table 5. The sample was homogeneous for all variables, except for the MoCA score (U=165.500; p>0.026; mean rank [CG= 11.97; PG= 19.03]). Although there was this difference in scores between the groups, all were classified according to the cut-off scores adjusted for education. The side most affected by Parkinson's disease was verified based on two measures: based on the motor

symptoms of the disease (assessed by the UPDRS-III) and by the step with the lowest swing time value during the ST.

Absolute errors were counted when performing the different levels of difficulty of the dual tasks in the sitting position and then while walking. The table below shows the value of the absolute error for each task difficulty. There was no effect between the groups in the sitting position ($F_{1,26}$=0.140; p=0.907) and during walking ($F_{1,26}$=1.300; p=0.265), nor was there any interaction effect between group*task (sitting: $F_{4,104}$=1.658; p=0.165; walking: $F_{4,104}$=0.102; p=0.982). However, effects of task difficulty were observed in both positions (sitting: $F_{4,104}$=19.269; p<0.001; walking: $F_{4,104}$=21.107; p<0.001). All the effects observed between the tasks are shown in Table 6.

Table 5. Mean and standard deviation values for the sample's anthropometric and clinical data.

	CG	PG	p-value
Sex (M/F)	9 / 6	9 / 6	-
Age (years)	67.27 ± 5.65	68.07 ± 6.50	0.722
Body mass (kg)	74.23 ± 13.30	74.42 ± 14.78	0.967
Height (m)	1.64 ± 0.10	1.65 ± 0.08	0.796
BMI (kg/m^2)	27.07 ± 4.18	27.27 ± 2.83	0.881
MMSE (points)	27.73 ± 2.22	28.13 ± 1.13	0.902
MoCA (points)	25.87 ± 1.68	27.40 ± 1.59	0.026
HY (points)	-	2.2 ± 0.32	-
UPDRS – III (points)	-	28.80 ± 11.13	-
Most affected side - UPDRS III (L/R)	-	5 / 10	-
Manual dominance (L/R)	7 / 7	8 / 6	-

Mean ± standard deviation. CG: control group; PG: Parkinson's disease group; M: male; F: female; kg: kilogram; m: meters; BMI: Body Mass Index; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; HY: Hoehn & Yahr Modified Scale; UPDRS: Unified Parkinson's Disease Rating Scale; L: left; R: right.

Table 6. Absolute error values presented by both groups when performing the cognitive task while seated and while walking.

	DT+Sitting			DT+Walking	
	CG	**PG**		**CG**	**PG**
VE^{**}_{ab}	2	1	$VE^{*}_{a,b}$	8	11
E^{**}_{ab}	0	1	$E^{**}_{a,b,c}$	2	8
M^{**}_{b}	2	8	M	10	21
RD	11	12	RD	30	36
D	21	15	D	52	59

DT: dual task; CG: control group; PG: Parkinson's disease group; VE: very easy; E: easy; M: moderate; RD: reasonably difficult; D: difficult.
*p<0.01
**p<0.001
[a] compared to RD task.
[b] compared to D task.
[c] compared to M task.

4.3.2 Effects of dual task difficulty on asymmetry of spatial-temporal and cortical parameters

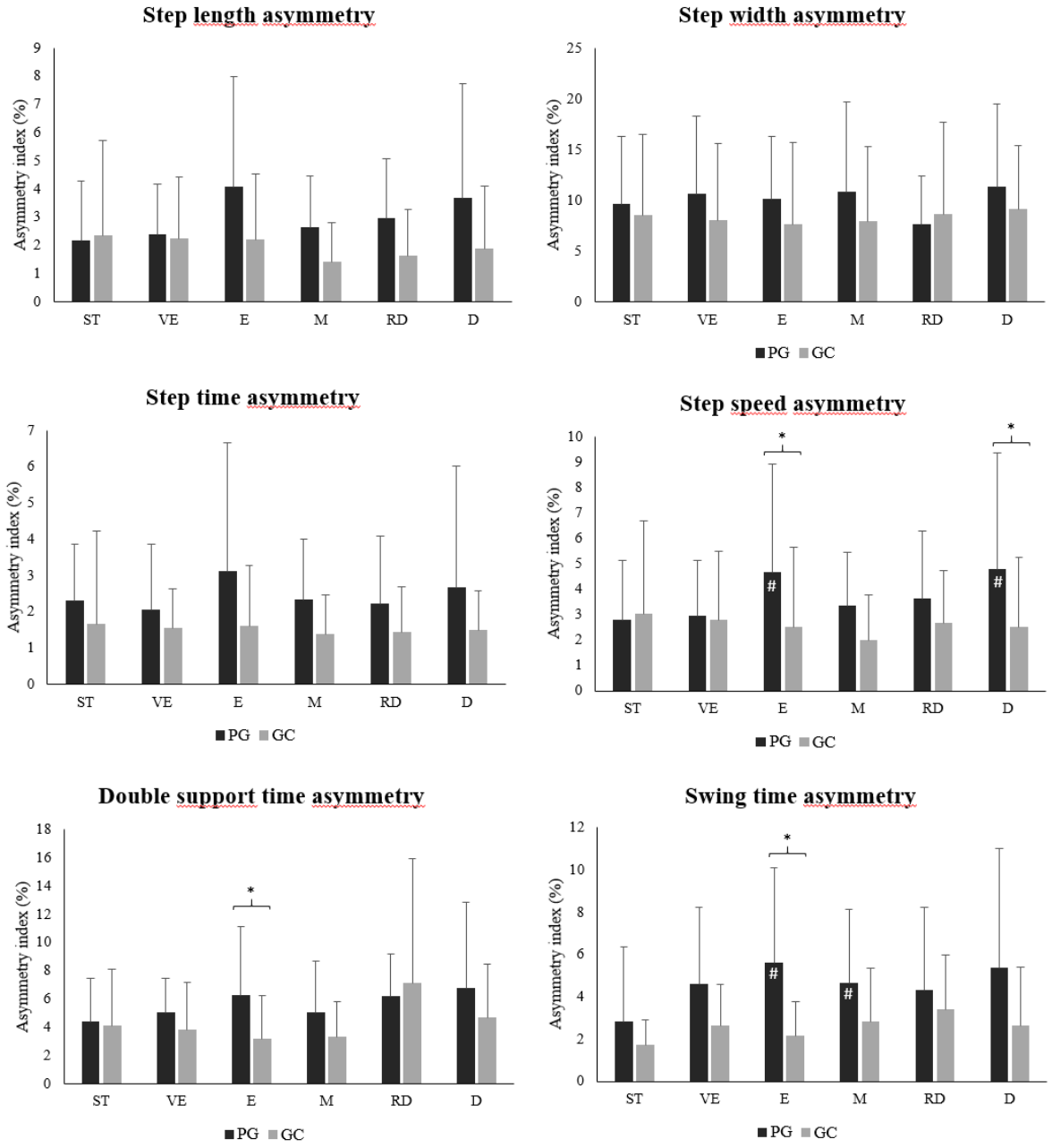
One individual from each group was excluded during the analysis process due to data errors. Therefore, all the analyses were carried out with 14 individuals in each group.

Spatial-temporal parameters

The Mann-Whitney test was carried out to compare the asymmetry of the spatial-temporal parameters between the groups (Figure 10). Compared to the CG, the results showed that the PG presented greater asymmetries for step speed (U=149.000; p=0.019), double support (U=147.000; p=0.024) and swing time (U= 141.000; p=0.050) in the E condition and greater asymmetry of step speed in the D task (U=152.00; p=0.012).

When checking the effects of task difficulty, the Friedman test only indicated the influence of task difficulty in the Parkinson's group on step speed asymmetry (X^2 =18.286; p=0.003) and swing time (X^2 =15.510; p=0.008). Step speed asymmetry was higher in the E and D conditions compared to ST (p=0.003 and 0.009, respectively). In addition, greater swing time asymmetry was also found in the E and M conditions compared to ST (p= 0.026 and p=0.006, respectively).

Figure 10. Asymmetry of spatial-temporal variables during gait without a dual task (ST) and with different difficulties of dual task.



CG: Control group; PG: Parkinson's disease group; ST: single task; VE: very easy; E: easy; M: moderate; RD: reasonably difficult; D: difficult. * indicates group differences; # indicates effects of task difficulty compared to ST.

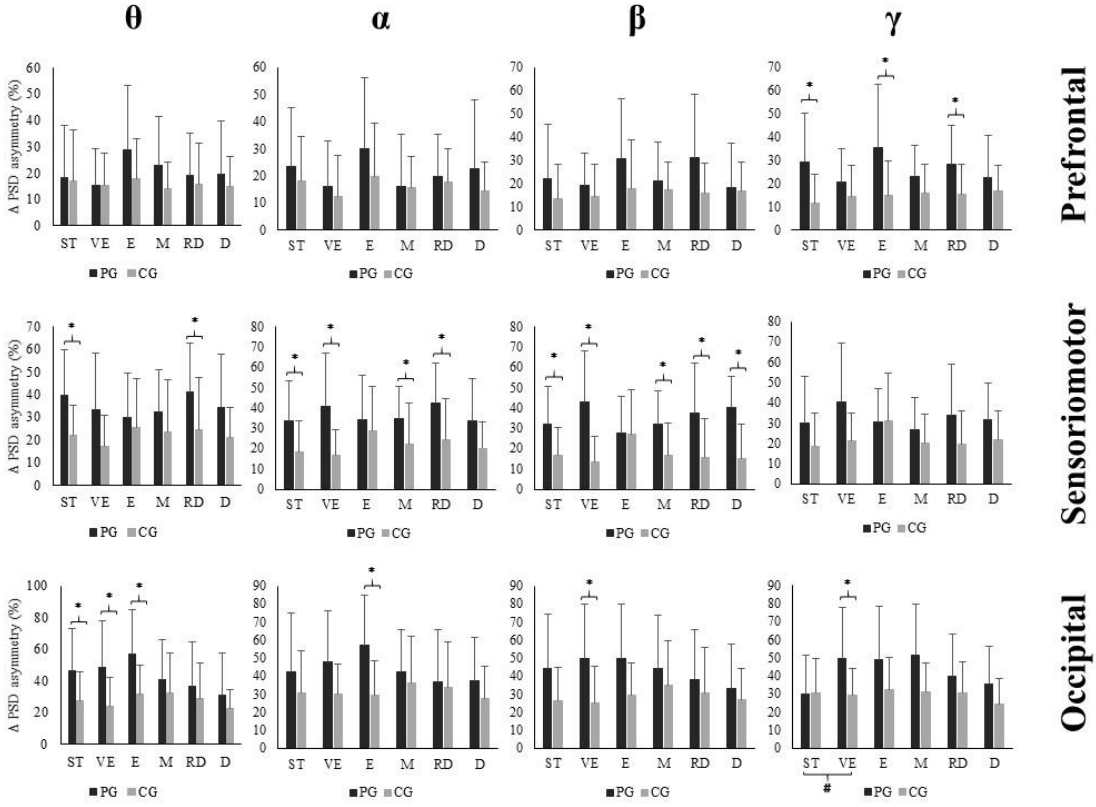
Cortical parameters

The Mann-Whitney test revealed a series of differences between the groups in cortical activity asymmetry (ΔPSD; Figure 11). The PG showed greater cortical asymmetry than the

CG in all these comparisons. The PG's ΔPSD asymmetry values in the **γ** band in the prefrontal area were higher during the ST (U = 143.00; z = 2.06; p = 0.039), E (U = 150.00; z = 2.38; p = 0.016) and RD (U = 153.00; z = 2.527; p = 0.011) tasks. In the sensorimotor region, the GP showed greater ΔPSD asymmetry in all bands. Specifically, the asymmetry was greater in the **θ** (ST [U = 150.00; z = 2.38; p = 0.016] and RD [U = 144.00, z = 2.11; p = 0.035]), **α** (ST [U = 144.00, z = 2.11; p = 0.035], VE [U = 151.00, z = 2.43; p = 0.014], M [U = 143.00, z = 2.06; p = 0.039] and RD [U = 146.00, z = 2.20; p = 0.027]) and **β** (ST [U = 156.00, z = 2.66; p = 0.007], VE [U = 166.00, z = 3.12; p = 0.001], M [U = 154.00, z = 2.57; p = 0.009], RD [U = 158.00, z = 2.75; p = 0.005] and D[U = 175.00, z = 3.53; p < 0.001]). Finally, in the occipital region, the ΔPSD of the GP was more asymmetrical in the **θ** bands (ST [U = 141.00, z = 1.97; p = 0.050], VE [U = 149.00, z = 2.34; p = 0.019] and E [U = 153.00, z = 2.52; p = 0.011]), **α** (E [U = 153.00, z = 2.52; p = 0.011]), **β** (VE [U = 146.00, z = 2.20; p = 0.027]) and **γ** (VE [U = 142.00, z = 2.02; p = 0.044]).

When checking the effects of the difficulty of the dual task on cortical asymmetry during walking, the Friedman test indicated effects in the sensorimotor region for the **β** band (X^2= 12.163, p = 0.033) and in the occipital region for the **β** (X^2= 13.265, p = 0.021) and **γ** (X^2= 13.265, p = 0.021) bands. However, when checking for interaction effects, the Bonferroni adjustment indicated a task effect only for the **γ** band in the occipital region (p = 0.05). During the VE condition, the ΔPSD asymmetry of the gamma band in the occipital region was greater compared to the ST condition.

Figure 11. The figure below presents the values of ΔPSD asymmetry index of theta, alpha, beta and gamma bands. Those values were calculated in three cortical regions: Prefrontal, Sensoriomotor and Occipital cortex during gait without a dual task (ST) and with different difficulties of dual task.



CG: Control group; PG: Parkinson's disease group; ST: single task; VE: very easy; E: easy; M: moderate; RD: reasonably difficult; D: difficult. * indicates group differences; # indicates effects of task difficulty only for PG. θ: theta banda; α: alpha band; β: beta band; γ: gamma band.

4.4 DISCUSSION

To our knowledge, this is the first study to investigate the effects of increasing dual-task difficulty on spatial-temporal and cortical asymmetry during walking in individuals with PD. Initially, three hypotheses were proposed, of which only two were confirmed: i) individuals with PD exhibit greater asymmetry in spatial-temporal parameters and cortical activity compared to neurologically healthy older adults; ii) task difficulty increased the asymmetry of step speed and swing time exclusively in individuals with PD. The following paragraphs will explore potential explanations for the observed effects and the lack of support for the remaining hypotheses.

The increasing difficulty of the task heightened spatial-temporal asymmetry, particularly in speed and swing time, but did not affect cortical activity asymmetry in either individuals with PD or neurologically healthy controls. Aging studies have demonstrated a reduction in hemispheric asymmetry among older adults, as explained by the HAROLD model. This model suggests that prefrontal activity during cognitive tasks becomes less lateralized in older adults compared to younger individuals, functioning as a compensatory mechanism for unilateral declines in neural efficiency (Hackney; Earhart, 2010; Li *et al*., 2009).

Although greater asymmetry was observed in speed and swing time, this asymmetry did not increase consistently with each level of task difficulty. For speed, asymmetry showed a pronounced rise between the simple, easy, and difficult tasks. In contrast, swing time asymmetry remained relatively stable, with differences primarily evident in the easy and moderate tasks compared to the simple tasks. Swing time has been identified as a sensitive variable for detecting gait asymmetries in individuals with PD, particularly in dual-task scenarios (Hackney; Earhart, 2010; Yogev *et al.*, 2007). However, task difficulty only amplified this asymmetry up to the moderate level, whereas step speed displayed two distinct thresholds, progressively increasing in the easy and difficult tasks.

Reductions in step speed may be associated with increased gait instability (Hak *et al.*, 2013) and are often interpreted as a cautious strategy to cope with the challenges posed by cognitive tasks (Rochester *et al.*, 2014). In this context, increased asymmetry in step speed may reflect an adaptive response to heightened cognitive demands. However, asymmetry variables have not been deemed reliable predictors of cognitive decline in individuals with PD (Morris *et al.*, 2017). Nonetheless, the increased difficulty of the dual task led to a higher number of cognitive task errors and induced a more asymmetrical gait pattern.

Consistent with the literature, individuals with PD demonstrated differences from their age-matched group in both cortical asymmetry and spatial-temporal gait parameters. Specifically, individuals with PD exhibited more pronounced asymmetrical activation in the prefrontal, sensorimotor, and occipital regions. In terms of spatial-temporal parameters, greater asymmetry was evident in individuals with PD, particularly during the easy task (speed, double support, and swing time) and the difficult task (swing time).

Certain brain functions are predominantly localized in one cerebral hemisphere, which enhances functionality and cognitive capacity (Duboc *et al.*, 2015) as the hemispheres can

work in parallel (Rogers; Zucca; Vallortigara, 2004). However, aging is associated with a reduction in hemispheric asymmetry, characterized by less lateralized prefrontal activation during cognitive tasks (Hackney; Earhart, 2010; Li *et al*., 2009). Interestingly, the opposite pattern appears to occur in individuals with PD, who exhibit increased cortical asymmetry. This phenomenon may be attributable to the pathophysiology of the disease, as dopaminergic neuron loss in the substantia nigra is often asymmetrical between hemispheres (Lewis *et al.*, 2009). Consequently, this heightened asymmetry could be interpreted as a negative indicator of neural dysfunction.

Cortical activation is closely linked to task complexity, with more demanding tasks eliciting higher levels of cortical engagement (Stuart *et al.*, 2018). In individuals with PD, reduced brain integrity—particularly in the striatum and hippocampus—is associated with poorer dual-task performance (Kim; Fraser, 2022). Dopaminergic medication has been shown to increase cortical activation (Araújo-Silva *et al.*, 2022) and heightened activity in the frontal, parietal, and motor cortices has been linked to compensatory mechanisms involving reduced striatal function and cerebellar adjustments that restore oscillatory coupling between the prefrontal cortex and premotor areas (Herz *et al.*, 2014; Nettersheim *et al.*, 2019).

In the present study, greater prefrontal asymmetry was observed in the gamma band when comparing individuals with PD to healthy controls. Dual tasks of executive function while walking overloads the demands on the frontal lobe, since inputs from the basal ganglia are compromised in PD (Plotnik; Giladi; Hausdorff, 2009). Additionally, increasing dual-task difficulty resulted in significant EEG activity changes in the beta and gamma bands in sensorimotor and occipital regions, but only in the PD group. Abnormalities in beta and delta frequency bands are recognized as markers of dyskinesia and cognitive decline in PD, respectively (Wang *et al.*, 2020). Elevated metabolic activity in the prefrontal cortex (PFC) has also been strongly associated with enhanced planning and attention during motor and cognitive tasks, supporting the concept of brain capacity adaptations in dual-task interference theories (Hamacher *et al.*, 2015). And to achieve successful motor functions , it depends on the interaction between various regions (frontal, parietal, subcortical, cerebelar and spinal cord). And alpha, beta and gamma bands show strong modulations in multiple parts of the motor system (van Wijk; Beek; Daffertshofer, 2012).

When performing a cognitive dual task while walking, regardless of the group, the increase in task difficulty resulted in a greater number of errors from the moderate level

onwards, compared to the very easy and easy task conditions. These results suggest a reduced resource capacity at this level, indicating that the participants were no longer able to perform the dual task efficiently. Thus, it is likely that they adopted a “posture first” strategy, prioritizing a safer gait over performance in the cognitive task. Furthermore, for most of the spatial-temporal variables, there was no significant effect of the cognitive task, reinforcing the idea that the participants prioritized gait control. This behavior reflects a common compensatory strategy in individuals with PD, especially in situations of greater cognitive demand. Motor dual-tasking is considered a valuable predictor of falls in pwPD, suggesting that avoiding dual-tasking situations, as well as implementing specific training for these conditions, could be an effective strategy for preventing falls in this population (Heinzel *et al.*, 2016).

The following limitations should be considered: i) the study did not assess whether the task difficulty level was equivalent across individuals. We recommend incorporating an individualized score to account for each participant's perceived difficulty; ii) for the analysis of EEG asymmetry, 180° turns were included. However, due to constraints during data processing, this information had to be retained in the analysis. Future studies should synchronize EEG and spatial-temporal signals to better isolate asymmetry related specifically to walking events and to differentiate the distinct effects of turning versus free walking; iii) while the study examined the magnitude of asymmetry, it did not determine which cerebral hemisphere exhibited greater activation at each level of task difficulty.

4.5 CONCLUSION

When performing walking with different cognitive task difficulties, individuals with PD exhibit greater asymmetry in spatial-temporal parameters and cortical activity compared to neurologically healthy older adults. The effects of task difficulty on asymmetry were exclusively in individuals with PD. There was no threshold of task difficulty for gait and cortical asymmetry; however, cognitive impairments on the errors of task were seeing since moderate task. The current literature evidenced that DT training improves motor abilities. So, we recommend that cognitive DT of executive functions with different difficulties should be included in rehabilitation programs.

REFERENCES

AL-YAHYA, E. *et al.* Cognitive motor interference while walking: a systematic review and meta-analysis. **Neuroscience and biobehavioral reviews**, [*s. l.*], v. 35, n. 3, p. 715–728, 2011. Available at: https://pubmed.ncbi.nlm.nih.gov/20833198/. Accessed at: 23 Nov. 2024.

ALCOCK, L.; O'BRIEN, T. D.; VANICEK, N. Association between somatosensory, visual and vestibular contributions to postural control, reactive balance capacity and healthy ageing in older women. **Health care for women international**, [*s. l.*], v. 39, n. 12, p. 1366–1380, 2018. Available at: https://pubmed.ncbi.nlm.nih.gov/30395787/. Accessed at: 22 Nov. 2024.

ARAÚJO-SILVA, F. *et al.* Temporal dynamics of cortical activity and postural control in response to the first levodopa dose of the day in people with Parkinson's disease. **Brain Research**, [*s. l.*], v. 1775, p. 147727, 2022.

BARBIERI, F. A. *et al.* Obstacle Avoidance Increases Asymmetry of Crossing Step in Individuals With Parkinson's Disease and Neurologically Healthy Individuals. **Journal of motor behavior**, [*s. l.*], v. 50, n. 1, p. 17–25, 2018. Available at: https://pubmed.ncbi.nlm.nih.gov/28632105/. Accessed at: 23 Nov. 2024.

BARONE, P. Neurotransmission in Parkinson's disease: beyond dopamine. **European journal of neurology**, [*s. l.*], v. 17, n. 3, p. 364–376, 2010. Available at: https://pubmed.ncbi.nlm.nih.gov/20050885/. Accessed at: 23 Nov. 2024.

BOONSTRA, T. A. *et al.* Parkinson's disease patients compensate for balance control asymmetry. **Journal of neurophysiology**, [*s. l.*], v. 112, n. 12, p. 3227–3239, 2014. Available at: https://pubmed.ncbi.nlm.nih.gov/25253475/. Accessed at: 23 Nov. 2024.

BRUCKI, S. M. D. *et al.* Sugestões para o uso do mini-exame do estado mental no Brasil. **Arquivos de Neuro-Psiquiatria**, [*s. l.*], v. 61, n. 3 B, p. 777–781, 2003. Available at: https://www.scielo.br/j/anp/a/YgRksxZVZ4b9j3gS4gw97NN/?lang=pt. Accessed at: 22 Nov. 2024.

BRYANT, M. S. *et al.* Acute and Long-Term Effects of Multidirectional Treadmill Training on Gait and Balance in Parkinson Disease. **PM & R : the journal of injury, function, and rehabilitation**, [*s. l.*], v. 8, n. 12, p. 1151–1158, 2016. Available at: https://pubmed.ncbi.nlm.nih.gov/27178378/. Accessed at: 22 Nov. 2024.

CESAR, K. G. *et al.* MoCA Test: normative and diagnostic accuracy data for seniors with heterogeneous educational levels in Brazil. **Arquivos de neuro-psiquiatria**, [*s. l.*], v. 77, n. 11, p. 775–781, 2019. Available at: https://pubmed.ncbi.nlm.nih.gov/31826133/. Accessed at: 23 Nov. 2024.

CLAASSEN, D. O. *et al.* Cortical asymmetry in Parkinson's disease: early susceptibility of the left hemisphere. **Brain and Behavior**, [*s. l.*], v. 6, n. 12, p. e00573, 2016. Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/brb3.573. Accessed at: 23 Nov. 2024.

COLOMAN, I. I.; CHIMAGOMEDOVA, A. S. [The influence of motor asymmetry on

cognitive functions in Parkinson's disease]. **Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova**, [*s. l.*], v. 120, p. 74, 2020. Available at: https://pubmed.ncbi.nlm.nih.gov/33205934/. Accessed at: 23 Nov. 2024.

DELORME, A. *et al.* EEGLAB, SIFT, NFT, BCILAB, and ERICA: New Tools for Advanced EEG Processing. **Computational Intelligence and Neuroscience**, [*s. l.*], v. 2011, n. 1, p. 130714, 2011. Available at: https://onlinelibrary.wiley.com/doi/full/10.1155/2011/130714. Accessed at: 23 Nov. 2024.

DINGWELL, J. B.; DAVIS, B. L.; FRAZIER, D. M. Use of an instrumented treadmill for real-time gait symmetry evaluation and feedback in normal and trans-tibial amputee subjects. **Prosthetics and orthotics international**, [*s. l.*], v. 20, n. 2, p. 101–110, 1996. Available at: https://pubmed.ncbi.nlm.nih.gov/8876003/. Accessed at: 22 Nov. 2024.

DJALDETTI, R.; ZIV, I.; MELAMED, E. The mystery of motor asymmetry in Parkinson's disease. **The Lancet. Neurology**, [*s. l.*], v. 5, n. 9, p. 796–802, 2006. Available at: https://pubmed.ncbi.nlm.nih.gov/16914408/. Accessed at: 23 Nov. 2024.

DUBOC, V. *et al.* Asymmetry of the Brain: Development and Implications. **Annual review of genetics**, [*s. l.*], v. 49, p. 647–672, 2015. Available at: https://pubmed.ncbi.nlm.nih.gov/26442849/. Accessed at: 23 Nov. 2024.

FARIA, M. H. *et al.* (A)symmetry during gait initiation in people with Parkinson's disease: A motor and cortical activity exploratory study. **Frontiers in aging neuroscience**, [*s. l.*], v. 15, 2023. Available at: https://pubmed.ncbi.nlm.nih.gov/37139089/. Accessed at: 23 Nov. 2024.

GOETZ, C. G. *et al.* Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. **Movement disorders : official journal of the Movement Disorder Society**, [*s. l.*], v. 19, n. 9, p. 1020–1028, 2004. Available at: https://pubmed.ncbi.nlm.nih.gov/15372591/. Accessed at: 22 Nov. 2024.

GWIN, J. T. *et al.* Removal of movement artifact from high-density EEG recorded during walking and running. **Journal of Neurophysiology**, [*s. l.*], v. 103, n. 6, p. 3526–3534, 2010.

HACKNEY, M. E.; EARHART, G. M. The effects of a secondary task on forward and backward walking in Parkinson's disease. **Neurorehabilitation and neural repair**, [*s. l.*], v. 24, n. 1, p. 97–106, 2010.

HAK, L. *et al.* Steps to Take to Enhance Gait Stability: The Effect of Stride Frequency, Stride Length, and Walking Speed on Local Dynamic Stability and Margins of Stability. **PLOS ONE**, [*s. l.*], v. 8, n. 12, p. e82842, 2013. Available at: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0082842. Accessed at: 23 Nov. 2024.

HAMACHER, Dennis *et al.* Brain activity during walking: A systematic review. **Neuroscience and biobehavioral reviews**, [*s. l.*], v. 57, p. 310–327, 2015. Available at: https://pubmed.ncbi.nlm.nih.gov/26306029/. Accessed at: 23 Nov. 2024.

HEINZEL, S. *et al.* Motor dual-tasking deficits predict falls in Parkinson's disease: A prospective study. **Parkinsonism & related disorders**, [*s. l.*], v. 26, p. 73–77, 2016. Available at: https://pubmed.ncbi.nlm.nih.gov/26997654/. Accessed at: 23 Nov. 2024.

HERZ, D. M. *et al.* Functional neuroimaging of motor control in Parkinson's disease: a meta-analysis. **Human brain mapping**, [*s. l.*], v. 35, n. 7, p. 3227–3237, 2014. Available at: https://pubmed.ncbi.nlm.nih.gov/24123553/. Accessed at: 23 Nov. 2024.

HERZOG, W. *et al.* Asymmetries in ground reaction force patterns in normal human gait. **Medicine and science in sports and exercise**, [*s. l.*], v. 21, n. 1, p. 110–114, 1989. Available at: https://pubmed.ncbi.nlm.nih.gov/2927295/. Accessed at: 22 Nov. 2024.

HUGHES, A. J. *et al.* Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. **Journal of neurology, neurosurgery, and psychiatry**, [*s. l.*], v. 55, n. 3, p. 181–184, 1992. Available at: https://pubmed.ncbi.nlm.nih.gov/1564476/. Accessed at: 22 Nov. 2024.

KAHYA, M. *et al.* Brain activity during dual task gait and balance in aging and age-related neurodegenerative conditions: A systematic review. **Experimental gerontology**, [*s. l.*], v. 128, 2019. Available at: https://pubmed.ncbi.nlm.nih.gov/31648005/. Accessed at: 23 Nov. 2024.

KELLY, V. E.; EUSTERBROCK, A. J.; SHUMWAY-COOK, A. A review of dual-task walking deficits in people with Parkinson's disease: motor and cognitive contributions, mechanisms, and clinical implications. **Parkinson's disease**, [*s. l.*], v. 2012, 2012. Available at: https://pubmed.ncbi.nlm.nih.gov/22135764/. Accessed at: 23 Nov. 2024.

KIM, H.; FRASER, S. Neural correlates of dual-task walking in people with central neurological disorders: a systematic review. **Journal of neurology**, [*s. l.*], v. 269, n. 5, p. 2378–2402, 2022. Available at: https://pubmed.ncbi.nlm.nih.gov/34989867/. Accessed at: 23 Nov. 2024.

KLEINER, M. *et al.* Assessing species biomass contributions in microbial communities via metaproteomics. **Nature Communications 2017 8:1**, [*s. l.*], v. 8, n. 1, p. 1–14, 2017. Available at: https://www.nature.com/articles/s41467-017-01544-x. Accessed at: 23 Nov. 2024.

LAPOINTE, L. L.; STIERWALT, J. A. G.; MAITLAND, C. G. Talking while walking: Cognitive loading and injurious falls in Parkinson's disease. **International Journal of Speech-Language Pathology**, [*s. l.*], v. 12, n. 5, p. 455–459, 2010.

LEWIS, M. M. *et al.* Asymmetrical lateral ventricular enlargement in Parkinson's disease. **European journal of neurology**, [*s. l.*], v. 16, n. 4, p. 475–481, 2009. Available at: https://pubmed.ncbi.nlm.nih.gov/19187264/. Accessed at: 23 Nov. 2024.

MARTÍNEZ-MARTÍN, P. *et al.* Unified Parkinson's Disease Rating Scale characteristics and structure. The Cooperative Multicentric Group. **Movement disorders : official journal of the Movement Disorder Society**, [*s. l.*], v. 9, n. 1, p. 76–83, 1994. Available at:

https://pubmed.ncbi.nlm.nih.gov/8139608/. Accessed at: 22 Nov. 2024.

MILLER-PATTERSON, C. *et al.* Motor asymmetry over time in Parkinson's disease. **Journal of the neurological sciences**, [*s. l.*], v. 393, p. 14–17, 2018. Available at: https://pubmed.ncbi.nlm.nih.gov/30096567/. Accessed at: 23 Nov. 2024.

MORRIS, R. *et al.* Gait Rather Than Cognition Predicts Decline in Specific Cognitive Domains in Early Parkinson's Disease. **The journals of gerontology. Series A, Biological sciences and medical sciences**, United States, v. 72, n. 12, p. 1656–1662, 2017.

NETTERSHEIM, F. S. *et al.* Dopamine substitution alters effective connectivity of cortical prefrontal, premotor, and motor regions during complex bimanual finger movements in Parkinson's disease. **NeuroImage**, [*s. l.*], v. 190, p. 118–132, 2019. Available at: https://pubmed.ncbi.nlm.nih.gov/29698732/. Accessed at: 23 Nov. 2024.

OOSTENVELD, R.; PRAAMSTRA, P. The five percent electrode system for high-resolution EEG and ERP measurements. **Clinical Neurophysiology**, [*s. l.*], v. 112, n. 4, p. 713–719, 2001.

OZDEMIR, R. A. *et al.* Cortical activity modulations underlying age-related performance differences during posture-cognition dual tasking. **Experimental brain research**, [*s. l.*], v. 234, n. 11, p. 3321–3334, 2016. Available at: https://pubmed.ncbi.nlm.nih.gov/27443853/. Accessed at: 23 Nov. 2024.

PETERSON, D. S. *et al.* Dual-task interference and brain structural connectivity in people with Parkinson's disease who freeze. **Journal of Neurology, Neurosurgery & Psychiatry**, [*s. l.*], v. 86, n. 7, p. 786–792, 2015. Available at: https://jnnp.bmj.com/content/86/7/786. Accessed at: 23 Nov. 2024.

PINTO, C. *et al.* Dual-task walking reduces lower limb range of motion in individuals with Parkinson's disease and freezing of gait: But does it happen during what events through the gait cycle? **PLoS ONE**, [*s. l.*], v. 15, n. 12, p. e0243133, 2020. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC7723257/. Accessed at: 23 Nov. 2024.

PLOTNIK, M. *et al.* Effects of cognitive function on gait and dual tasking abilities in patients with Parkinson's disease suffering from motor response fluctuations. **Experimental brain research**, [*s. l.*], v. 208, n. 2, p. 169–179, 2011. Available at: https://pubmed.ncbi.nlm.nih.gov/21063692/. Accessed at: 23 Nov. 2024.

PLOTNIK, M. *et al.* Is freezing of gait in Parkinson's disease related to asymmetric motor function? **Annals of neurology**, [*s. l.*], v. 57, n. 5, p. 656–663, 2005. Available at: https://pubmed.ncbi.nlm.nih.gov/15852404/. Accessed at: 23 Nov. 2024.

PLOTNIK, M.; GILADI, N.; HAUSDORFF, J. M. Bilateral coordination of gait and Parkinson's disease: the effects of dual tasking. **Journal of neurology, neurosurgery, and psychiatry**, [*s. l.*], v. 80, n. 3, p. 347–350, 2009. Available at: https://pubmed.ncbi.nlm.nih.gov/19228674/. Accessed at: 23 Nov. 2024.

PLOTNIK, M.; GILADI, N.; HAUSDORFF, J. M. Bilateral coordination of walking and freezing of gait in Parkinson's disease. **The European journal of neuroscience**, [*s. l.*], v. 27, n. 8, p. 1999–2006, 2008. Available at: https://pubmed.ncbi.nlm.nih.gov/18412621/. Accessed at: 23 Nov. 2024.

RADÜNTZ, T. *et al.* EEG artifact elimination by extraction of ICA-component features using image processing algorithms. **Journal of Neuroscience Methods**, [*s. l.*], v. 243, p. 84–93, 2015.

RAFFEGEAU, T. E. *et al.* A meta-analysis: Parkinson's disease and dual-task walking. **Parkinsonism & related disorders**, [*s. l.*], v. 62, p. 28–35, 2019. Available at: https://pubmed.ncbi.nlm.nih.gov/30594454/. Accessed at: 23 Nov. 2024.

ROCHESTER, L. *et al.* Attending to the task: interference effects of functional tasks on walking in Parkinson's disease and the roles of cognition, depression, fatigue, and balance. **Archives of physical medicine and rehabilitation**, [*s. l.*], v. 85, n. 10, p. 1578–1585, 2004. Available at: https://pubmed.ncbi.nlm.nih.gov/15468014/. Accessed at: 23 Nov. 2024.

ROCHESTER, L. *et al.* The nature of dual-task interference during gait in incident Parkinson's disease. **Neuroscience**, [*s. l.*], v. 265, p. 83–94, 2014. Available at: https://pubmed.ncbi.nlm.nih.gov/24508154/. Accessed at: 23 Nov. 2024.

ROGERS, L. J.; ZUCCA, P.; VALLORTIGARA, G. Advantages of having a lateralized brain. **Proceedings. Biological sciences**, [*s. l.*], v. 271 Suppl 6, n. Suppl 6, 2004. Available at: https://pubmed.ncbi.nlm.nih.gov/15801592/. Accessed at: 23 Nov. 2024.

RUTHRUFF, E.; PASHLER, H. E.; KLAASSEN, A. Processing bottlenecks in dual-task performance: structural limitation or strategic postponement?. **Psychonomic bulletin & review**, [*s. l.*], v. 8, n. 1, p. 73–80, 2001. Available at: https://pubmed.ncbi.nlm.nih.gov/11340869/. Accessed at: 23 Nov. 2024.

SANTINELLI, F. B. *et al.* Cortical activity and gait parameter characteristics in people with multiple sclerosis during unobstructed gait and obstacle avoidance. **Gait & posture**, [*s. l.*], v. 86, p. 226–232, 2021. Available at: https://pubmed.ncbi.nlm.nih.gov/33773240/. Accessed at: 23 Nov. 2024.

STERN, Y. Cognitive reserve. **Neuropsychologia**, [*s. l.*], v. 47, n. 10, p. 2015–2028, 2009. Available at: https://pubmed.ncbi.nlm.nih.gov/19467352/. Accessed at: 23 Nov. 2024.

STUART, S. *et al.* **Cortical activity during walking and balance tasks in older adults and in people with Parkinson's disease: A structured review**. [*S. l.*]: Elsevier Ireland Ltd, 2018. Available at: https://pubmed.ncbi.nlm.nih.gov/29903649/. Accessed at: 6 Jan. 2021.

TAKAKUSAKI, K. *et al.* Role of basal ganglia-brainstem pathways in the control of motor behaviors. **Neuroscience research**, [*s. l.*], v. 50, n. 2, p. 137–151, 2004. Available at: https://pubmed.ncbi.nlm.nih.gov/15380321/. Accessed at: 23 Nov. 2024.

TROPINI, G. *et al.* Altered directional connectivity in Parkinson's disease during

performance of a visually guided task. **NeuroImage**, [*s. l.*], v. 56, n. 4, p. 2144–2156, 2011. Available at: https://pubmed.ncbi.nlm.nih.gov/21402160/. Accessed at: 23 Nov. 2024.

VAN WIJK, B. C. M.; BEEK, P. J.; DAFFERTSHOFER, A. Neural synchrony within the motor system: what have we learned so far?. **Frontiers in Human Neuroscience**, [*s. l.*], v. 6, n. SEPTEMBER, p. 252, 2012. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC3432872/. Accessed at: 23 Nov. 2024.

VERREYT, N. *et al.* Cognitive differences between patients with left-sided and right-sided Parkinson's disease. A review. **Neuropsychology review**, [*s. l.*], v. 21, n. 4, p. 405–424, 2011. Available at: https://pubmed.ncbi.nlm.nih.gov/21956794/. Accessed at: 23 Nov. 2024.

VERVOORT, G. *et al.* Dual-task-related neural connectivity changes in patients with Parkinson' disease. **Neuroscience**, [*s. l.*], v. 317, p. 36–46, 2016. Available at: https://pubmed.ncbi.nlm.nih.gov/26762801/. Accessed at: 23 Nov. 2024.

WANG, Q. *et al.* Characterization of EEG Data Revealing Relationships With Cognitive and Motor Symptoms in Parkinson's Disease: A Systematic Review. **Frontiers in aging neuroscience**, [*s. l.*], v. 12, 2020. Available at: https://pubmed.ncbi.nlm.nih.gov/33240076/. Accessed at: 23 Nov. 2024.

WHITTIER, T. *et al.* The Cognitive Demands of Gait Retraining in Runners: An EEG Study. **Journal of Motor Behavior**, [*s. l.*], v. 52, n. 3, p. 360–371, 2020.

WOOLLACOTT, M.; SHUMWAY-COOK, A. Attention and the control of posture and gait: A review of an emerging area of research. **Gait and Posture**, [*s. l.*], v. 16, n. 1, p. 1–14, 2002. Available at: https://pubmed.ncbi.nlm.nih.gov/12127181/. Accessed at: 23 Nov. 2024.

YOGEV, G. *et al.* Gait asymmetry in patients with Parkinson's disease and elderly fallers: When does the bilateral coordination of gait require attention? **Experimental Brain Research**, [*s. l.*], v. 177, n. 3, p. 336–346, 2007. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16972073. Accessed at: 30 Mar. 2020.

YUVARAJ, R. *et al.* On the analysis of EEG power, frequency and asymmetry in Parkinson's disease during emotion processing. **Behavioral and Brain Functions**, [*s. l.*], v. 10, n. 1, p. 1–19, 2014. Available at: https://link.springer.com/articles/10.1186/1744-9081-10-12. Accessed at: 23 Nov. 2024.

ZGALJARDIC, D. *et al.* An examination of executive dysfunction associated with frontostriatal circuitry in Parkinson's disease. **Journal of clinical and experimental neuropsychology**, [*s. l.*], v. 28, n. 7, p. 1127–1144, 2006. Available at: https://pubmed.ncbi.nlm.nih.gov/16840240/. Accessed at: 23 Nov. 2024.

CHAPTER 5

FINAL REMARKS

5.1 Final remarks

The thesis investigated asymmetry of gait in pwPD and analyzed the effect of PD on asymmetry of spatial-temporal parameters, intersegmental coordination and neural activity. Table 7 presents a synthesis of data from the current literature, highlighting the main findings of this thesis and offering recommendations for future studies.

We can draw some conclusions from the results obtained by the thesis:

a) Are individuals with PD always asymmetrical?

According to the studies included in the systematic review, gait is not always asymmetrical in individuals with Parkinson's disease (PD). However, the lack of standardization among these studies makes it difficult to identify the causes of the absence of asymmetry in gait. On the other hand, the meta-analysis carried out confirmed that the main variable for identifying gait asymmetry is swing time.

In all the three studies carried out in this thesis, it was found that the gait of pwPD showed asymmetrical characteristics when compared to the control group, both for spatial-temporal and cortical variables, and under the influence of a dual task. There is a gap in the literature regarding the asymmetrical manifestation of neural parameters in PD. This study contributes to the identification of this characteristic by showing that, even in the absence of a dual task, cortical activity was more asymmetrical in individuals with PD than in controls.

However, the addition of challenging activities in walking, such as obstacles and dual tasks, did not significantly increase asymmetry, contrary to initial expectations. Furthermore, performing the task of circumvention an obstacle on the most affected side by the disease did not worsen coordination deficits, although it did show greater asymmetry. This finding corroborates previous studies that have found no correlation between gait asymmetry and motor coordination (Plotnik; Giladi; Hausdorff, 2009).

b) Dual task as a model to study gait asymmetry in PD

The negative effects of a dual task (DT) on walking are widely reported in the literature. In people with Parkinson's disease (PD), DT is expected to intensify motor deficits due to competition for attentional resources. Previous studies have shown that DTs increase gait asymmetry in these individuals, worsen bilateral coordination between limbs and increase the risk of falls.

Unexpectedly, our findings did not confirm that increasing the level of difficulty intensified asymmetry. One possible bias identified was the lack of adequate leveling of difficulties according to individual abilities, which may have contributed to the lack of progression in asymmetry as the tasks became more complex. Even so, corroborating the literature, gait DTs proved to be good indicators of asymmetry between individuals with PD and their healthy peers.

c) Intersegmental coordination and gait asymmetry in gait of pwPD

Few studies have investigated the relationship between asymmetry and coordination in the gait of pwPD. Among the existing ones, two aspects stand out: gait was assessed in free walking situations, and the individuals had episodes of freezing. In these cases, greater asymmetry and worse bilateral coordination between the lower limbs were characteristics associated with more advanced stages of the disease and progressive gait impairment. However, the consensus on the relationship between asymmetry and coordination remains uncertain, suggesting that the mechanisms regulating these variables may be distinct.

Studies have often focused on bilateral coordination between lower limbs. However, the marked muscular rigidity in individuals with PD, especially axial rigidity, can compromise intersegmental coordination, which is relevant in contexts that simulate everyday challenges. For example, the task of circumvention an obstacle has been shown to be more challenging and potentially dangerous for the side most affected by the disease. This study found that people with PD had a lower coordination pattern compared to healthy individuals. Although the more impaired side intensified the asymmetry of spatial-temporal parameters, this asymmetry did not directly impact the coordination pattern. These findings corroborate previous studies which also failed to identify a clear relationship between worse bilateral coordination and increased symptoms of asymmetry during gait.

d) Limitations, future suggestions and practical applications

One limitation of this thesis was the inability to analyze gait asymmetry according to different phases of the gait cycle due to the lack of synchronization between the equipment used. To better understand the mechanisms underlying asymmetry, coordination, and cortical activity, examining each phase of the gait cycle could provide valuable insights.

Although the present study did not identify significant impairments caused by dual-tasking in gait asymmetry among individuals with PD, we recommend that future research investigates settings that simulate participants' daily lives. This would enable a more comprehensive understanding of how asymmetry impacts activities of daily living. Furthermore, we emphasize the importance of adjusting task difficulty levels to match each individual's cognitive abilities.

Finally, all three studies demonstrated the asymmetry-related deficits in individuals with PD compared to their healthy peers. We encourage health and rehabilitation professionals to focus on the challenges posed by asymmetry, developing strategies to mitigate its effects and improve the gait of these individuals.

Table 7. The table presents a synthesis of data from the current literature, highlighting the main findings of this thesis and offering recommendations for future studies.

Current literature	Main findings of the thesis	Future recommendations
• The motor symptoms of PD are asymmetrical (Sant et al., 2008; Hughes, et al., 2002), including walking (Plotnik et al., 2008). • Performing a DT compromises bilateral symmetry and coordination during walking in individuals with PD (Yogev et al., 2007). • No standardization of the type and difficulty of the task. • It is necessary to understand why the gait in PD asymmetrical and what factors may contribute to this.	**Study #1** • PwPD showed greater gait asymmetry in most spatial-temporal variables vs. NHI • Swing time asymmetry was most sensitive variable • Dopaminergic medication partly improved GA • Kinetic, EMG and brain activity parameters asymmetry need further studies • High variability in asymmetry measures across studies limited generalization **Study #2** • Side most affect by PD does not impairs the axial and lower limb coordination in a high extent during an obstacle circumvention. • A cognitive dual task minimally affected the coordination during OC. • PD and NHI present differences of axial and lower limbs intersegmental coordination. **Study #3** • The effects of task difficulty on asymmetry were exclusively in individuals with PD. • Individuals with PD exhibit greater asymmetry in spatial-temporal parameters and cortical activity compared to NHI. • Cognitive impairments on the errors of task were seeing since moderate task.	• GA in pwPD in free-living environments should be explored for future studies. • Define a measure that best represents gait asymmetry, due to the wide variety of indices. • To level the difficulty of the cognitive task for each participant in the study. •Verify the variables of spatial-temporal asymmetry, cortical activity and intersegmental coordination according to each phase of gait. • To check whether the strategies used to avoid an obstacle

REFERENCES

HUGHES, A. J. et al. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. **Brain**, v. 125, n. Pt 4, p. 861-70, 2002.

PLOTNIK, M.; GILADI, N.; HAUSDORFF, J. M. Bilateral coordination of walking and freezing of gait in Parkinson's disease. **The European Journal of Neuroscience**, v. 27, p. 1999–2006, 2008.

PLOTNIK, M.; GILADI, N.; HAUSDORFF, J. M. Bilateral coordination of gait and Parkinson's disease: the effects of dual tasking. **Journal of neurology, neurosurgery, and psychiatry**, v. 80, n. 3, p. 347–350, 2009.

SANT, C. R. et al. Abordagem fisioterapêutica na doença de Parkinson. **Revista Brasileira de Ciências do Envelhecimento Humano**, v. 5, n. 1, p. 80-89, 2008.

YOGEV, G. et al. Gait asymmetry in patients with Parkinson's disease and elderly fallers: When does the bilateral coordination of gait require attention? **Experimental Brain Research**, v. 177, n. 3, p. 336-346, 2007.

APPENDICES

APPENDIX A – Description of the terms used for paper searching in each database.

- PubMed

#1	(Parkin*[tw]) AND ((asymm*[tw]) OR symm*) AND ((((gait[tw]) OR walk*[tw]) OR locomotion[tw]) OR mobility[tw])

Note: tw = text words.

- Cochrane Library

#1	Parkin* AND (asymm* OR symm*) AND (gait OR walk* OR locomotion OR mobility)

- Lilacs

#1	(Parkin*) AND (asymm*) OR (symm*) AND (gait) OR (walk*) OR (locomotion) OR (mobility)

- SCOPUS – Science Direct

#1	Parkinson AND asymmetry (gait OR walk OR mobility OR locomotion)

- PEDro

#1	Parkin* asymm* gait
#2	Parkin* asymm* walk*
#3	Parkin* asymm* locomotion
#4	Parkin* asymm* mobility

APPENDIX B – Questions of appraisal tool adapted from Galna et al. (2015).

Question		Scoring criteria
1. Research aims or questions stated clearly		1 - Yes; 0,5 – yes, lacking detail or clarity; 0 – no
2. Participants detailed	Age	1 – Yes; 0 – No
	Sex	1 – Yes; 0 – No
	Height	1 – Yes; 0 – No
	Disease stage	1 – Yes; 0 – No
	UPDRS - Part III	1 – Yes; 0 – No
	Subtotal (average)	
3. Recruitment and sampling methods described		1 - Yes; 0.5 – yes, lacking detail or clarity; 0 – no
4. Inclusion and exclusion criteria detailed		1 - Yes; 0.5 – yes, lacking detail or clarity; 0 – no
5. Controlled co-variates	Medication status	1 – Yes; 0 – No
	Time of diagnosis	1 – Yes; 0 – No
	Disease stage	1 – Yes; 0 – No
	Walking Speed	1 – Yes; 0 – No
	Freezing of gait	1 – Yes; 0 – No
	Subtotal (average)	
6. Key outcome variables clearly described		1 – Yes; 0.5 – only some defined; 0.5 – yes, lacking detail or clarity; 0 – no
7. Adequate methodology able to repeat study	Participant sampling	1 – Yes; 0 – No
	Equipment	1 – Yes; 0 – No
	Procedure	1 – Yes; 0 – No
	Data processing	1 – Yes; 0 – No
	Statistical analysis	1 – Yes; 0 – No
	Subtotal (average)	
8. Methodology able to answer research question	Participant sampling	1 – Yes; 0 – No
	Equipment	1 – Yes; 0 – No
	Procedure	1 – Yes; 0 – No
	Data processing	1 – Yes; 0 – No
	Statistical analysis	1 – Yes; 0 – No
	Subtotal (average)	
9. Reliability of the methodology stated		1 – Yes; 0 – No
10. Internal validity of the methodology stated		1 – Yes; 0 – No
11. Research questions answered adequately in the discussion		1 – Yes; 0 – No
12. Key findings supported by the results		1 – Yes; 0 – No
13. Key findings interpreted in a logical manner which is supported by references		1 – Yes; 0 – No
14. Clinical implications stated		1 – Yes; 0.5 – yes, lacking detail or clarity; 0 - No

APPENDIX C – Table with basic information about the studies included at systematic review.

Authors (year)	Country*	Title	Journal
(Bailo *et al.*, 2024)	Italy	Characterization of walking in mild Parkinson's disease: Reliability, validity and discriminant ability of the six-minute walk test instrumented with a single inertial sensor	Sensors
(Baltadjieva *et al.*, 2006)	Israel	Marked alterations in the gait timing and rhythmicity of patients with de novo Parkinson's disease	European Journal of Neuroscience
(Barbieri *et al.*, 2018)	Brazil	Obstacle avoidance increases asymmetry of crossing step in individuals with Parkinson's disease and neurologically healthy individuals	Journal of Motor Behavior
(Barbosa *et al.*, 2024)	France	3D kinematics quantifies gait response to levodopa earlier and to a more comprehensive extent than the MDS-unified Parkinson's disease rating scale in patients with motor complications	Movement Disorders
(Brodie *et al.*, 2015)	Australia	Symmetry matched auditory cues improve gait steadiness in most people with Parkinson's disease but not in healthy older people	Journal of Parkinson's Disease
(Buckley *et al.*, 2019)	United Kingdom	Upper body accelerations as a biomarker of gait impairment in the early stages of Parkinson's disease	Gait & Posture
(Danoudis; Iansek; Simpson, 2012)	Australia	Freezing of gait in Parkinson's disease: Further insights into pathophysiological mechanisms	Parkinsonism & Related Disorders
(De Bartolo *et al.*, 2020)	Italy	Effect of different music genres on gait patterns in Parkinson's disease	Neurological Sciences
(Del Din; Godfrey; Rochester, 2016)	United Kingdom	Validation of an accelerometer to quantify a comprehensive battery of gait characteristics in healthy older adults and Parkinson's disease: Toward clinical and at home use	IEEE Journal of Biomedical and Health Informatics
(Del Din *et al.*, 2016)	United Kingdom	Free-living gait characteristics in ageing and Parkinson's disease: Impact of environment and ambulatory bout length	Journal of NeuroEngineering and Rehabilitation
(Djurić-Jovičić *et al.*, 2017)	Serbia	Selection of gait parameters for differential diagnostics of patients with de novo Parkinson's disease	Neurological Research
(Ferreira *et al.*, 2022)	Brazil	Machine learning models for Parkinson's disease detection and stage classification based on spatial-temporal gait parameters	Gait & Posture
(Fling; Curtze; Horak, 2018)	United States of America	Gait asymmetry in people with Parkinson's disease is linked to reduced integrity of callosal sensorimotor regions	Frontiers in Neurology

(Galna *et al.*, 2015)	United Kingdom	Progression of gait dysfunction in incident Parkinson's disease: Impact of medication and phenotype	Movement Disorders
(Grajić *et al.*, 2015)	Serbia	Gait in drug naïve patients with de novo Parkinson's disease--altered but symmetric	Neurological Research
(Gilmore *et al.*, 2019)	Canada	Forward and backward walking in Parkinson disease: A factor analysis	Gait & Posture
(Godi *et al.*, 2021)	Italy	A pathophysiological model of gait captures the details of the impairment of pace/rhythm, variability and asymmetry in Parkinsonian patients at distinct stages of the disease	Scientific Reports
(Hackney; Earhart, 2010)	United States of America	The effects of a secondary task on forward and backward walking in Parkinson's disease	Neurorehabilitation and Neural Repair
(Iosa *et al.*, 2016)	Italy	Loss of fractal gait harmony in Parkinson's Disease	Clinical Neurophysiology
(Keloth *et al.*, 2021)	Australia	Muscle activation strategies of people with early-stage Parkinson’s during walking	Journal of NeuroEngineering and Rehabilitation
(Kleiner *et al.*, 2018)	Italy	Analyzing gait variability and dual-task interference in patients with Parkinson’s disease and freezing by means of the word-color Stroop test	Aging Clinical and Experimental Research
(Koh *et al.*, 2019)	Republic of Korea	Influences of elbow, shoulder, trunk motion and temporospatial parameters on arm swing asymmetry of Parkinson's disease during walking	Human Movement Science
(Leavy *et al.*, 2018)	Sweden	Patient-reported and performance-based measures of walking in mild–moderate Parkinson's disease	Brain and Behavior
(Lee *et al.*, 2020)	Republic of Korea	Gait characteristics under imposed challenge speed conditions in patients with Parkinson’s disease during overground walking	Sensors
(Lencioni *et al.*, 2021)	Italy	Strategies for maintaining dynamic balance in persons with neurological disorders during overground walking	Journal of Engineering in Medicine
(Liu *et al.*, 2022)	China	Quantitative assessment of gait characteristics in patients with Parkinson's disease using 2D video	Parkinsonism and Related Disorders
(Martínez *et al.*, 2018)	Spain	Kinematic and kinetic patterns related to free-walking in Parkinson’s disease	Sensors
(Miller *et al.*, 1996)	United States of America	Components of EMG symmetry and variability in parkinsonian and healthy elderly gait	Electroencephalography and Clinical Neurophysiology

(Morris *et al.*, 2017)	United Kingdom	Gait rather than cognition predicts decline in specific cognitive domains in early Parkinson's disease	Journals of Gerontology: Medical Sciences
(Morris *et al.*, 2017)	United Kingdom	A model of free-living gait: A factor analysis in Parkinson's disease	Gait & Posture
(Nanhoe-Mahabier *et al.*, 2011)	Netherlands	Walking patterns in Parkinson's disease with and without freezing of gait	Neuroscience
(Pereira *et al.*, 2019)	Brazil	The effects of habitual footwear in gait outcomes in people with Parkinson’s disease	Gait & Posture
(Plotnik; Giladi; Hausdorff, 2007)	Israel	A new measure for quantifying the bilateral coordination of human gait: Effects of aging and Parkinson's disease	Experimental Brain Research
(Ren *et al.*, 2015)	United States of America	Veering in hemi-Parkinson's disease: Primacy of visual over motor contributions	Vision Research
(Seuthe *et al.*, 2024)	Germany	Gait asymmetry and symptom laterality in Parkinson’s disease: two of a kind?	Journal of Neurology
(Vervoort *et al.*, 2015)	Belgium	Distal motor deficit contributions to postural instability and gait disorder in Parkinson's disease	Behavioural Brain Research
(Vervoort, G *et al.*, 2016)	Belgium	Dual-task-related neural connectivity changes in patients with Parkinson' disease	Neuroscience
(Wu *et al.*, 2021)	China	Mild gait impairment and its potential diagnostic value in patients with early-stage Parkinson's disease	Behavioural Neurology
(Yogev *et al.*, 2007)	Israel	Gait asymmetry in patients with Parkinson's disease and elderly fallers: when does bilateral coordination of gait require attention?	Experimental Brain Research

*based on the information provided by the corresponding author.

APPENDIX D – Methodological quality appraisal results. Each question is the average of the evaluation of three authors. The last column presents the total score for each paper. The last line presents the average for each question.

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Total score
Bailo et al. (2024)	1	0.8	1	1	0	1	1	1	1	1	1	1	1	1	12.8
Baltadjieva et al. (2006)	1	0.8	1	1	0	1	1	1	0	0	1	1	1	0.5	10.3
Barbieri et al. (2018a)	1	0.8	1	1	0	1	0.9	1	0	0	1	1	1	0	9.7
Barbosa et al. (2024)	1	0.8	0.75	0.75	0	0.75	0.9	0.9	0	0	1	1	1	1	9.9
Brodie et al. (2015)	1	0.8	0.25	0.5	0	1	0.9	0.9	0	0	1	1	0.5	0.75	8.6
Buckley et al. (2019)	1	0.9	1	1	0	0.75	0.8	1	0	0	1	1	1	0.75	10.2
Danoudis et al. (2012)	1	0.9	0.5	0.75	0	1	0.7	0.9	0	0	0.5	1	0.5	0.25	8.0
De Bartolo et al. (2020)	1	0.6	0.25	0.75	0	1	1	1	0	0	1	1	1	1	9.6
Del Din et al. (2016)	1	0.9	1	0.5	0	1	0.9	1	0	1	1	1	1	1	11.3
Del Din et al. (2016)	1	0.9	1	0.5	0	1	0.9	1	0	0.5	1	1	1	0.75	10.5
Djurić-Jovičić et al. (2017)	1	0.8	0.75	0.5	0	1	0.9	1	0	0	1	1	1	1	9.9
Ferreira et al. (2022)	1	1	0.5	1	0	1	1	1	1	0	1	1	1	1	11.5
Fling, Curtze, Horak (2018)	1	0.8	0.25	0	0	0.75	0.8	0.8	0	0	1	1	1	0	7.4
Galna et al. (2015)	1	0.8	1	1	0	0.75	1	1	0	0	0.5	1	1	0	9.1
Grajić et al. (2015)	1	0.8	1	0.5	0	0.5	0.8	0.8	0	0	0.5	0.5	0.5	0	6.9
Gilmore et al. (2019)	1	0.7	1	0.5	0	1	0.9	0.8	0	0	1	1	0.5	1	9.4
Godi et al. (2021)	1	0.6	1	1	0	1	1	1	1	1	1	1	1	1	12.6
Hackney, Earhart (2010)	1	0.8	1	0.75	0	1	0.9	1	0	0	0	1	1	1	9.5
Iosa et al. (2016)	1	0.8	0.5	0.25	0	1	0.9	0.9	0	0	1	1	1	0.5	8.9
Keloth et al. (2021)	1	1	1	0.75	0	1	1	1	0	0	1	1	1	0.5	10.3
Kleiner et al. (2018)	1	0.9	0.75	1	0	1	1	0.9	0	0	0.5	1	0	0.5	8.6
Koh et al. (2019)	1	1	1	1	0.2	0.5	0.7	0.9	0	0	1	0.5	0.5	0.25	8.6
Leavy et al. (2018)	1	0.8	1	0.75	0	1	1	1	0	0	0.5	1	1	1	10.1
Lee et al. (2020)	1	1	1	1	0	1	1	1	1	0	1	1	1	1	12.0
Lencioni et al. (2021)	1	0.8	0.25	0.75	0	1	1	1	0	0	1	1	1	1	9.8
Liu et al. (2022)	1	1	0.5	1	0	1	1	1	0	1	1	1	1	0.75	11.3
Martínez et al. (2018)	1	0.9	1	0.5	0	1	1	1	1	1	1	1	1	1	12.4
Miller et al. (1996)	1	0.4	0.5	0.75	0	1	0.9	0.9	0	0	1	1	0	0	7.5
Morris et al. (2017a)	1	1	1	1	0	1	1	1	1	1	1	1	1	1	13.0
Morris et al. (2017b)	1	0.6	0.75	1	0	0.75	0.9	1	0	1	0.5	1	1	1	10.5
Nanhoe-Mahabier et al. (2011)	1	0.8	0.75	0.75	0.2	1	1	1	0	0	0.5	1	1	1	10.0
Pereira et al. (2019)	1	0.4	0.5	1	0	1	0.7	0.9	0	0	1	1	1	1	9.5
Plotnik et al. (2007)	1	0.8	1	1	0	1	0.9	0.9	0	0	1	1	1	1	10.6
Ren et al. (2015)	1	0.8	1	1	0	1	1	1	0	0	1	1	1	0.5	10.3
Seuthe et al. (2024)	1	0.8	0.25	1	0	1	1	1	0	0	1	1	1	1	10.1
Vervoort et al. (2015)	1	0.7	1	1	0	0.75	1	1	0.5	0.5	1	1	1	0.25	10.7
Vervoort et al. (2016)	1	0.8	0.5	1	0	1	1	1	0	0	1	1	1	0.5	9.8
Wu et al. (2021)	1	1	1	1	0	1	0.9	0.9	0	0	1	1	1	1	10.8
Yogev et al. (2007)	1	0.7	1	1	0	1	0.9	0.9	0	0	1	1	1	0.5	10.0
Means by item	**1**	**0.81**	**0.78**	**0.81**	**0.01**	**0.94**	**0.93**	**0.96**	**0.15**	**0.21**	**0.88**	**0.97**	**0.88**	**0.70**	**10.0**

APPENDIX E – Equations, indexes, and other methods employed to calculate asymmetry during gait

Authors	Method to calculate GA
Bailo et al. (2024)	**Harmonic Ratio (HR)** - Ratio between the sum of the amplitudes of the in-phase harmonics and the sum of the amplitudes of the out-of-phase harmonics; **Improved HR** - Ratio between the power of the in-phase harmonics and the sum of in-phase and out-of phase harmonics power.
Baltadjieva et al. (2006)	**Gait asymmetry** = 100 x |ln(SSWT/LSWT)|
Barbieri et al. (2018)	**Symmetric index** = $\frac{\text{(value of LAL - value of MAL)}}{\text{(value of LAL + value of MAL)}}$ x 100%
Barbosa et al. (2024)	**Asymmetry index** = (right side - left side)/(rigth side + left side)
Brodie et al. (2015)	**Mean asymmetry (MA)** **Absolute paired-step asymmetry (AA)**
Buckley et al. (2019)	**Spatiotemporal asymmetry -** (Step time asymmetry, Swing time asymmetry, Stance time asymmetry) - Lord, Galna, Rochester (2013) **Upper body acceleration symmetry** - Autocorrelation symmetry (Auto sym) and HR.
Danoudis, Iansek & Simpson (2012)	**Asymmetry =** |right measure - left measure|
De Bartolo et al. (2020)	**Symmetry index =** the percentage of overlapping between curve accelerations of right and left step
Del Din et al. (2016)	**Asymmetry =** | Average left (steps) - Average right (steps) |
Del Din, Godfrey & Rochester (2016)	**Asymmetry =** |Average left - Average right|

Djurić-Jovičić et al. (2017)	**Step time asymmetry** = left step time - right step **Stride time asymmetry =** left stride time - right stride time **Step length asymmetry** = right step length - left step length
Ferreira et al. (2022)	**Symmetric index** = $\frac{\text{(value of LAL - value of MAL)}}{\text{(value of LAL + value of MAL)}} \times 100\%$
Fling, Curtze & Horak (2018)	**Asymmetry** = |1 - left/right| x 100
Galna et al. (2015)	**Asymmetry =** |right measure - left measure|
Gilmore et al. (2019)	Extracted from the "PKMAS" Software
Godi et al. (2021)	**Asymmetry** = |ln(left/right)| x 100
Grajić et al. (2015)	**Asymmetry = statistical comparison considering:** Body sides: left leg X right leg Side of PD-onset: leg of the side of disease onset X contralateral leg
Hackney & Earhart (2010)	**Gait asymmetry =** 100 x |ln(SSWT/LSWT)|
Iosa et al. (2016)	**Symmetry ratio index** = ratio between longer step and shorter step within 1 stride; **Gai asymmetry index** = |ln (shorter swing time/longer swing time)|
Keloth et al. (2021)	**Asymmetry index** = 100 - ([higher value of sEMG RMS/lower value of sEMG RMS] x 100)

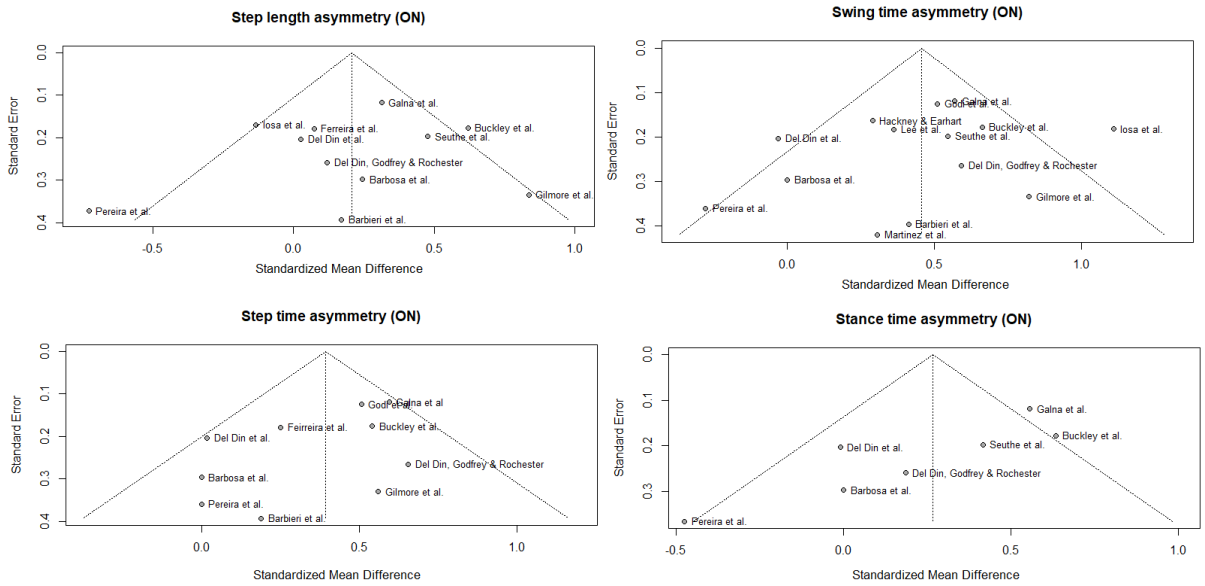
Kleiner et al. (2018)	**Step length asymmetry** = ([máx amplitude - min amplitude]/max amplitude) x 100%
Koh et al. (2019)	**Symmetry angle** = 100% x ((45° - arctan (small side / large side))/ 90°)
Leavy et al. (2018)	Based in Lord, Galna, Verghese et al. (2013)
Lee et al. (2020)	**Gait asymmetry =** 100 x |ln(SSWT/LSWT)|
Lencioni et al. (2021)	**Asymmetry: statistical comparison considering:** Lower limb (LL) as repeated measure factor (More/Less Affected and Non-Dominant/Dominant)
Liu et al. (2022)	**Symmetry angle** = 100% x ((45° - arctan (greater side/lesser side))/ 90°) Did not mention the step length asymmetry index
Martínez et al. (2018)	**Gait asymmetry** = 100 x |ln(SSWT/LSWT)|
Miller et al. (1996)	**Symmetry magnitude (Sm) and Symmetry phase (Sp) -** The bilateral symmetry for each muscle was computed from the LCEAs
Morris et al. (2017a)	Based in Lord, Galna, Verghese et al. (2013)
Morris et al. (2017b)	**Asymmetry** = |average left - average right|
Nanhoe-Mahabier et al. (2011)	**Step length asymmetry** = ([max amplitude - min amplitude]/max amplitude) x 100% **Step time asymmetry** = ([max time - min time]/max time) x 100%

Pereira et al. (2019)	Extracted from the "GAITRite" Software
Plotnik, Gilardi & Hausdorff (2007)	**Gait asymmetry** = 100 x |ln(SSWT/LSWT)|
Ren et al. (2015)	**Step asymmetry =** difference in the average stride lengths between the left and right legs
Seuthe et al. (2024)	**Asymmetry index** = (right side - left side)/(rigth side + left side)
Vervoort et al. (2015)	Based in Lord, Galna, Verghese et al. (2013)
Vervoort et al. (2016)	**Asymmetry** was calculated between the dominant (D) and non-dominant (ND) leg
Wu et al. (2021)	$\%AI = \frac{\max(\text{Left side value, Right side value}) - \min(\text{Left side value, Right side value})}{\max(\text{Left side value, Right side value})} \times 100$
Yogev et al., 2007	**Gait asymmetry =** 100 x |ln(SSWT/LSWT)|

SSWT: short swing time; LSWT: long swing time; LAL: least affected limb; MAL: most affected limb; EMG: eletromyography; RMS: root mean square; max: maximum; min: minimum.

Lord S, Galna B, Rochester L. Moving forward on gait measurement: toward a more refined approach. Mov Disord. 2013;28:1534–1543.
Lord S, Galna B, Verghese J, Coleman S, Burn D, Rochester L. Independent domains of gait in older adults and associated motor and nonmotor attributes: validation of a factor analysis approach. J Gerontol A Biol Sci Med Sci. 2013;68(7):820-827.

APPENDIX F – Funnel plots of step length asymmetry, swing time asymmetry, step time asymmetry and stance time asymmetry for the comparison between pwPD at ON state vs. NHI.



APPENDIX G – Asymmetric spatial-temporal parameters of PG compared to CG during the approach and circumvention phases to the more and less affected side during the obstacle circumvention with and without a dual task.

	OC				OC + DT				Main effects			Interaction effects			
Approach phase	**MORE AFFECTED SIDE**		**LESS AFFECTED SIDE**		**MORE AFFECTED SIDE**		**LESS AFFECTED SIDE**		Group (G)	Task (T)	Side (S)	G x T	G x S	T x S	G x T x S
	PG	**CG**	**PG**	**CG**	**PG**	**CG**	**PG**	**CG**							
SL asym	3.95 ± 4.50	3.58 ± 2.96	3.36 ± 3.75	4.08 ± 3.29	4.84 ± 7.22$^{*\#}$	2.35 ± 2.26	5.94 ± 5.78$^{*\#}$	2.78 ± 1.52	*ns*	*ns*	*ns*	$F_{1,30}$= 4.427, p=0.044, n^2=0.129	*ns*	*ns*	*ns*
SW asym	16.64 ± 16.34	17.29 ± 15.17	16.35 ± 15.62	18.41 ± 15.13	11.90 ± 12.64	11.14 ± 13.42	12.38 ± 8.22	17.12 ± 15.38	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
ST asym	1.50 ± 1.21*	1.37 ± 1.42	2.22 ± 3.27*	0.92 ± 0.78	2.16 ± 1.64*	1.15 ± 0.84	2.26 ± 2.64*	0.98 ± 0.90	$F_{1,30}$= 4.843, p=0.036, n^2=0.139	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
SS asym	5.36 ± 8.21$^{£}$	3.15 ± 2.18$^{£}$	7.48 ± 7.03$^{£}$	4.62 ± 2.69$^{£}$	4.60 ± 6.18	2.42 ± 1.74	5.95 ± 6.34	2.61 ± 1.36	*ns*	$F_{1,30}$= 4.735, p=0.038, n^2=0.136	*ns*	*ns*	*ns*	*ns*	*ns*
DS asym	4.33 ± 4.64	2.64 ± 2.54	6.15 ± 5.31	5.06 ± 3.84	4.63 ± 3.02	3.73 ± 3.00	4.59 ± 5.50	3.12 ± 2.28	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
Circumvention phase	**PG**	**CG**	**PG**	**CG**	**PG**	**CG**	**PG**	**CG**							
SL asym	2.63 ± 3.14	3.36 ± 3.89	3.18 ± 4.42	3.10 ± 1.42	5.16 ± 5.63$^{*\#}$	2.88 ± 2.77	4.64 ± 5.10$^{*\#}$	2.04 ± 1.86	*ns*	*ns*	*ns*	$F_{1,31}$= 9.982, p=0.004, n^2=0.244	*ns*	*ns*	*ns*
SW asym	10.51 ± 11.93	10.33 ± 9.88	14.26 ± 12.97	9.31 ± 13.89	11.74 ± 10.55	13.25 ± 16.96	17.64 ± 15.31	7.05 ± 6.79	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
ST asym	1.79 ± 1.28*	1.18 ± 1.48	2.35 ± 2.38*	1.17 ± 0.84	1.98 ± 1.73*	1.14 ± 0.76	2.86 ± 2.57*	1.64 ± 1.54	$F_{1,31}$= 7.544, p=0.010, n^2=0.196	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
SS asym	3.10 ± 2.60$^{\$}$	3.84 ± 3.91$^{\$}$	5.33 ± 5.86$^{\$}$	3.84 ± 1.73$^{\$}$	4.44 ± 5.03*	2.70 ± 1.89	4.99 ± 5.09*	2.16 ± 1.83	*ns*	*ns*	*ns*	$F_{1,31}$= 6.547, p=0.016, n^2=0.174	*ns*	*ns*	*ns*
DS asym	7.41 ± 5.10$^{*£}$	3.56 ± 2.86$^{£}$	7.89 ± 6.68$^{*£}$	4.58 ± 3.74$^{£}$	5.65 ± 4.30*	3.01 ± 2.41	5.77 ± 6.54*	3.72 ± 3.17	$F_{1,31}$= 6.076, p=0.019, n^2=0.164	$F_{1,31}$= 4.577, p=0.04, n^2=0.129	*ns*	*ns*	*ns*	*ns*	*ns*

SL: step length; SW: step width; ST: step time; SS: step speed; DS: double support time; asym: asymmetry; PG: Parkinson's disease group; CG: control group; * GP > GC; $^{£}$ OC > OC + DT; $^{\#}$ GP = OC + DT > OC; $^{\$}$ GC = OC > OC+DT.

ANEXXES

ANNEX I – ETHICS COMMITTEE APPROVAL

UNESP - FACULDADE DE CIÊNCIAS CAMPUS BAURU - JÚLIO DE MESQUITA FILHO

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: EFEITO DA MEDICAÇÃO, TAREFA DUPLA E ASSIMETRIA NO COMPORTAMENTO DA ATIVIDADE DO CÓRTEX CEREBRAL DURANTE A LOCOMOÇÃO EM IDOSOS COM DOENÇA DE PARKINSON

Pesquisador: Fabio Augusto Barbieri

Área Temática:

Versão: 1

CAAE: 78660517.2.0000.5398

Instituição Proponente: UNIVERSIDADE ESTADUAL PAULISTA JULIO DE MESQUITA FILHO

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.422.821

Apresentação do Projeto:

O Projeto abarca três estudos sobre a locomoção em idosos com Doença de Parkinson (DP), para compreensão do efeito da medicação utilizada por tal população,realização de tarefa dupla ao andar e assimetria no comportamento da atividade do córtex durante a locomoção.

Objetivo da Pesquisa:

Compreensão de fatores que possam dificultar ou facilitar a atividade de locomoção de pessoas com Doença de Parkinson; compreender atividade cerebral e efeitos de medicamento e da assimetria na locomoção e na realização de tarefa concomitante.

Avaliação dos Riscos e Benefícios:

Há riscos de queda, mas a equipe prevê tais riscos e planeja acompanhar a atividade, com profissional próximo ao participante. Os achados dos estudos poderão contribuir de forma significativa para a população com DP, na medida em que puder favorecer a locomoção e a segurança ao mover-se.

Comentários e Considerações sobre a Pesquisa:

Pesquisa relevante, com projeto consistente e bem elaborado, que poderá melhorar a qualidade de vida de pessoas com DP.

Endereço: Av. Luiz Edmundo Carrijo Coube, nº 14-01
Bairro: CENTRO **CEP:** 17.033-360
UF: SP **Município:** BAURU
Telefone: (14)3103-9400 **Fax:** (14)3103-9400 **E-mail:** cepesquisa@fc.unesp.br

UNESP - FACULDADE DE CIÊNCIAS CAMPUS BAURU - JÚLIO DE MESQUITA FILHO

Continuação do Parecer: 2.422.821

Considerações sobre os Termos de apresentação obrigatória:

Termos bem elaborados e de acordo com a resolução 466.

Recomendações:

Orientar o participante e o cuidador sobre horários de início e de término de cada etapa do estudo e avaliar com os mesmos as necessidades relacionadas à permanência no laboratório para estudo. Aqueles cujo efeito da medicação será analisada precisam ser informados sobre horário e administração do remédio no dia de pesquisa.

Conclusões ou Pendências e Lista de Inadequações:

Estudo adequado e cuidadoso, que poderá ser aperfeiçoado se observadas as recomendações.

Considerações Finais a critério do CEP:

Projeto considerado aprovado por estar em conformidade com os parâmetros legais, metodológicos e éticos analisados pelo colegiado.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1000636.pdf	03/10/2017 10:10:19		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE03_Is.doc	03/10/2017 10:07:57	Fabio Augusto Barbieri	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE02_Is.doc	03/10/2017 10:07:45	Fabio Augusto Barbieri	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE01_Is.doc	03/10/2017 10:07:32	Fabio Augusto Barbieri	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_detalhado.docx	02/10/2017 17:46:17	Fabio Augusto Barbieri	Aceito
Folha de Rosto	folha_de_rosto.pdf	02/10/2017 17:45:34	Fabio Augusto Barbieri	Aceito

Situação do Parecer:

Aprovado

Endereço: Av. Luiz Edmundo Carrijo Coube, nº 14-01
Bairro: CENTRO **CEP:** 17.033-360
UF: SP **Município:** BAURU
Telefone: (14)3103-9400 **Fax:** (14)3103-9400 **E-mail:** cepesquisa@fc.unesp.br

UNESP - FACULDADE DE CIÊNCIAS CAMPUS BAURU - JÚLIO DE MESQUITA FILHO

Continuação do Parecer: 2.422.821

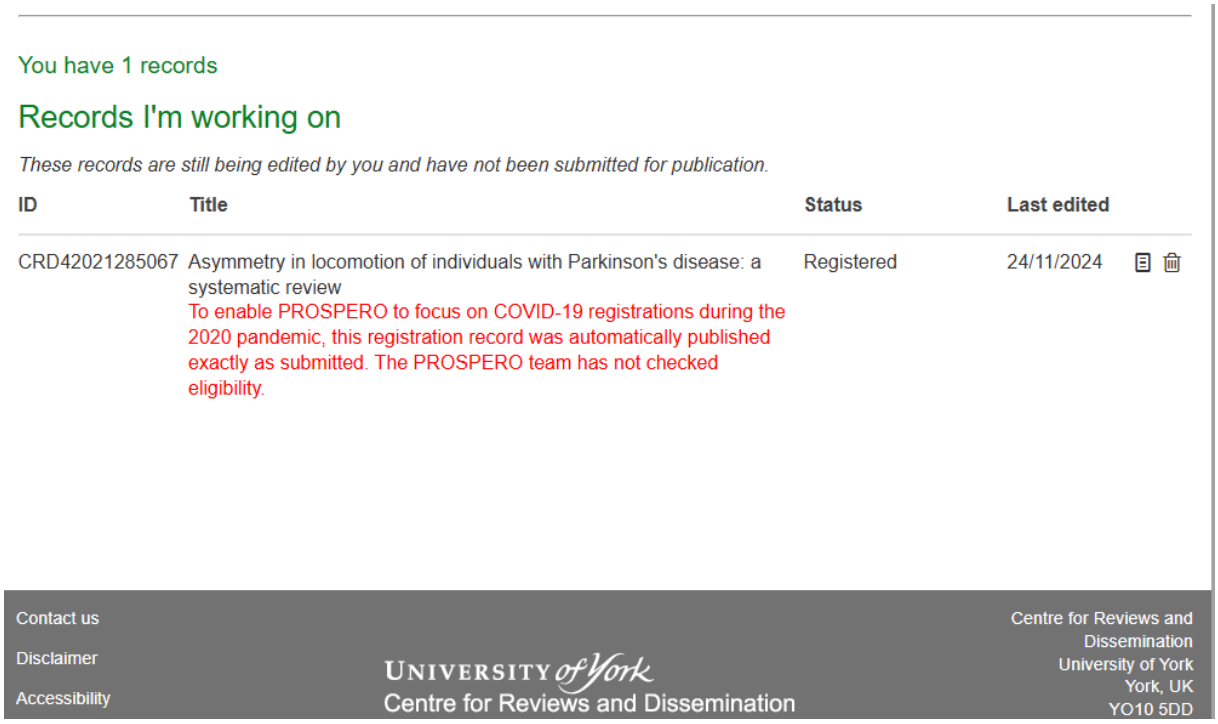
Necessita Apreciação da CONEP:
Não

BAURU, 07 de Dezembro de 2017

Assinado por:
Mário Lázaro Camargo
(Coordenador)

Endereço: Av. Luiz Edmundo Carrijo Coube, nº 14-01
Bairro: CENTRO **CEP:** 17.033-360
UF: SP **Município:** BAURU
Telefone: (14)3103-9400 **Fax:** (14)3103-9400 **E-mail:** cepesquisa@fc.unesp.br

ANNEX II – PROSPERO REGISTRATION NUMBER



You have 1 records

Records I'm working on

These records are still being edited by you and have not been submitted for publication.

ID	Title	Status	Last edited
CRD42021285067	Asymmetry in locomotion of individuals with Parkinson's disease: a systematic review To enable PROSPERO to focus on COVID-19 registrations during the 2020 pandemic, this registration record was automatically published exactly as submitted. The PROSPERO team has not checked eligibility.	Registered	24/11/2024

Contact us
Disclaimer
Accessibility

UNIVERSITY of York
Centre for Reviews and Dissemination

Centre for Reviews and Dissemination
University of York
York, UK
YO10 5DD