

**Universitat
de Lleida**



**UNIVERSITY
OF TURKU**

Doctoral Thesis

**The Efficacy of a Gamified Virtual
Reality Environment combined with
tDCS in Treadmill-Based Gait
Rehabilitation for Parkinson's Disease**

Pere Bosch-Barceló

A thesis submitted in candidacy for the degree of Doctor, jointly
awarded by the University of Lleida and the University of Turku

PhD Programme in Comprehensive Care and Health Services – University of Lleida

PhD Programme in Nursing Science – University of Turku

Supervised by

Dr. Helena Fernández-Lago

Dr. Anni Pakarinen

Dr. Katja Joronen

Monitored by

Dr. Anna Axelin

Dr. Joan Blanco Blanco

This doctoral thesis has been completed under joint supervision (Cotutelle) between the Faculty of Medicine at the University of Turku, Finland and the Department of Nursing and Physiotherapy at the University of Lleida, Spain.

The originality of this publication has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service

Reviewed by

Professor Katherine McGilton, PhD; KITE: Research Institute:
Toronto Rehabilitation: UHN.

Associate Professor Lisa Cranley, PhD; Lawrence S
Bloomberg, Faculty of Nursing, University of Toronto

Opponent

Professor Miguel Ángel Fernández del Olmo, PhD; University King Juan Carlos
(URJC): Faculty of Education, Sport and Interdisciplinary Studies: Research
Center in Sport Sciences.

«The most important step a man can take. It's not the first one, is it?
It's the next one. Always the next step»

Brandon Sanderson

Agraïments – Acknowledgements – Agradecimientos

Finalitzar un projecte de l'envergadura d'aquesta tesi doctoral hauria estat impossible sense l'ajuda que han aportat nombroses persones i institucions, de diferents formes i nivells, totes elles imprescindibles.

Aquesta tesi ha estat possible gràcies al suport econòmic de l'Institut de Salut Carlos III (projecte PI20/00403), la Universitat de Lleida, mitjançant la seva convocatòria per a investigadors predoctorals, i l'Institut de Recerca Biomèdica de Lleida, que va aportar l'espai i el suport necessaris per dur a terme les intervencions. També vull agrair al Grup de Recerca en Cures en Salut (GReCS) per acollir-me al començament d'aquest projecte de tesi, i a l'Associació de Parkinson de les Terres de Lleida, sense la qual no haurien estat possibles els resultats obtinguts.

A mi directora de tesis, la Dra. Helena Fernández, para quien no tengo palabras suficientes para agradecer todo lo que ha hecho por mí. Gracias por abrirme las puertas de tu proyecto y tu investigación y ser mi guía durante cada uno de los pasos que he dado a lo largo de estos cuatro años. Por tu apoyo constante, tus consejos y por motivarme siempre a afrontar el siguiente reto. Cierro esta etapa agradecido por todas las experiencias y aprendizajes que hemos pasado, que han impulsado enormemente mi desarrollo como investigador y me han enriquecido a nivel personal.

To my co-supervisors, Dr. Anni Pakarinen and Dr. Katja Joronen: Anni, thank you for providing your experience and knowledge to walk the extra mile in this path. Your thorough revisions and advice have been irreplaceable, and I've grown to be a better researcher thanks to them. And for welcoming me to Turku, making me feel at home from day one and giving me a glimpse into what living in Finland truly feels like for three amazing months. To Katja, thank you for your help in making it possible for me to join this cotutelle project, and for your willingness to assist with last-minute problems without hesitation.

Als meus tutors, el Dr. Joan Blanco i la Dra. Anna Axelin: Joan, gràcies pel teu suport i acompanyament al llarg d'aquesta tesi. Anna, thank you for warmly welcoming me to UTU's Department of Nursing Science and for your valuable feedback along this project.

A la Dra. Esther Rubinat, per haver confiat en mi quan havia de començar aquest viatge, i per permetre'm dedicar el meu temps i recursos a iniciar aquesta tesi. Per acollir-me al grup, pels teus bons consells, i pel teu suport, tranquil·litat i confiança.

A la Dra. Montserrat Gea, per estar sempre disposada a donar-me un cop de mà amb qualsevol problema, per la teva proximitat, la teva capacitat de resolució i per fer-me sentir acompanyat fins i tot en els moments més complicats. Aquesta cotutela no hauria estat possible sense la teva ajuda.

A tot l'equip d'intervencions, pel vostre compromís, esforç i dedicació al llarg de tot el projecte. A la Carol, per animar-me a entrar al món de la recerca; a l'Oriol i la Maria, per la vostra ajuda a cada pas del projecte; a la Yesmina i als alumnes, pel vostre ajut constant; i especialment al Carles, que ha estat un pilar fonamental durant aquests anys: pel teu suport constant, per ser-hi sempre que fes falta, ja fos per prendre un cafè o per donar un cop de mà per tirar endavant aquesta tesi. Sense vosaltres, res d'això hauria estat possible.

A tots els meus companys del GReCS, i especialment al Filip i l'Erica, pels bons moments i professionalitat al llarg d'aquests anys; i en José Tomás, pels grans consells tot just arribar que encara recordo.

A totes les persones amb Parkinson i fisioterapeutes que heu fet possible aquesta tesi amb la vostra participació, temps i esforç. La vostra generositat ha estat fonamental per donar sentit i valor a aquest treball.

A l'Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS), i especialment en Roland, en Joan i la M. Dolors, per donar-me l'oportunitat de col·laborar en projectes que han estat un gran aprenentatge i m'han ajudat a créixer com a investigador.

A la Neus, per ser una referent de la feina ben feta i el meu primer suport al món de la recerca. Al meu grup d'amics, que tant m'han acompanyat en aquest camí: gràcies per ser-hi sempre, tant si fa dies com si fa mesos que no ens veiem, i per sa vostra visita a Finlàndia. Sou, de veritat, sa meva segona família.

A na Lluc, per a qui no hi ha paraules que puguin expressar el que significa per a mi el teu suport dia rere dia. Per ser el meu far, per acompanyar-me i aguantar-me durant quatre llargs anys de pujades i baixades, per ser com ets i fer-me costat a cada passa d'aquest viatge. No tinc cap dubte que aquesta tesi no estaria on està sense tu al meu costat. De tot cor, gràcies.

A sa meva mare i al meu pare, per ser sempre al meu costat i creure en mi sense reserves. Gràcies per sa vostra confiança, pels ànims inesgotables, pels bons consells i per tot allò que feu sense demanar res a canvi. I gràcies també per ses mil videotrucades que, tot i sa distància, m'han fet sentir-me a prop i com a casa.

I per acabar, el meu agraïment i reconeixement als qui, tot i que ja no hi són, han deixat una empremta inesborrable en aquest viatge.

«Journey before destination»

Contents

Agraïments – Acknowledgements – Agradecimientos.....	6
Contents	8
List of Figures	12
List of Abbreviations	14
Abstract	16
Resum	18
Tiivistelmä.....	20
List of Scientific Articles	22
Chapter 1. Parkinson’s Disease: Clinical and Epidemiological Overview	24
1.1 Definition and Pathophysiology	26
1.2. Epidemiology and demographic trends	27
1.3. Disease progression and staging	28
1.3.1 Prodromal Phase	28
1.3.2 Early to Mid-Stage PD.....	28
1.3.3 Advanced Stage	29
1.3.4 Subtypes and Disease Variability	29
1.3.5 Staging Systems	29
1.4 Key symptomatology: motor and non-motor symptoms.....	30
1.4.1 Motor Symptoms	31
1.4.2 Non-Motor Symptoms	32
1.5 Impact on autonomy, quality of life, and healthcare systems	33
1.5.1 Loss of Autonomy and Functional Independence	33
1.5.2 Impact on Quality of Life.....	34
1.5.3 Burden on Healthcare Systems and Society.....	34
1.6 Conventional treatment for Parkinson’s Disease	34
2.1 Neurophysiology of Gait in Healthy Adults.....	40
2.2 Neural Mechanisms of Gait Dysfunction in Parkinson’s Disease	40
2.2.1 Basal Ganglia Dysfunction and Loss of Automaticity	40
2.2.2 Impaired Internal Cueing and Movement Scaling	41
2.2.3 Cortical Compensation and Attentional Overload	41
2.3 PD-Specific Gait Alterations	41
2.3.1 Freezing of Gait.....	42
2.3.2 Festination and Shuffling Gait.....	42
2.3.3 Gait Variability and Asymmetry	42

2.3.4 Dual task Gait Impairment	43
2.4 Postural Control Impairments and Balance Dysfunction	43
2.4.1 Impaired Anticipatory and Reactive Postural Responses.....	43
2.4.2 Rigidity and Postural Reflex Impairment.....	44
2.4.3 Balance Impairment Under Dual Task Conditions	44
2.5 Clinical Consequences of Gait and Balance Dysfunction	44
2.5.1 Falls and Fall-Related Injuries	44
2.5.2 Loss of Functional Independence.....	45
2.5.3 Psychosocial and Cognitive Impact	45
Chapter 3. Rehabilitation Approaches in Parkinson’s Disease	46
3.1 Conventional Physiotherapy and Motor Training	48
3.1.1 Clinical Benefits and Evidence Base	48
3.1.3 Implementation in Clinical Practice	48
3.2 Evidence for Task-Specific Training and Cueing Strategies.....	49
3.2.1 Task-Specific Training.....	49
3.2.2 External Cueing Strategies.....	49
3.2.3 Treadmill as a Cue-Based Training Strategy.....	50
3.3 Limitations of Conventional Rehabilitation	50
3.4.1 Limited Access to Specialized Rehabilitation	50
3.4.2 Adherence and Motivation Challenges	51
3.4.3 Insufficient Intensity and Dose.....	51
Chapter 4. The use of Technology in Healthcare and Rehabilitation	54
4.1 Technologies in Healthcare	56
4.1.1 Early Steps of Virtual Reality in Healthcare	56
4.1.2 Use of Virtual Reality and Exergames in 2000s and early 2010s.....	56
4.2 The Role of Virtual Reality in Healthcare and Parkinson’s Disease	57
4.2.1 Current position of Virtual Reality in Healthcare.....	57
4.2.2 Integration of Virtual Reality in Treadmill Training	57
4.2.3 Strengths and Weaknesses.....	58
4.3 Gamification: Enhancing Engagement and Adherence.....	59
4.3.1 What Is Gamification and How Is It Used	59
4.3.2 Frameworks for Gamification Use	60
4.3.3 Use of Gamification in Neurorehabilitation Settings	62
Chapter 5. tDCS in Parkinson’s Disease Rehabilitation	64
5.1 Introduction and evolution of brain stimulation in clinical neuroscience	66
5.2 Introduction to tDCS.....	66

5.3 Rationale for Using tDCS in Motor Rehabilitation for PD	67
5.4 Combining tDCS with Treadmill Gait Training in PD	67
5.5 Considerations and Challenges in tDCS Application	68
Chapter 6. Justification and Research Aim	70
6.1 The Case for Technology-Enhanced, Gamified Rehabilitation	72
6.2 Rationale for the addition of tDCS	72
6.3 Theoretical and Clinical Relevance	74
Objectives.....	76
General objective	78
Specific objectives	78
Specific objective I	78
Specific objective II	78
Specific objective III	78
Specific objective IV	78
Methodology	80
Methodology to address specific objectives I & II	82
Methodology to address specific objective III	90
Methodology to address specific objective IV	94
Articles.....	98
Article I: Gamification Integration in Technological Devices for Motor Rehabilitation in Parkinson’s Disease: A Scoping Review	100
Article II: A gamified virtual environment intervention for gait rehabilitation in Parkinson’s Disease: co-creation and feasibility study	102
Article III: A treadmill training program in a gamified virtual reality environment combined with transcranial direct current stimulation in Parkinson’s Disease: Study protocol for a randomized controlled trial	104
Article IV: A treadmill training program in a gamified virtual reality environment combined with transcranial direct current stimulation in Parkinson’s Disease: Preliminary results of a mixed methods randomized controlled trial	106
A treadmill training program in a gamified virtual reality environment combined with transcranial direct current stimulation in Parkinson’s Disease: Preliminary results of a mixed methods randomized controlled trial	¡Error! Marcador no definido.
Abstract	¡Error! Marcador no definido.
Introduction	¡Error! Marcador no definido.
Materials and methods.....	¡Error! Marcador no definido.
Trial design	¡Error! Marcador no definido.
Participants	¡Error! Marcador no definido.
Ethics approval	¡Error! Marcador no definido.

Randomization and blinding	¡Error! Marcador no definido.
Interventions	¡Error! Marcador no definido.
Outcome measures	¡Error! Marcador no definido.
Quantitative measures	¡Error! Marcador no definido.
Qualitative measures.....	¡Error! Marcador no definido.
Analysis	¡Error! Marcador no definido.
Integration of Quantitative and Qualitative Data	¡Error! Marcador no definido.
Quantitative Analysis.....	¡Error! Marcador no definido.
Qualitative Analysis	¡Error! Marcador no definido.
Results.....	¡Error! Marcador no definido.
Participant Characteristics.....	¡Error! Marcador no definido.
Changes in Gait Parameters Under Single and Dual Task Conditions.....	¡Error! Marcador no definido.
Cognitive-Motor Integration and Dual Task Effects .	¡Error! Marcador no definido.
Clinical Outcomes	¡Error! Marcador no definido.
Engagement, Motivation, and Acceptability	¡Error! Marcador no definido.
Discussion	¡Error! Marcador no definido.
Gait Outcomes: Objective Measures and Subjective Experiences	¡Error! Marcador no definido.
Cognitive-Motor Integration	¡Error! Marcador no definido.
Clinical Outcomes	¡Error! Marcador no definido.
Motivation and adherence to intervention.....	¡Error! Marcador no definido.
Strengths and Limitations.....	¡Error! Marcador no definido.
Conclusions	¡Error! Marcador no definido.
References	¡Error! Marcador no definido.
Discussion	108
Objective I.....	110
Objective II.....	111
Objective III & IV	112
Mechanisms and theoretical implications	113
Comparison with previous studies.....	117
Strengths and limitations.....	119
Clinical and research implications	121
Conclusions	124
References	128

List of Figures

Figure 1. Clinical symptoms and progression of Parkinson’s Disease. From Kalia & Lang (Kalia & Lang, 2015)	311
Figure 2. Treadmill + Virtual Reality training set-up. From Mirelman et al. (Mirelman et al., 2016) - V-TIME project.....	588
Figure 3. Gamification, from Hamari et al. (Hamari et al., 2014)	599
Figure 4. Octalysis Framework's Eight Core Drives (Chou, 2019)	61
Figure 5. Conceptual framework for the integration of treadmill gait training, GVRE and tDCS in a Venn diagram format.....	74

List of Abbreviations

PD	Parkinson's Disease
GVRE	Gamified Virtual Reality Environment
VR	Virtual Reality
DT	Dual Task
RCT	Randomized Controlled Trial
FoG	Freezing of Gait
MDS- UPDRS	Motor Disorder Society - United Parkinson's Disease Rating Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SD	Standard Deviation
MCID	Minimal Clinically Important Differences
CI	Confidence Interval
DTM	Motor DT
DTV	Verbal Fluency DT
DTA	Arithmetic DT
PCC	Population, Concept and Context
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
FES-I	Falls Efficacy Scale International
GReCS	Grup de Recerca en Cures en Salut
PIGD	Postural Instability Gait Disorder
DBS	Deep Brain Stimulation
DLPFC	Dorsolateral Prefrontal Cortex
JBI	Joanna Briggs Institute
HRQoL	Health Related Quality of Life
PEBL	The Psychology Experiment Building Language
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
IPAQ	International Physical Activity Questionnaire
H&Y	Hoehn & Yahr
PDQ39	Parkinson's Disease Questionnaire 39
ITC-SOPI	International Television Commision - Sense of Presence Inventory
SSQ	Simulator Sickness Questionnaire

The Efficacy of a Gamified Virtual Reality Environment combined with tDCS in Treadmill-Based Gait Rehabilitation for Parkinson's Disease

Abstract

Objectives: The general objective of this dissertation was to determine the efficacy of combining a gamified virtual reality environment (GVRE) with transcranial direct current stimulation (tDCS) in treadmill-based gait rehabilitation for individuals with Parkinson's disease (PD). To achieve this goal, we set several specific objectives: (1) to synthesize existing evidence on the use of gamification in technological devices for motor rehabilitation in PD (article I), (2) to design, develop, and evaluate the feasibility of a GVRE gait rehabilitation intervention tailored to people with PD (article II), (3) to design a study protocol for a randomized controlled trial (RCT) evaluating the combined intervention of GVRE and tDCS in gait rehabilitation for PD (article III), and (4) to assess preliminary outcomes from the RCT regarding gait variables, clinical assessment and user experience (article IV).

Methodology: To address specific objectives 1 and 2, a scoping review and a co-creation feasibility study were conducted. The scoping review identified the extent and characteristics of gamified technology use in PD rehabilitation. The feasibility study was carried out using participatory design methodologies with people with PD and healthcare professionals. To address objectives 3 and 4, a mixed-methods RCT was developed and conducted. The trial enrolled individuals with PD to randomly receive gait rehabilitation training in one of three groups: (1) treadmill + GVRE + tDCS; (2) treadmill + GVRE; (3) treadmill. Quantitative outcomes included gait parameters, executive function assessment and clinical measures; qualitative data captured participant experience and satisfaction.

Results: Gamification was found to enhance motivation, engagement, and adherence in PD rehabilitation technologies. The designed intervention was feasible and well-received, emphasizing simplicity, personalization, and safety. Preliminary findings from the RCT suggest that the combined use of treadmill, GVRE and tDCS is not significantly better at improving gait parameters than its control counterparts. However, participants in the Treadmill+GVRE and Treadmill+GVRE+tDCS groups reported subjective improvements in stride regulation, walking confidence, and cognitive awareness. Select cognitive gains, including improved inhibitory control, emerged at follow-up, suggesting possible delayed effects of neuromodulation. Participants reported high acceptability and engagement to the GVRE intervention.

Conclusions: The integration of GVRE and tDCS into gait rehabilitation for PD proved an effective tool to enhance engagement, but potential improvements regarding gait-related outcomes are unclear. Future research should aim to conduct further research with larger, more diverse sample sizes and further personalize gamified content based

on aimed experience and characteristics of individuals with PD. Interventions should aim to balance cognitive load, physical challenge, and motivational support to meet the unique needs of people with PD.

Keywords: Parkinson's Disease; Gait; Rehabilitation; Virtual Reality; Gamification; tDCS.

L'eficàcia d'un entorn de realitat virtual gamificat combinat amb tDCS en la rehabilitació de la marxa en cinta de córrer per a la malaltia de Parkinson

Resum

Objectius: L'objectiu general d'aquesta tesi ha estat determinar l'eficàcia de combinar un entorn de realitat virtual gamificat (GVRE) amb estimulació transcranial per corrent directa (tDCS) en la rehabilitació de la marxa mitjançant cinta de córrer en persones amb malaltia de Parkinson (PD). Per assolir aquest objectiu, es van establir diversos objectius específics: (1) sintetitzar l'evidència existent sobre l'ús de la gamificació en dispositius tecnològics per a la rehabilitació motora en la PD (article I), (2) dissenyar, desenvolupar i avaluar la viabilitat d'una intervenció de rehabilitació de la marxa mitjançant GVRE adaptada a persones amb PD (article II), (3) dissenyar un protocol d'estudi per a un assaig clínic aleatoritzat (RCT) que avalués la intervenció combinada de GVRE i tDCS en la rehabilitació de la marxa per a la PD (article III), i (4) analitzar els resultats preliminars del RCT pel que fa a variables de la marxa, avaluacions clíniques i experiència d'usuari (article IV).

Metodologia: Per abordar els objectius específics 1 i 2, es van dur a terme una revisió exploratòria i un estudi de viabilitat mitjançant co-creació. La revisió exploratòria va identificar l'abast i les característiques de l'ús de la tecnologia gamificada en la rehabilitació de la MP. L'estudi de viabilitat es va desenvolupar amb metodologies de disseny participatiu amb persones amb PD i fisioterapeutes. Per als objectius 3 i 4, es va dissenyar i executar un RCT amb enfocament mixt. L'assaig va incloure persones amb PD aleatoritzades en tres grups d'entrenament de la marxa: (1) cinta de córrer + GVRE + tDCS; (2) cinta de córrer + GVRE; (3) només cinta de córrer. Els resultats quantitatius incloïen paràmetres de marxa, proves de funció executiva i mesures clíniques; les dades qualitatives recullen l'experiència i satisfacció dels participants.

Resultats: La gamificació va demostrar afavorir la motivació, implicació i adherència en tecnologies de rehabilitació per a la MP. La intervenció dissenyada va resultar viable i ben acollida, destacant-se per la seva simplicitat, personalització i seguretat. Els resultats preliminars del RCT suggereixen que la combinació de cinta de córrer, GVRE i tDCS no millora significativament els paràmetres de marxa respecte als grups control. Tanmateix, els participants dels grups Cinta+GVRE i Cinta+GVRE+tDCS van reportar millores subjectives en la regulació de la foulada, confiança en la marxa i consciència cognitiva. Es van observar alguns guanys cognitius, com la millora del control inhibitori en el seguiment, suggerint possibles efectes retardats de la neuromodulació. L'acceptació i implicació amb la GVRE va ser alta entre els participants, tot i que el gaudi va ser variable.

Conclusions: La integració del GVRE i la tDCS en la rehabilitació de la marxa per a la PD es mostra com una eina prometedora per millorar la implicació, tot i que els efectes

sobre els resultats motors objectius romanen incerts. Futurs estudis haurien de completar l'RCT amb una mostra més àmplia i diversa, i personalitzar encara més els continguts gamificats segons les característiques i experiències de les persones amb MP. Les intervencions han de buscar un equilibri entre càrrega cognitiva, desafiament físic i suport motivacional per adaptar-se a les necessitats específiques d'aquesta població.

Paraules clau: Malaltia de Parkinson; Marxa; Rehabilitació; Realitat Virtual; Gamificació; tDCS.

Pelillistetyn virtuaalitodellisuusympäristön ja tDCS:n yhdistelmän teho juoksumattopohjaisessa kävelykuntoutuksessa Parkinsonin tautia sairastavilla

Tiivistelmä

Tavoitteet: Tämän väitöskirjatutkimuksen päätavoitteena oli arvioida pelillisen virtuaalitodellisuusympäristön (GVRE) ja transkraniaalisen tasavirta-stimulaation (tDCS) yhdistämisen vaikuttavuutta Parkinsonin tautia (PD) sairastavien henkilöiden juoksumatolla toteutettavassa kävelykuntoutuksessa. Tutkimukselle asetettiin seuraavat alatavoitteet: (1) koota ja analysoida olemassa oleva tutkimusnäyttö pelillisyydestä PD-potilaiden motorisen kuntoutuksen teknologioissa (artikkeli I), (2) suunnitella, kehittää ja arvioida GVRE-pohjaisen kävelykuntoutusinterventio soveltuvuutta GVRE-pohjaisen kävelykuntoutusinterventio soveltuvuutta ja hyväksyttävyyttä PD-potilaiden näkökulmasta (artikkeli II), (3) laatia satunnaistetun kontrolloidun tutkimuksen (RCT) tutkimusprotokolla yhdistetyn GVRE- ja tDCS-interventio vaikuttavuuden arvioimiseksi (artikkeli III), ja (4) arvioida RCT-tutkimuksen alustavia tuloksia kävelymuuttujien, kliinisten mittarien ja käyttäjäkokemusten osalta (artikkeli IV).

Menetelmät: Tavoitteiden 1 ja 2 saavuttamiseksi toteutettiin kirjallisuuskatsaus ja yhteiskehittämiseen perustuva soveltuvuustutkimus. Soveltuvuustutkimus toteutettiin yhteiskehittämisen menetelmin yhteistyössä PD-potilaiden ja terveydenhuollon ammattilaisten kanssa. Tavoitteiden 3 ja 4 osalta suunniteltiin ja toteutettiin monimenetelmällinen RCT-tutkimus, jossa osallistujat jaettiin satunnaisesti kolmeen ryhmään: (1) juoksumatto + GVRE + tDCS, (2) juoksumatto + GVRE, (3) pelkkä juoksumatto. Kvantitatiivinen aineisto koostui kävelyparametreista, toiminnanohjauksen arvioista ja kliinisistä mittareista, kun taas kvalitatiivinen aineisto keräsi tietoa osallistujien kokemuksista ja tyytyväisyydestä interventioon.

Tulokset: Pelillisyyden havaittiin edistävän motivaatiota, sitoutumista ja hoitoon sitoutumista PD-potilaiden kuntoutusteknologioissa. Soveltuvuustutkimuksen tulosten mukaan interventio oli toteuttamiskelpoinen ja osallistujien mielestä selkeä, turvallinen ja yksilöllisesti räätälöitävissä. RCT-tutkimuksen alustavat tulokset viittaavat siihen, että juoksumaton, GVRE:n ja tDCS:n yhdistelmällä ei saavuteta merkittävästi parempia kävelytuloksia verrattuna kontrolliryhmiin. GVRE- ja tDCS-ryhmissä osallistujat raportoivat kuitenkin subjektiivisia parannuksia askelpituuden hallinnassa, kävelyvarmuudessa sekä kognitiivisessa tietoisuudessa. Lisäksi joitakin kognitiivisia hyötyjä, kuten estokyvyn paranemista, ilmeni viiveellä, mikä voi viitata transkraniaalisen neuromodulaation viivästyneisiin vaikutusmekanismeihin. Osallistujat suhtautuivat interventioon pääosin myönteisesti ja sitoutuivat siihen hyvin, vaikka GVRE-ympäristön koettu miellyttävyys vaihteli yksilöiden välillä.

Johtopäätökset: GVRE:n ja tDCS:n yhdistäminen Parkinsonin taudin kävelykuntoutukseen näyttäytyy lupaavana lähestymistapana erityisesti osallistujien

sitoutumisen vahvistamisessa, vaikka vaikutukset objektiivisiin kävelyparametreihin jäävät edelleen epäselviksi. Jatkossa tutkimusten tulisi hyödyntää suurempia ja heterogeenisempiä otoksia sekä kehittää pelillisten sisältöjen yksilöllistämistä PD-potilaiden tarpeiden ja kokemusten mukaisesti. Interventioiden suunnittelussa olisi pyrittävä tasapainottamaan kognitiivinen kuormitus, fyysinen haastavuus ja motivaation tukeminen, jotta ne vastaisivat PD:n monimuotoisiin kuntoutustarpeisiin mahdollisimman tarkasti.

Avainsanat: Parkinsonin tauti; Kävely; Kuntoutus; Virtuaalitodellisuus; Pelillisuus; tDCS.

List of Scientific Articles

Article I: Gamification Integration in Technological Devices for Motor Rehabilitation in Parkinson's Disease: A Scoping Review

Article II: A gamified virtual environment intervention for gait rehabilitation in Parkinson's Disease: co-creation and feasibility study

Article III: A treadmill training program in a gamified virtual reality environment combined with transcranial direct current stimulation in Parkinson's Disease: Study protocol for a randomized controlled trial

Article IV: A treadmill training program in a gamified virtual reality environment combined with transcranial direct current stimulation in Parkinson's Disease: Preliminary results of a mixed methods randomized controlled trial

The original publications have been reproduced with the permission of the copyright holders.

Chapter 1. Parkinson's Disease: Clinical and Epidemiological Overview

1.1 Definition and Pathophysiology

Parkinson's disease (PD) is a progressive, neurodegenerative disorder that primarily affects the motor system, although non-motor manifestations are increasingly recognized as central to its clinical presentation. The disease is classically defined by the cardinal motor features of bradykinesia, resting tremor, rigidity, and postural instability, which result from the degeneration of dopaminergic neurons in the substantia nigra pars compacta and subsequent dopamine depletion in the nigrostriatal pathway (Kalia & Lang, 2015). However, PD is now understood to involve widespread multisystemic neuropathology, affecting multiple neurotransmitter systems and neural networks beyond the basal ganglia, with pathological changes beginning years before clinical diagnosis (Kouli et al., 2018).

The hallmark neuropathological feature of PD is the accumulation of misfolded α -synuclein, forming Lewy bodies and Lewy neurites, which contribute to cellular dysfunction and death (Poewe et al., 2017). The progressive propagation of α -synuclein pathology follows a characteristic pattern, as first proposed by Braak and colleagues (Braak et al., 2003), beginning in the dorsal motor nucleus of the vagus and the olfactory bulb, and ascending to cortical regions in later stages. This staging model has shaped the current understanding of PD's characteristic prodromal phase and non-motor symptoms, such as anosmia, sleep behavior disorders and constipation, which often precede the appearance of clear motor signs.

At a systemic level, the dysregulation of basal ganglia-thalamo-cortical circuits is under many of the motor manifestations of PD. Dopamine loss in the striatum leads to an imbalance in the direct and indirect pathways of the basal ganglia, producing increased inhibitory signals to the thalamus and reduced facilitation of motor cortex activity (Obeso et al., 2008). This imbalance disrupts automatic movement control, making voluntary movement initiation and scaling require more effort and become inefficient. This dysfunction becomes particularly evident in gait disturbances, which are often resistant to dopaminergic treatment and tend to worsen as the disease progresses (Mirelman et al., 2019).

In addition to the motor circuit pathology, non-dopaminergic systems are also affected, which contribute to a wide spectrum of non-motor symptoms, including cognitive impairment, mood disorders, sleep disturbances, and autonomic dysfunction. These symptoms substantially impact quality of life and may emerge independently of motor severity (Chaudhuri & Schapira, 2009; Müller et al., 2013).

Genetically, while most PD cases are idiopathic, approximately 10–15% are associated with identifiable genetic mutations (Blauwendraat et al., 2020). These genetic forms have facilitated advances in disease modeling and have contributed to the current understanding that PD is not a singular disease entity,

but a syndrome with heterogeneous pathological mechanisms, clinical trajectories, and therapeutic responses.

1.2. Epidemiology and demographic trends

PD is the fastest-growing neurological disorder globally, both in terms of prevalence and disability burden (Dorsey et al., 2018). Recent estimations point out that more than 8.5 million individuals were living with PD worldwide in 2019. This figure is projected to double by 2040 due to increasing life expectancy and population aging (Feigin et al., 2017; GBD 2019 Diseases and Injuries Collaborators, 2020). This expected rise is especially marked in low and middle-income countries, where diagnostic capacity, surveillance and specialized care infrastructures are still developing, potentially underestimating the current prevalence and burden PD represents.

The age-dependent nature of PD is a defining feature of its epidemiology. Incidence increases exponentially with age, particularly after 60 years, although 5–10% of cases are classified as young-onset PD, occurring before the age of 50 (Marras et al., 2019). The global incidence is estimated at 10–20 per 100,000 person per year, while the prevalence ranges between 100 and 300 per 100,000 people, with considerable regional variation depending on population structure and healthcare system reporting (Tysnes & Storstein, 2017).

Sex differences are also notable: men are approximately 1.5 times more likely to develop PD than women, although this ratio may vary by geography. In Spain, some estimates suggest a male-to-female incidence ratio exceeding 2:1 (Wooten et al., 2004). While the biological basis for this disparity is not completely understood, hypotheses include protective effects of estrogen, differences in dopaminergic neuron density, or exposure to environmental risk factors (Gillies et al., 2014). These sex-related epidemiological trends may influence response to treatment and progression of the disease, highlighting the importance of personalized approaches to rehabilitation.

From a geographic perspective, PD prevalence is historically higher in industrialized regions, especially in North America and Europe. However, rising rates are being reported in Asia and Latin America, reflecting demographic aging and improved diagnostic methods (Pringsheim et al., 2014). These shifts highlight the global nature of PD as an emerging public health challenge.

Beyond its prevalence, the burden PD poses is substantial. According to the Global Burden of Disease Study in 2019 (GBD 2019 Diseases and Injuries Collaborators, 2020), the number of years lost due to poor health, disability, or early death attributable to PD increased by over 80% between 2000 and 2019. This burden is not only a reflection of motor decline but also of non-motor symptoms, caregiver dependency and reduced participation in daily life, making it one of the leading causes of neurological disability worldwide.

People with PD experience a progression of functionality impairment that is strongly associated with mobility limitations, such as reduced gait speed, postural instability, and falls. These manifestations often emerge in the middle to late stages of the disease and are among the most disabling, leading to institutionalization and increased mortality risk (Bloem et al., 2020). They are also among the least responsive to pharmacological treatment, reinforcing the need for rehabilitative strategies that address motor decline in ecologically valid, sustainable ways (Nonnekes et al., 2016).

1.3. Disease progression and staging

PD is a clinically varied and chronic progressive neurodegenerative disorder, with an onset that is often subtle and an evolution that spans decades. Its progression implies not only the worsening of motor symptoms, but also the appearance and accumulation of non-motor disturbances that deeply shape the disease course and therapeutic needs (Kalia & Lang, 2015; Postuma et al., 2015). Understanding this progression is essential for contextualizing rehabilitation strategies, particularly those aimed at mitigating gait dysfunction, which often emerges as a key source of disability in later stages (Bloem et al., 2021).

1.3.1 Prodromal Phase

The prodromal phase refers to a preclinical period during which neurodegenerative changes are underway, but classic motor symptoms have not yet appeared. During this stage, individuals may present with REM sleep behavior disorder, constipation, hyposmia, depression, or autonomic dysfunction, all symptoms linked to early α -synuclein pathology (Heinzel et al., 2019). Longitudinal studies show that individuals with sleep behavior disorders have a particularly high risk of converting to these mentioned α -synuclein pathologies, often within 10 years (Postuma et al., 2019).

1.3.2 Early to Mid-Stage PD

The motor phase begins when the disease becomes clinically manifest, typically with asymmetric bradykinesia, often accompanied by resting tremor or rigidity. In early stages, patients usually respond well to dopaminergic therapy and retain independence in daily activities (Kalia & Lang, 2015; Postuma et al., 2015). However, gait alterations may already be detectable through subtle signs such as a reduced arm swing, stride length variability, or difficulties in turning, which may not yet be functionally limiting but represent an early disruption of automatic movement control (J. Hausdorff et al., 2003).

As the disease progresses into the mid-stage, motor symptoms become bilateral, and postural instability, lack of spontaneous movement and gait irregularities intensify. Functional impairments become more noticeable, and motor complications such as the onset of dyskinesia emerge as a secondary effect of chronic levodopa therapy. These complications often need an increased

medication dosing, incorporation of adjunctive therapies and adjustments to daily routines (Fox et al., 2018).

1.3.3 Advanced Stage

The advanced stage of PD is marked by profound and poorly levodopa-responsive motor symptoms, including freezing of gait (FoG), festinating gait, balance loss, and postural instability, which become leading causes of falls and institutionalization (Bloem et al., 2020). These symptoms are often resistant to both pharmacological and surgical treatments, making them a large therapeutic challenge (Nonnekes et al., 2016).

In parallel, non-motor complications such as cognitive decline, apathy, pain, fatigue, and orthostatic hypotension become dominant sources of morbidity (Chaudhuri & Schapira, 2009). This wide array of symptoms calls for a multidisciplinary approach, which often includes motor rehabilitation, neuropsychological support, and palliative care (Bloem et al., 2021).

Patients at this stage may also become resistant to the effects of pharmacological treatment in relation to certain functions, especially postural control and gait initiation. These domains are governed by non-dopaminergic circuits, including cholinergic and noradrenergic systems, and need for innovative therapeutic approaches, such as sensory cueing, assistive technology, and intensive physiotherapy (Nieuwboer et al., 2009a; Nonnekes et al., 2016).

1.3.4 Subtypes and Disease Variability

PD is increasingly viewed not as a single disease entity but as a syndrome comprising multiple disease subtypes. Among the most commonly characterized are:

- Tremor-dominant PD, often linked to slower progression and better prognosis.
- Postural instability and gait disorder phenotype, often known as PIGD, is associated with faster decline, cognitive impairment, and increased fall risk.
- Akinetic-rigid subtype, typically more resistant to treatment and associated with earlier development of axial symptoms.

PD subtype classification is clinically relevant, as it can help predict the course of gait decline and responsiveness to rehabilitative interventions. For example, individuals with early PIGD traits are often less responsive to dopaminergic therapy and may benefit more from early, intensive physiotherapy (Fereshtehnejad et al., 2017; Thenganatt & Jankovic, 2014).

1.3.5 Staging Systems

Several tools have been developed to describe the temporal progression and severity of PD:

The Hoehn and Yahr (H&Y) scale, introduced in 1967, remains the most widely used staging system for its simplicity. It classifies motor disability across five stages, from unilateral symptoms (Stage 1) to confinement to bed or wheelchair (Stage 5). Despite its limitations, especially its lack of sensitivity to non-motor symptoms, it remains useful in both clinical practice and trial stratification (Hoehn & Yahr, 1967).

The Unified Parkinson's Disease Rating Scale (UPDRS) and its updated version, the Movement Disorder Society–UPDRS (MDS-UPDRS) are the most comprehensive instruments for grading disease severity. The MDS-UPDRS consists of four parts: (I) non-motor experiences of daily living, (II) motor experiences of daily living, (III) motor examination, and (IV) motor complications (Goetz et al., 2008). It offers an exhaustive and multidimensional assessment of disease burden and is considered the gold standard for longitudinal tracking.

Recent emerging approaches increasingly advocate for data-driven evaluation systems that move beyond traditional clinical phenotypes, aiming to integrate biomarkers, neuroimaging, genetic profiles and digital health data to better capture the complexity and heterogeneity of PD. These models reflect a shift toward precision medicine, where the goal is not only to classify patients more accurately, but also to pair individual experience with specific interventions (Espay et al., 2017).

Within this context, ecologically valid, real-world metrics are gaining prominence. Wearable devices and sensor-based technologies allow for the continuous monitoring of gait, activity patterns, and motor fluctuations in patients' natural environments. In contrast with clinic-based evaluations, these tools capture fluctuations, compensatory behaviors and contextual performance, providing a more realistic and representative data on patient day-to-day function (Del Din et al., 2016; Lipsmeier et al., 2018). These insights are key to personalize therapy, monitor progression, and evaluate treatment response in a dynamic, patient-centered way.

1.4 Key symptomatology: motor and non-motor symptoms

The clinical expression of PD is traditionally focused on motor dysfunction, but the current landscape in research has now clearly established that non-motor symptoms form a fundamental part of the disease, often preceding motor signs and contributing significantly to disability and reduced quality of life, especially in later stages (Chaudhuri & Schapira, 2009) (Figure 1). The presence of specific motor and non-motor symptoms varies substantially between individuals and across disease stages, which contributes to the variety and heterogeneity between individuals (Titova et al., 2017).

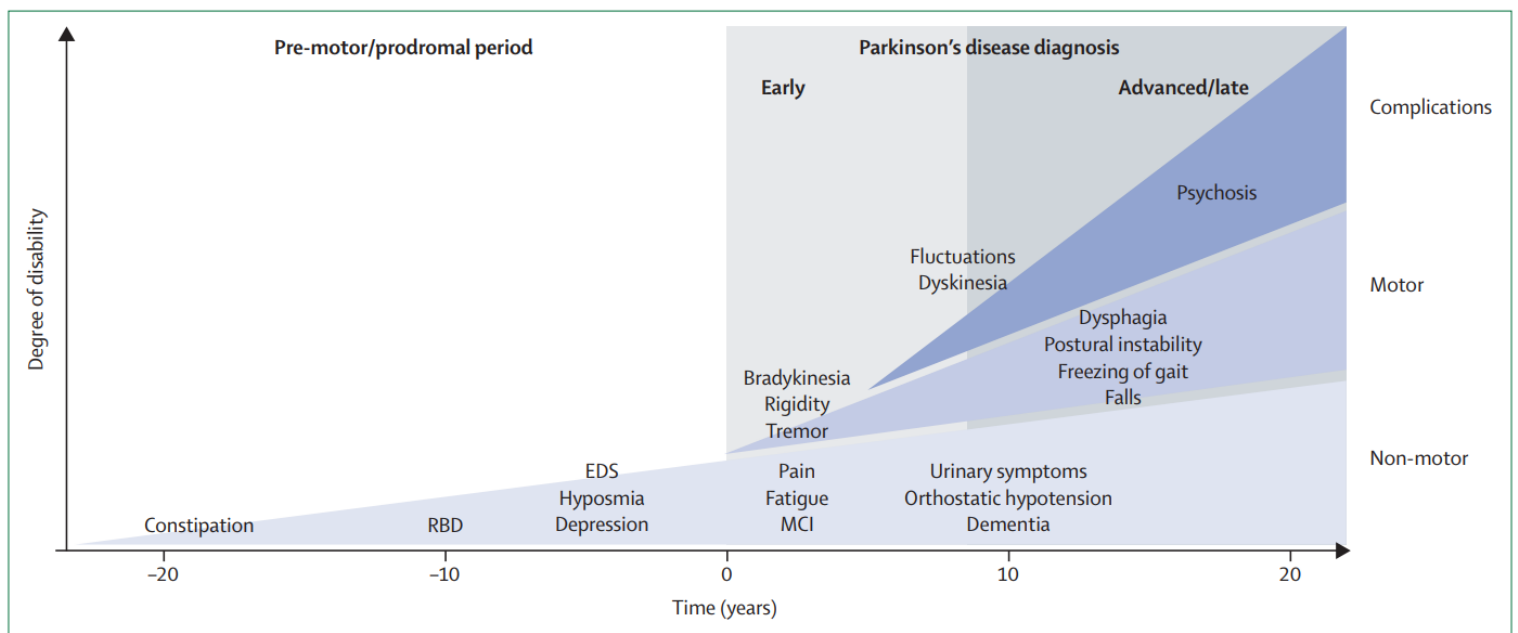


Figure 1. Clinical symptoms and progression of Parkinson's Disease. From Kalia & Lang (Kalia & Lang, 2015)

1.4.1 Motor Symptoms

There are four cardinal motor features of PD, which include bradykinesia, rigidity, resting tremor, and postural instability, with current diagnosis relying on the presence of bradykinesia and at least one of the others (Postuma et al., 2015). These signs reflect progressive degeneration of dopaminergic neurons within the nigrostriatal pathway, leading to dysfunction in basal ganglia circuits involved in voluntary motor control (Kalia & Lang, 2015).

- Bradykinesia is defined as slowness in the initiation and execution of movement and is considered the hallmark of PD. It typically manifests as reduced arm swing, facial hypomimia, diminished fine motor skills such as micrographia or issues with buttoning, and a general slowing of daily activities. Beyond simple slowness, bradykinesia often involves a decline of movement amplitude and speed in a progressive way during repetition (Berardelli et al., 2001).
- Rigidity refers to increased resistance to passive movement throughout the range of motion, independent of movement velocity. It can present uniformly or with a superimposed tremor component and often begins unilaterally before becoming more generalized. Clinically, rigidity may be subtle and revealed only during contralateral activation maneuvers, especially in early disease. Over time, it contributes to stiffness, reduced joint mobility, and loss of fluidity in movement, which affect functional activities such as rising from a chair or dressing (Kalia & Lang, 2015).
- Resting tremor, which often begins unilaterally, usually affects the distal limbs, consisting of a "pill-rolling" movement at a frequency of 4–6 Hz.

Parkinsonian tremor can also be present on the arms, legs, chin, lips and trunk, and can be substantially increased by stress or emotion. Although it is one of the most recognizable features, tremor is notably absent in approximately 20–30% of patients and may have less functional impact than other motor symptoms (Jankovic, 2008)

- Postural instability usually develops later in the disease course and is characterized by impaired balance and an increased risk of falls. It reflects dysfunction in postural reflexes and automatic anticipatory responses, and it is often resistant to dopaminergic therapy. Early postural instability is associated with more aggressive disease progression and is a defining feature of the PIGD phenotype (Bloem et al., 2001).

In addition to these core four cardinal features, patients frequently exhibit gait disturbances, hypophonia, dysphagia, and FoG, all of which reflect a broader impairment in motor automatisms and sensorimotor integration. These manifestations are especially relevant for rehabilitation strategies, including those based on external cueing and task-specific motor training (Jankovic, 2008; Kalia & Lang, 2015).

1.4.2 Non-Motor Symptoms

Non-motor symptoms are now recognized as core clinical features of PD, often more disabling than motor symptoms and contributing significantly to institutionalization, caregiver burden, and reduced quality of life (Chaudhuri et al., 2006). Key non-motor domains include:

- Neuropsychiatric symptoms: Depression, anxiety, apathy, and psychosis are common and often underdiagnosed. Cognitive impairment, which can range from mild cognitive impairment and executive dysfunction to dementia, affects a substantial proportion of patients, with estimates suggesting that up to 80% will develop dementia in the long term. Hallucinations and delusions may emerge in later stages, often exacerbated by dopaminergic medications (Aarsland et al., 2017).
- Autonomic dysfunction: Symptoms such as orthostatic hypotension, constipation, and sexual dysfunction are frequent and may be among the earliest indicators of PD pathology. Their presence reflects the involvement of the peripheral and central autonomic nervous system in the disease course (Chen et al., 2020).
- Sleep disturbances: These include REM sleep behavior disorders, insomnia, excessive daytime sleepiness, and fragmented sleep, with significant implications for cognitive and motor wellbeing (Iranzo et al., 2013).
- Sensory symptoms: Olfactory loss, known as hyposmia, is highly prevalent and often precedes motor symptoms by several years. Other symptoms

include pain, paresthesia, and altered thermal sensitivity (Leite Silva et al., 2023).

- Fatigue: A highly prevalent but poorly understood symptom, fatigue in PD is often independent of motor function or mood and is a major contributor to functional impairment (Kluger et al., 2016).

These non-motor domains are increasingly being integrated into clinical assessments, such as the MDS-UPDRS Part I. Their recognition has prompted a shift toward rehabilitation strategies that consider and target them in combination with the motor components (Goetz et al., 2008).

1.5 Impact on autonomy, quality of life, and healthcare systems

The progressive and multidimensional nature of PD leads to a progressive loss of functional autonomy, affecting basically every domain of daily living (Martinez-Martin et al., 2011). This loss is often gradual and implies major ramifications: it disrupts social roles, limits mobility and self-care, imposes psychological strain, and increases dependence on caregivers and institutional support. The burden is experienced not only at the individual level but is also reflected in societal and economic terms, through increased healthcare use, caregiver burnout, and rising long-term care costs (Bloem et al., 2021; Yang et al., 2020).

1.5.1 Loss of Autonomy and Functional Independence

Autonomy in PD is compromised early by motor deficits such as tremor and rigidity and later by postural instability, FoG and falls, which restrict free movement and reduce confidence in ambulation. These symptoms lead to activity limitations and often result in avoidance behavior, which can further accelerate loss of conditioning and social withdrawal (Ellis et al., 2013).

IADLs such as cooking, shopping, managing finances, or navigating public transport are often among the first domains affected. With disease progression, even basic ADLs like dressing, bathing, or feeding become impaired. Gait impairment and postural instability are among the strongest predictors of loss of independence, institutionalization, and caregiver burden (Martínez-Martín et al., 2014; Rosenthal et al., 2010)

Cognitive decline further undermines functional capacity by compromising executive function, attention, and visuospatial abilities, which are functions essential for safe mobility and dual tasking (Aarsland et al., 2017). These cognitive-motor interactions are especially relevant when considering the design of rehabilitation technologies that attempt to balance motor and cognitive components.

1.5.2 Impact on Quality of Life

PD imposes a substantial and multidimensional burden on health-related quality of life (HRQoL). Studies consistently show that both motor and non-motor symptoms are independently associated with lower HRQoL scores, with non-motor symptoms, particularly depression, fatigue, and sleep disturbances appearing as key contributors (Carod-Artal et al., 2007).

Loss of mobility and fear of falling often lead to reduced social participation, isolation and a progressive loss of identity and self-efficacy. These experiences are particularly relevant in individuals with more severe gait impairments or frequent falls, who report higher levels of anxiety, embarrassment, and avoidance of public spaces (Ellis et al., 2013). These psychological aspects may exacerbate disengagement from physical activity, creating a self-perpetuating cycle of immobility and disability.

1.5.3 Burden on Healthcare Systems and Society

The societal and economic impact of PD is significant and projected to increase with global aging. In Europe, the annual direct and indirect costs of PD are estimated at €13.9 billion, including expenses related to pharmacological treatment, hospitalizations, assistive devices, outpatient services, and informal caregiving (Olesen et al., 2012).

Falls and fall-related injuries, particularly fractures, represent one of the most expensive and preventable reasons for healthcare use in PD, often leading to emergency admissions, surgery, and prolonged rehabilitation or nursing home stays (Hely et al., 2005). Similarly, cognitive decline and dementia can lead to earlier institutionalization, adding long-term care costs to an already overloaded system.

The burden is also increased by the informal care provided by family members, which often goes underrecognized in health policy but accounts for a substantial portion of total costs. Caregiver strain has been associated with higher rates of depression, anxiety, and social isolation among carers themselves (Martinez-Martin et al., 2011).

Efforts to optimize motor function and gait, reduce fall risk, and maintain engagement through strategic approaches are therefore not only clinically justified but also economically relevant. Technologies that enhance adherence and efficacy of rehabilitation have the potential to reduce pressure on both formal and informal care systems.

1.6 Conventional treatment for Parkinson's Disease

Conventional treatment of PD has long centered on pharmacological, and, in few selected cases, surgical approaches aimed at alleviating motor symptoms through dopaminergic regulation. While these treatments offer meaningful

symptomatic relief, particularly in the early stages, their long-term effectiveness is often compromised by disease progression, motor complications, and limited efficacy on non-motor symptoms and axial impairments (Poewe & Mahlkecht, 2020).

Pharmacotherapy remains the main course for PD management, with levodopa, a dopamine precursor capable of crossing the blood-brain barrier, being the most effective and widely used agent. When administered in combination with a dopa-decarboxylase inhibitor such as carbidopa or benserazide, levodopa enhances central bioavailability while minimizing peripheral side effects (Poewe et al., 2017). Despite its proven efficacy, chronic use frequently leads to secondary effects like motor fluctuations and dyskinesias, particularly in younger patients or with high cumulative doses (Olanow et al., 2001).

Dopamine agonists, such as pramipexole and ropinirole, directly stimulate dopamine receptors and are often used in early disease or as adjuncts to levodopa. Although they delay the presence of motor complications, they are associated with a higher incidence of neuropsychiatric side effects, including impulse control disorders (Weintraub et al., 2010). Other pharmacological classes include monoamine oxidase B inhibitors (e.g., selegiline, rasagiline), which reduce dopamine breakdown, and catechol-O-methyltransferase inhibitors, which extend levodopa's half-life (Poewe & Mahlkecht, 2020).

For patients with advanced disease and refractory motor complications, deep brain stimulation (DBS) represents a surgical alternative. DBS involves the precise implantation of electrodes into subcortical targets, most commonly the subthalamic nucleus or internal globus pallidus, to deliver continuous high-frequency stimulation that modulates pathological neural activity (Hariz & Blomstedt, 2022). This intervention reliably leads to significant improvements in cardinal motor symptoms and substantially reduces dopaminergic medication requirements (Hariz & Blomstedt, 2022). However, it is not suitable for all patients and may have limited or even adverse impacts on gait, balance, and cognitive domains, which are areas increasingly recognized as major contributors to disability in PD (Bloem et al., 2021).

Importantly, neither pharmacological nor surgical treatments substantially modify the underlying disease course or adequately address non-dopaminergic symptoms such as cognitive decline, autonomic dysfunction, or axial motor features like FoG and balance loss (Chaudhuri et al., 2006). These limitations highlight the need for integrative and multidisciplinary strategies that extend beyond symptomatic control to support functional autonomy and quality of life across disease stages.

As such, there has been a growing shift toward incorporating rehabilitation interventions earlier in the care continuum as an approach that recognizes the complementary role of physiotherapy, cognitive training, and assistive

technologies in optimizing outcomes and promoting sustained engagement with meaningful activities (Keus et al., 2009).

Chapter 2. Gait and Postural Control in Parkinson's Disease

2.1 Neurophysiology of Gait in Healthy Adults

Gait is often taken for granted as a basic and routinary activity. However, in reality walking is a highly coordinated process that depends on the interaction of multiple brain and body systems. These include motor and sensory areas, as well as parts of the brain responsible for balance, timing, and adaptation to the environment. In healthy adults, gait is typically automatic: it requires little conscious effort, which allows individuals to walk and talk or pay attention to their surroundings at the same time (Takakusaki, 2017).

The brain areas most involved in gait include the motor cortex, which helps initiate movement, and areas like the basal ganglia and cerebellum, which help regulate the rhythm, timing, and smoothness of walking. These regions communicate with the brainstem and spinal cord, where specialized circuits can generate the basic stepping rhythm even without constant control from the brain (Grillner & El Manira, 2020).

Walking also depends heavily on sensory feedback. Vision, touch, proprioception and the vestibular system all provide real-time information that allows for the adjustment of steps, avoidance of obstacles, and upright posture (Takakusaki, 2017).

Finally, while much of walking happens automatically, the brain can shift into more active control when needed, such as when climbing stairs, walking in crowded spaces, or managing simultaneous tasks. This ability to switch between automatic and conscious control is a key feature of healthy gait, and one that is often lost or disrupted in PD (Maillet et al., 2012; Wu et al., 2015).

2.2 Neural Mechanisms of Gait Dysfunction in Parkinson's Disease

Gait dysfunction in PD reflects the progressive breakdown of the neural systems that, as previously mentioned, normally support automatic, adaptive locomotion. Unlike healthy gait, which is largely regulated at a subcortical level and requires minimal conscious control, gait in PD becomes slower, more variable, less rhythmic, and increasingly dependent on cognitive resources. These changes are not solely attributable to dopaminergic loss but result from general disruption across motor, sensory, and cognitive systems (Wu et al., 2015).

2.2.1 Basal Ganglia Dysfunction and Loss of Automaticity

The basal ganglia, and particularly the striatum, play a critical role in initiating and modulating automatic and habitual motor programs. In PD, degeneration of dopaminergic neurons in the substantia nigra leads to a substantial reduction in striatal dopamine, particularly in the posterior putamen, which is heavily involved in sensorimotor control (Obeso et al., 2008). This dopaminergic deficit disrupts the balance between the facilitatory and inhibitory pathways of the basal ganglia,

resulting in excessive inhibition of the thalamocortical motor loop. The consequence is bradykinesia, reduced amplitude of movement and impaired initiation, all features that heavily affect gait dynamics, especially in the preparatory and transitional phases of walking.

Moreover, this dysfunction affects the automaticity of gait, forcing individuals to rely on cortical resources for step planning and execution. This shift leads to cognitive-motor interference, where concurrent task conditions heavily degrade performance and increase fall risk (Yogev-Seligmann et al., 2008).

2.2.2 Impaired Internal Cueing and Movement Scaling

Another characteristic part of PD gait dysfunction is the loss of internal cueing mechanisms. In healthy individuals, the basal ganglia assist in the generation of internal timing cues that direct the rhythm and sequencing of repetitive motor acts, such as stepping. In PD, the failure of this internal metronome leads to gait hypokinesia, reduced stride length, and rhythm irregularities (J. Hausdorff et al., 2003). This explains why external cueing, either being auditory (metronomes), visual (floor markers), or tactile (vibration) can temporarily restore gait parameters. Such cues effectively skip those defective basal ganglia circuits by engaging alternative cortical and cerebellar pathways, a strategy that has been used in cue-based rehabilitation interventions.

2.2.3 Cortical Compensation and Attentional Overload

As PD progresses and the basal ganglia become less efficient, people with PD increasingly depend on conscious effort and executive control to manage walking. Instead of relying on automatic systems, intentional active thought is needed about how to move, especially in challenging situations. Brain imaging studies have shown that during walking, individuals with PD use brain areas like the prefrontal cortex, supplementary motor area, and premotor cortex more than healthy individuals, particularly when performing simultaneous tasks or navigating complex environments (Maillet et al., 2012).

While this mental compensation can help maintain mobility early on, it also increases the cognitive load. Since attention is limited, performing two tasks at once can easily overwhelm the system, which often reveals early walking problems and predicts future fall risk (Yogev-Seligmann et al., 2008).

On top of that, factors like fatigue, anxiety, and memory or thinking difficulties can make things worse, leading to more unstable walking, FoG episodes, and fear of falling, especially in unfamiliar or stressful situations (Rochester et al., 2014).

2.3 PD-Specific Gait Alterations

Gait alterations in PD are among the most distinctive and disabling motor features of the disease. They reflect the progressive breakdown of automatic motor control, disrupted internal cueing, and increasing cognitive load associated with

locomotion. These abnormalities emerge subtly in early stages and intensify over time, often becoming poorly responsive to pharmacological treatment. Their presence significantly predicts fall risk, loss of independence, and reduced quality of life, making them a critical focus for both assessment and intervention (J. M. Hausdorff et al., 2003).

2.3.1 Freezing of Gait

FoG is defined as a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk. Patients commonly describe it as feeling as if their feet are "glued to the floor." FoG typically occurs during gait initiation, turning, navigating narrow spaces, or under time pressure, particularly in complex or emotionally charged situations (Nieuwboer & Giladi, 2013).

FoG is seen in up to 50% of people with advanced PD and in a significantly lower number of early-stage patients, frequently those with the PIGD phenotype. It is usually exacerbated by performing multiple tasks concurrently, stress, or fatigue, and is often unpredictable, making it both distressing and dangerous. Importantly, FoG is frequently poorly responsive to levodopa, and in some cases, may even worsen with dopaminergic therapy (Nutt et al., 2011; Pozzi et al., 2019).

Clinically, FoG episodes can last from a few seconds to over a minute and may lead to falls, loss of confidence, and activity avoidance. Several phenotypes have been described, including trembling in place, complete akinesia, and shuffling with small steps (Nutt et al., 2011).

2.3.2 Festination and Shuffling Gait

Festination refers to a progressive increase in gait cadence coupled with a decrease in step length, foot drag and diminished toe clearance, often resulting in forward-leaning posture and the appearance of uncontrolled, rapid stepping (Morris et al., 2001). It can be seen as a compensatory response to postural instability, and it frequently precedes or accompanies FoG episodes. This shuffling gait pattern is one of the earliest and most common gait signs in PD. It contributes to stability loss, reduced walking efficiency, and increased fall risk, particularly in unfamiliar or packed environments (Bloem et al., 2004).

The underlying mechanism reflects slow movement scaling and impaired feedforward control, both of which reduce the ability to regulate momentum and make corrective postural adjustments during walking (Morris et al., 2001).

2.3.3 Gait Variability and Asymmetry

Even before gait disturbances become clinically apparent, patients with PD often exhibit increased stride-to-stride variability, which is a key biomarker of loss of automaticity and motor control. This irregularity in step timing and length is exacerbated by walking and performing concurrent tasks and correlates with executive dysfunction and fall history (J. M. Hausdorff et al., 2003).

Asymmetry is another early hallmark, often manifesting as reduced arm swing or unilateral stride shortening. As the disease progresses, this asymmetry tends to worsen, particularly in patients with more lateralized motor symptoms (Plotnik et al., 2007).

2.3.4 Dual task Gait Impairment

Healthy individuals walk with minimal cognitive effort, but in PD, gait becomes increasingly attentionally demanding. Adding a secondary task, either cognitive or motor, often leads to marked gait deterioration. This concept of gait in concurrence with a simultaneous task, which could be represented as walking while talking, carrying a cup of coffee or dodging people in a crowd, is commonly known as Dual Task (DT). In PD, DT is often correlated with reduced speed, increased variability, shorter steps, and even FoG episodes (Yogev-Seligmann et al., 2008).

This phenomenon reflects both cognitive-motor interference and the breakdown of automaticity, and it has direct, severe implications for real-world safety. Gait performance in DT conditions is now considered a sensitive marker of functional decline and a valuable target for cue-based or cognitive-motor rehabilitation interventions (Yogev-Seligmann et al., 2008).

2.4 Postural Control Impairments and Balance Dysfunction

Postural instability is one of the most disabling features of PD and a leading cause of falls, injuries, and loss of independence. Unlike bradykinesia and tremor, postural control deficits tend to appear later in the progression of the disease, are often poorly responsive to dopaminergic therapy, and progress despite pharmacological or surgical treatment (Bloem et al., 2001; Nonnekes et al., 2016).

2.4.1 Impaired Anticipatory and Reactive Postural Responses

People with PD demonstrate a marked reduction in anticipatory postural adjustments, especially when initiating movement. For example, prior to stepping forward, healthy individuals generate a brief shift of body weight toward the stance leg; in PD, this shift is diminished or delayed, leading to start hesitation or FoG (Hu et al., 2024).

Similarly, reactive postural responses to perturbations, such as sudden pushes or balance challenges, are often slow, small in amplitude, and poorly scaled. Instead of making an appropriate corrective step, patients may take multiple small steps, lose balance, or fall (Schoneburg et al., 2013). The result is an individual that is less able to anticipate movement demands and less responsive to real-time threats to balance.

2.4.2 Rigidity and Postural Reflex Impairment

PD is, as previously stated, characterized by rigidity, which implies an increased tone in the neck, trunk, and proximal musculature that reduces flexibility and postural adaptability. This rigidity interferes with trunk rotation, arm swing, and counterbalancing mechanisms, all of which are critical for dynamic stability during gait, particularly while turning or changing direction (Horak et al., 2005). In addition, postural reflexes are profoundly impaired. Clinical tests such as the pull test in MDS-UPDS, where a patient is pulled backward to assess compensatory stepping, are often used to reveal delayed or absent responses, particularly in advanced PD (Goetz et al., 2008).

2.4.3 Balance Impairment Under Dual Task Conditions

A growing body of research shows that alterations to executive function and attentional deficits exacerbate postural instability in PD. Under DT conditions, individuals with PD exhibit greater sway, delayed responses, and increased fall risk (Rochester et al., 2014). This has severe implications, since individuals with PD must concentrate more intensely on maintaining posture, but their limited cognitive resources are quickly overwhelmed by DT situations, emotional stress, or environmental demands. This creates a narrow window for safe and adaptable movement.

2.5 Clinical Consequences of Gait and Balance Dysfunction

Gait and postural impairments evolve progressively and often become poorly responsive to pharmacological therapy, especially in advanced stages. Their presence is a strong predictor of adverse outcomes, including falls, loss of independence, and institutionalization (Bloem et al., 2004; Nonnekes et al., 2016).

2.5.1 Falls and Fall-Related Injuries

Falls are among the most common and serious complications of PD, with studies estimating that over 60% of patients fall annually, and about two-thirds of these fall recurrently (Pickering et al., 2007). Falls in PD are typically multifactorial, involving postural instability, FoG, impaired turning, and cognitive-motor interference, particularly under DT conditions (Bloem et al., 2001).

The consequences of falls are substantial. Physical injuries such as hip fractures, head trauma, and soft tissue damage are frequent. Moreover, the fear of falling, even in the absence of injury, often leads to activity restriction, deconditioning, and social withdrawal, ultimately entering a repeating cycle of immobility and increased (M. K. Y. Mak & Pang, 2009). Falls are also a leading cause of hospitalization and nursing home placement in PD populations (Fasano et al., 2017). Importantly, fall risk is influenced not only by motor severity but also by cognitive decline, medication timing, and environmental demands, reinforcing the need for multidimensional prevention strategies (Rochester et al., 2014).

2.5.2 Loss of Functional Independence

Gait and balance disturbances lead to progressive dependence on ADLs and IADLs. Difficulties often emerge in going upstairs, turning in tight spaces, initiating gait, and navigating complex environments (Foster et al., 2014). This decline in mobility significantly reduces functional autonomy and forces adaptations such as the use of assistive devices, home modifications, or caregiver support (Martínez-Martín et al., 2014).

Such transitions can carry substantial psychological impact, including loss of self-efficacy, identity disruption, and depression (M. K. Y. Mak & Pang, 2009). Reduced mobility often limits participation in meaningful roles, contributing to broader declines in social engagement and life satisfaction (Foster et al., 2014).

2.5.3 Psychosocial and Cognitive Impact

The psychosocial burden of gait and balance dysfunction is significant. Patients with PD often experience embarrassment or stigma due to visible gait abnormalities, particularly FoG, festination, or falls in public spaces. This frequently results in avoidance of social situations, isolation, and reduced quality of life (M. K. Y. Mak & Pang, 2009). From a cognitive perspective, gait in PD becomes increasingly attentionally demanding. The degradation of automaticity requires compensatory cortical engagement, especially in the prefrontal and supplementary motor areas (Rochester et al., 2014). In individuals with executive dysfunction, this attentional overload leads to DT failure, contributing to FoG, shuffling gait and instability (Yogev-Seligmann et al., 2008).

Chapter 3. Rehabilitation Approaches in Parkinson's Disease

3.1 Conventional Physiotherapy and Motor Training

Physiotherapy has been established as a key part of supportive care in PD, aiming to maintain mobility, optimize physical function, reduce fall risk, and preserve independence across disease stages. While it does not modify the underlying neurodegenerative process, conventional physiotherapy plays a central role in symptom management, particularly in addressing gait, balance, posture, and functional mobility (Tomlinson et al., 2012).

3.1.1 Clinical Benefits and Evidence Base

Evidence from multiple systematic reviews and meta-analyses supports the efficacy of conventional physiotherapy in improving motor symptoms and functional outcomes in PD. For example, a systematic review and meta-analysis by Tomlinson et al. (Tomlinson et al., 2012) analyzing 39 randomized controlled trials found significant benefits of physiotherapy in gait speed, balance, and functional mobility when compared to no intervention.

Regular physiotherapy has also been shown to reduce fall frequency, enhance postural control and improve ADLs. Benefits are typically greatest when therapy is intensive, task-specific, and sustained over time (Allen et al., 2011).

There is also evidence that structured exercise can enhance neuroplasticity and support the maintenance of functional networks involved in movement control, particularly when initiated in earlier stages of disease (Keus et al., 2009; Petzinger et al., 2013). These insights have led to increased interest in using physiotherapy not just for symptom relief but as a potential disease-modifying addition.

3.1.3 Implementation in Clinical Practice

Despite its growing evidence base, the implementation of physiotherapy in real-world clinical practice remains variable. Access to specialized physiotherapists is often limited by geographic barriers, cost, or lack of referral pathways, especially in resource-limited settings. Moreover, while physiotherapy is often prescribed in response to a fall or functional decline, early and preventive engagement remains the exception rather than the norm (Keus et al., 2009).

International guidelines recommend that physiotherapy be initiated early in the disease course and tailored to evolving clinical needs. However, long-term adherence is frequently poor, particularly in unsupervised home programs, highlighting the importance of motivation, supervision, and patient engagement strategies.

3.2 Evidence for Task-Specific Training and Cueing Strategies

Due to the growing understanding of motor control and plasticity in PD approaches to physiotherapy interventions have evolved. Increasingly, evidence supports the use of task-specific training paradigms and external cueing strategies to target core deficits in gait and postural control (Nieuwboer et al., 2009b). These approaches go beyond general conditioning, highlighting the training of functional motor behaviors through repetitive, context-relevant practice, and the strategic use of external stimuli to compensate for impaired internal cueing mechanisms (Khobkhun et al., 2020).

3.2.1 Task-Specific Training

Task-specific training involves repetitive practice of goal-directed functional movements, such as walking, turning, or navigating obstacles. It is based on principles of motor learning, including contextual relevance, repetition, specificity, and feedback-driven adaptation (Kwakkel et al., 2007). In PD, where automatic motor gestures are compromised due to basal ganglia dysfunction, Task-specific training reinforces movement patterns via cortical and cerebellar pathways, offering a viable route for behavioral compensation (Nieuwboer et al., 2009c).

Randomized controlled trials have shown that task-specific training leads to improvements in:

- Gait speed and stride length
- Turning performance and dynamic balance
- Confidence in mobility and fear of falling

Previous research demonstrated that gait training focused on increasing step length significantly improved walking speed in individuals with PD (Morris et al., 2010). Similarly, interventions involving DT gait training, which simulate real-world cognitive-motor demands, have been shown to enhance gait stability and reduce fall risk (Strouwen et al., 2016).

Task-specific approaches are particularly valuable because they match ecological demands, targeting the very challenges patients face in daily life. However, they often require specialized supervision due to safety concerns, repetitive delivery and lack of motivation, which can be barriers to sustained treatment (Rochester et al., 2007).

3.2.2 External Cueing Strategies

A defining feature of PD is the impaired ability to generate internal cues for movement initiation and sequencing, manifested in situations like FoG, reduced stride length, and bradykinesia. External cues can bypass the affected basal ganglia circuits, activating alternative neural pathways and restoring motor output, particularly during gait (Nieuwboer et al., 2009a).

Cueing strategies are commonly categorized into auditory, visual, and tactile modalities, each targeting specific aspects of gait dysfunction in PD. Auditory cues, such as metronomes, rhythmic music or verbal prompts, have been shown to normalize cadence, increase stride length, and reduce gait variability. These effects are thought to arise from mechanisms that synchronize motor output with external rhythmic inputs, engaging both cerebellar and cortical networks (Thaut et al., 1996). Visual cues, including transverse floor markings or projected laser lines act as spatial indicators that help adjust steps and overcome freezing episodes by engaging visual and motor planning circuits (Azulay et al., 1999). Tactile cues, such as vibratory pulses delivered through wearable devices, represent a promising and less explored domain. Nowadays often referred to as haptic feedback, these cues may assist in modulating gait initiation and rhythmicity, offering a practical advantage for remote or home-based application (Ginis et al., 2017). A review of cueing therapies concluded that external cues improve gait parameters across multiple studies, with auditory cues yielding the most consistent results for gait speed, though individual responsiveness varies (Rocha et al., 2014)

3.2.3 Treadmill as a Cue-Based Training Strategy

Cueing strategies and task-specific training are often synergistic: practicing functional movements in the presence of structured external stimuli reinforces sensorimotor integration and may promote long-term plasticity (Petzinger et al., 2013). These principles are relevant for many emerging rehabilitation technologies, wearable cueing systems and immersive interventions, which varied feedback in immersive and motivating formats. In this context, treadmill training represents a well-established, relevant and effective platform for delivering cue-based gait interventions. By providing a repetitive, controlled, and rhythmic environment, treadmill walking inherently offers external pacing that may help restore temporal and spatial gait parameters, particularly speed and stride length (Mehrholz et al., 2009, 2017). This mechanical regularity can act as a built-in cue, facilitating a more automatic gait and reducing variability.

3.3 Limitations of Conventional Rehabilitation

Despite the growing body of evidence supporting physiotherapy and multidisciplinary care in PD, several limitations hinder the widespread effectiveness, accessibility, and sustainability of conventional rehabilitation. These barriers include the clinical, systemic, and patient-related domains and are particularly relevant when considering the long-term needs of individuals living with a degenerative, chronic condition like PD.

3.4.1 Limited Access to Specialized Rehabilitation

One of the most present barriers is limited access to trained rehabilitation professionals, particularly physiotherapists and occupational therapists with PD-specific expertise (Tomlinson et al., 2012). Access often varies by geographic

region, health system structure, and insurance coverage. In many regions, especially outside urban centers, patients are either referred late in the disease course or not at all (M. K. Mak et al., 2017).

Even when services are available, the frequency and duration of sessions are frequently insufficient to induce meaningful neuroplastic change. Many patients receive sporadic, short-term interventions, often reactive to functional deterioration rather than proactively designed for disease progression (Petzinger et al., 2013).

3.4.2 Adherence and Motivation Challenges

Adherence to rehabilitation programs, especially home-based or unsupervised, tends to be low in PD, particularly as disease progresses. Factors contributing to poor adherence include:

- Lack of immediate feedback or reinforcement
- Fatigue, apathy, or depression (which as mentioned, is a prevalent non-motor symptom in PD)
- Cognitive impairment, which affects task retention and goal orientation
- Low self-efficacy and fear of falling, leading to avoidance behavior

These challenges are compounded when interventions are monotonous or perceived as irrelevant to daily life, highlighting the need for programs that are engaging, rewarding, and personalized to functional goals (Ellis & Rochester, 2018; Foster et al., 2014; M. K. Mak et al., 2017).

3.4.3 Insufficient Intensity and Dose

Rehabilitation in PD is often limited not so much by session frequency alone, but by fragmented delivery and insufficient long-term treatment. While some studies suggest that more intensive training can amplify neuroplasticity and functional gains, these protocols are rarely feasible in routine care. Instead, many patients receive therapy in short, reactive bursts, with little sustained follow-up or structured progression (Keus et al., 2009).

The result is often a therapeutic dose that fails to match the chronic and evolving nature of PD. Home-based programs, though widely prescribed, tend to suffer from low adherence and lack of customization, especially when not actively supported (Foster et al., 2014; Keus et al., 2009). In this context, dose should be understood not only in terms of frequency or volume, but also through its capacity to deliver meaningful, task-specific and sustained sessions.

Moderately dosed interventions, particularly those that are engaging, accessible, and embedded in everyday function, may offer comparable or superior outcomes, especially in real-world settings (Nieuwboer et al., 2009a). The challenge is not only to increase exercise dosing, but to deliver interventions that prioritize long-

term engagement, adaptability, and relevance to the individual's goals and context.

Chapter 4. The use of Technology in Healthcare and Rehabilitation

4.1 Technologies in Healthcare

4.1.1 Early Steps of Virtual Reality in Healthcare

The term "virtual reality" (VR) gained popularity in the 1980s, largely due to the work of Jaron Lanier, founder of VPL Research. Previous immersive iterations, such as Heilig's Sensorama, had been created as immersive tools for multisensory experiences (Heilig, 1961), but Lanier's work formalized the concept of VR as an interactive digital space. His team at VPL developed some of the first commercial VR devices, including data gloves and head-mounted displays (Lanier & Biocca, 1992). During this period, VR captured public attention and began to be explored beyond entertainment, most notably in military and medical domains.

In the 1990s and 2000s, researchers and clinicians started investigating the potential of VR for therapeutic purposes. Initial applications included the use of VR exposure therapy for treating phobias and post-traumatic stress disorder for Vietnam war veterans (Rothbaum et al., 2001). These early medical applications established the foundations of VR's potential uses as a safe and controlled environment for a wide array of interventions.

4.1.2 Use of Virtual Reality and Exergames in 2000s and early 2010s

While the first steps of VR date back to the mid-20th century, the integration of immersive and interactive technologies into healthcare did not gain mainstream momentum until the early 21st century. This shift was largely driven by the rise of consumer-accessible motion-sensing platforms such as the Nintendo Wii and Microsoft Kinect (Rizzo et al., 2011). These systems introduced a new genre of interactive digital applications known as exergames: games that combine exercise with game-based mechanics to promote physical activity and engagement (Calcaterra et al., 2023).

Originally developed for entertainment, the Wii (released in 2006) and Kinect (launched in 2010) quickly gained attention from researchers and clinicians for their potential to support rehabilitation. The motion-sensing capabilities of these platforms allowed users to perform whole-body movements, making them particularly suitable for motor training and balance exercises in both clinical and home settings. Their affordability, ease of use and availability facilitated their adoption even more in rehabilitation programs for stroke survivors, older adults, and individuals with neurological conditions such as PD (Barry et al., 2014).

Exergames offered a novel solution to longstanding issues in rehabilitation, such as the challenge of maintaining patient motivation and adherence over extended therapy periods. By combining therapeutic movements and engaging gameplay patterns, these systems promoted participation and provided immediate feedback on performance. Studies have shown that exergaming can improve balance, coordination, and even cognitive function, suggesting a promising

bridge between traditional physiotherapy and emerging digital interventions (Goble et al., 2014).

Although not fully immersive in the sense of contemporary VR systems, the Wii and Kinect platforms introduced the foundational concept of technology in rehabilitation via an interactive, sensor-based experience, leading the way for the more immersive and clinically tailored VR solutions that would follow.

4.2 The Role of Virtual Reality in Healthcare and Parkinson's Disease

4.2.1 Current position of Virtual Reality in Healthcare

Nowadays, VR is broadly defined as a computer-generated simulation of a three-dimensional environment that can be interacted with by a person using special electronic equipment, such as a helmet with a screen inside (nowadays known as headset) or gloves fitted with sensors (Milgram & Kishino, 1994). VR systems vary in their level of immersion, ranging from non-immersive, screen-based simulations to fully immersive head-mounted displays.

In neurorehabilitation, VR is becoming increasingly recognized as a valuable tool with which to provide a safe and replicable environment for specialized training. Its ability to provide repetitive, task-oriented, and feedback-enriched environments aligns well with the principles of motor learning and neuroplasticity (Laver et al., 2017). Clinicians have adopted VR to support rehabilitation goals in a wide variety of patients, such as those recovering from stroke, traumatic brain injury, and other neurological conditions.

As the prevalence of PD continues to rise globally, so does the demand for scalable, personalized, and cognitively engaging rehabilitation options. In this context, VR is particularly well-suited to meet these evolving clinical needs. (Petzinger et al., 2013).

4.2.2 Integration of Virtual Reality in Treadmill Training

Gait training, particularly, is well posed to greatly benefit from VR integration. Treadmill training, long regarded as a staple intervention for PD due to its well-documented effects on gait speed, stride length, and postural stability (Mehrholz et al., 2015), often falls short in addressing critical cognitive dimensions of walking. People with PD frequently experience impairments in executive function and attention, factors that can compromise DT gait and increase fall risk (Kelly et al., 2012). Additionally, conventional treadmill programs often struggle to maintain patient motivation and long-term adherence.

One of the earliest studies to combine VR with treadmill training for PD patients was conducted by Mirelman et al. in 2011 (Mirelman et al., 2011). This study demonstrated that treadmill training augmented with VR was feasible and could

enhance gait performance under complex conditions, such as DT walking and obstacle negotiation, while also improving certain cognitive functions. Subsequent research, such as the V-TIME trials (Mirelman et al., 2016), explored the effects of treadmill training combined with VR on fall risk and cognitive performance of older adults, including people with PD.



Figure 2. Treadmill + Virtual Reality training set-up. From Mirelman et al. (Mirelman et al., 2016)- V-TIME project

When combined with immersive VR, treadmill-based rehabilitation can overcome many of these limitations. VR environments can simulate real-world walking challenges, such as navigating through crowded spaces, avoiding obstacles, or responding to unexpected distractors, thereby promoting the integration of cognitive and motor skills in a safe, adaptable setting (Dockx et al., 2016). These ecologically valid scenarios are not only functionally relevant but also inherently entertaining, providing a more enjoyable and sustainable therapeutic experience (Kwon et al., 2023).

4.2.3 Strengths and Weaknesses

Technology-based interventions in PD rehabilitation, such as motion-sensor-enhanced treadmills, robotic gait devices, and mobile health applications enable clinicians to tailor task difficulty and repetition, monitor progress with objective metrics, and deliver multisensory cues designed to enhance neuroplasticity (Mehrholtz et al., 2017). Moreover, such tools offer the potential to extend therapeutic reach beyond the clinic, addressing critical issues of accessibility, safety and continuity of care in a growing, aging population.

Despite these advantages, several challenges remain. Many technological interventions in PD still lack standardization in their design and evaluation frameworks. Without rigorous clinical validation, their long-term efficacy and real-world applicability remain uncertain (Dockx et al., 2016). Usability concerns and

the need for more personalized and therapeutically grounded content have limited the widespread adoption of VR-based tools in clinical settings. And finally, and especially relevant, adherence shows no improvement in comparison to traditional physiotherapy interventions, which poses a key issue when facing the wide array of non-motor symptoms in PD that hinder motivation (Dockx et al., 2016).

4.3 Gamification: Enhancing Engagement and Adherence

4.3.1 What Is Gamification and How Is It Used

The widespread adoption of technology in an ever-growing set of daily life aspects often brings with it the use of mechanics inspired by games to enhance user engagement. This concept, coined by Deterding et al. (Deterding et al., 2011) as “the use of game design elements in non-game contexts,” is commonly known as gamification. This refers to the use of motivational features to enhance services with the goal of eliciting game-like psychological experiences and promoting specific behaviors (Hamari et al., 2014). Huotari and Hamari (Huotari & Hamari, 2012) emphasize that gamification aims to produce the same kinds of mental engagement and emotional responses typically associated with playing games. Based on these definitions, gamification consists of three key components: (1) the motivational elements that are intentionally designed and integrated, (2) the psychological responses these elements trigger, and (3) the subsequent changes or effects on user behavior (Figure 3 by (Hamari et al., 2014)).

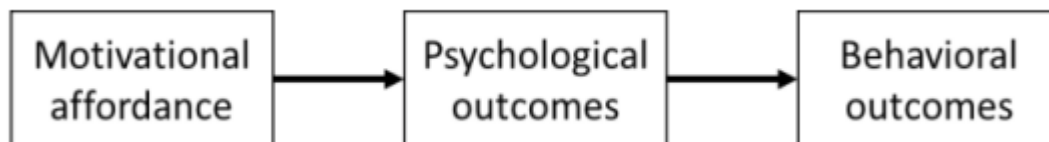


Figure 3. Gamification, from Hamari et al. (Hamari et al., 2014)

When discussing gamification, it is essential to understand the typical design elements it incorporates. Common mechanics include points, which offer immediate feedback and track progress; badges and achievements, which signal accomplishments and foster a sense of mastery; and leaderboards, which introduce competition and social comparison. Other frequently used components include levels to indicate advancement, challenges to promote effort, and clear goals to provide structure. In addition, some gamified systems incorporate narratives or themes to create immersive, story-driven experiences, as well as virtual rewards, feedback mechanisms, and progress indicators to make users' progress visible and rewarding (Hamari et al., 2014; Li et al., 2023; Werbach & Hunter, 2012). These elements are typically chosen to tap into users' intrinsic and extrinsic motivations, aiming to replicate the motivational pull of games in practical, goal-oriented settings (Deci & Ryan, 2008; Li et al., 2023).

4.3.2 Frameworks for Gamification Use

While gamification elements such as points, badges, and leaderboards are widely used, their effectiveness often depends on how they are structured and aligned with users' intrinsic motivations. To guide more intentional design, several conceptual frameworks have been developed. One widely known model is Octalysis, created by Yu-kai Chou (2019) (Chou, 2019), which outlines eight core drives that spark human motivation (Figure 4):

- **Epic Meaning and Calling:** Users are motivated when they believe they are part of something larger than themselves or contributing to a meaningful mission.
- **Development and Accomplishment:** This drive is fueled by users' desire to make progress, achieve goals, and overcome challenges, often supported by metrics like levels or badges.
- **Empowerment of Creativity and Feedback:** Motivation increases when users can express creativity, make meaningful decisions, and receive clear, constructive feedback on their actions.
- **Ownership and Possession:** Users become more engaged when they feel a sense of ownership over assets, such as virtual goods, profiles, or progress, which they can improve or personalize.
- **Social Influence and Relatedness:** Social comparison, competition, collaboration, and recognition from others can significantly drive user engagement and sustained participation.
- **Scarcity and Impatience:** When access to rewards or experiences is limited or delayed, users often feel a stronger urge to act quickly, increasing perceived value and urgency.
- **Unpredictability and Curiosity:** Uncertainty and the prospect of surprise or novel experiences encourage users to stay engaged and seek out what's next.
- **Loss and Avoidance:** Users are motivated to avoid losing progress, missing rewards, or falling behind, which can be leveraged to encourage consistent engagement.

This framework encourages designers and developers to go beyond superficial gamification and strategically apply these core drives based on the device and the end-users expected experience and journey.



Figure 4. Octalysis Framework's Eight Core Drives (Chou, 2019)

Recent academic work has evaluated and applied the Octalysis framework across a variety of domains, offering insights into its practical strengths and limitations. Research by Weber et al. (Weber et al., 2022) investigated Octalysis as a tool for design and evaluation in Human-Computer Interaction education. They found that while the framework helps structure gamification around motivational principles, its complexity can present challenges for novice designers, suggesting that guided application or simplification may be necessary in educational contexts. Further, a bibliometric analysis by Mohanty and Christopher (2023) (Mohanty & Christopher B, 2023) identified a growing body of literature citing Octalysis in training-related studies, highlighting its rising relevance and adaptability beyond digital entertainment.

This emphasis on intentional, user-centered design is also observed in broader revision findings. A large-scale synthesis by Gellner et al. (Gellner et al., 2021) covering 41 studies on gamification in education, found that while gamification generally leads to moderate improvements in learning outcomes, its strongest effects lie in enhancing motivation and engagement. Importantly, the study highlights that outcomes vary depending on the type of gamification elements used, the educational context, and the duration of the intervention. Similarly, the Octalysis framework recommends adapting motivational strategies to distinct phases of user experience and core drives (Chou, 2019). Without initial feasibility studies, it is difficult to assess whether a gamified intervention is not only technically functional but also motivating in the desired ways and cognitively fit for its intended audience.

This kind of feasibility testing allows developers and researchers to examine how users interact with early prototypes of gamified apps or devices, identify usability barriers, gauge psychological responses, and refine motivational mechanics in

line with design goals (Bowen et al., 2009). It also helps in avoiding the issues of “surface-level” gamification, such as relying solely on points or badges, by enabling iterative feedback and adjustment loops.

4.3.3 Use of Gamification in Neurorehabilitation Settings

In healthcare rehabilitation settings, the integration of such elements into digital platforms also aims to create more stimulating and demanding experiences, thus improving user motivation and adherence (Alfieri et al., 2022). When addressing specifically neurorehabilitation, gamification has gained attention for its potential to convert repetitive therapeutic tasks into meaningful and enjoyable experiences. This approach can be grounded on frameworks like the Self-Determination Theory, which emphasizes the psychological needs of autonomy, competence, and relatedness as essential drivers of intrinsic motivation (Deci & Ryan, 2008)

In PD rehabilitation, gamification addresses several barriers to adherence, including apathy, fatigue, and reduced expectations of recovery. By incorporating interactive elements, such as progress tracking, engaging performance feedback, socially relevant features, and immersive narrative structures gamified interventions can enhance the perceived relevance and personal meaning of rehabilitation activities, making them more appealing and motivating for users. (Koivisto & Malik, 2021). These elements are particularly effective for people with PD, who may experience motivational deficits and cognitive decline. Through consistent adherence to training and goal-oriented feedback, gamification can be a powerful tool in facilitating the development and consolidation of motor and cognitive strategies affected by PD (Barry et al., 2014).

Chapter 5. tDCS in Parkinson's Disease Rehabilitation

5.1 Introduction and evolution of brain stimulation in clinical neuroscience

The use of brain stimulation to modulate behavior and support neurological recovery has undergone a profound transformation over the last century. Initially rooted in invasive electrophysiological experiments in both animals and humans, the field has matured into a sophisticated landscape of non-invasive neuromodulation technologies. The progression from DBS for movement disorders to techniques like transcranial magnetic stimulation and transcranial electrical stimulation reflects a broader shift in clinical neuroscience, going from targeting focal lesions to modulating distributed neural networks to support adaptive plasticity.

In recent years, brain stimulation has evolved from a purely investigative tool into a therapeutic approach, particularly in the context of neurorehabilitation for stroke and neurodegenerative conditions such as PD. This shift reflects an increasing recognition that motor and cognitive functions depend on coordinated activity across both cortical and subcortical regions. In this context, non-invasive methods such as transcranial direct current stimulation (tDCS) are being explored as practical tools to modulate these networks and support rehabilitation.

tDCS delivers a constant, low-intensity current through scalp electrodes, subtly modulating neuronal membrane potentials without directly inducing action potentials. By shifting cortical excitability in a polarity-specific manner, tDCS can modulate the likelihood of neural firing in response to ongoing activity, thus facilitating synaptic plasticity (Lefaucheur et al., 2017; Nitsche & Paulus, 2000).

Alongside tDCS, other NIBS techniques have developed in parallel. TMS, introduced by Barker et al. (Barker et al., 1985), enables focal activation of cortical neurons through magnetic induction and has become a widely used diagnostic and therapeutic tool. Repetitive transcranial magnetic stimulation and transcranial random noise stimulation offer additional modes of neuromodulation, though their broader clinical adoption remains more limited. Compared to these, tDCS is particularly well suited for integration with physical and cognitive training paradigms due to its portability, safety profile, and cost-effectiveness.

5.2 Introduction to tDCS

Transcranial Direct Current Stimulation (tDCS) is a non-invasive brain stimulation technique that has gained significant attention in the fields of neurorehabilitation and cognitive neuroscience. The method involves the application of a low-intensity direct current (typically ranging from 1 to 2 milliamperes - mA) through electrodes placed on the scalp. By modulating neuronal membrane potentials, tDCS can modify the excitability of targeted brain regions, influencing cortical activity without directly triggering action potentials (Lefaucheur et al., 2017; Nitsche & Paulus, 2000).

The two primary electrode types used in tDCS are the anode and cathode. Anodal stimulation generally increases cortical excitability, making neurons more likely to fire in response to incoming signals, while cathodal stimulation typically decreases excitability. The effects of tDCS are thought to derive from shifts in resting membrane potential and alterations in neurotransmitter systems (Rizvi et al., 2023).

The clinical applications of tDCS have expanded rapidly, with research demonstrating its potential to enhance learning, memory, attention, and motor performance across a variety of populations, including healthy individuals and those with neurological disorders. Its advantages include ease of administration, low cost, overall safe application, and the ability to pair stimulation with concurrent behavioral or physical interventions for synergistic effects (Buch et al., 2017). Given its neuromodulatory capacity and this compatibility with task-based therapies, tDCS is increasingly being explored as an adjunct to traditional rehabilitation strategies.

5.3 Rationale for Using tDCS in Motor Rehabilitation for PD

In PD, where motor learning and consolidation are notably impaired due to the previously mentioned disrupted basal ganglia circuitry and reduced dopaminergic transmission, tDCS has emerged as a potentially effective adjunct to enhance rehabilitation outcomes (Duan & Zhang, 2024).

Motor skill learning in PD is characterized by slower acquisition, reduced retention, and impaired automatization. These deficits are believed to derive from decreased synaptic plasticity and altered effective connectivity in motor-related neural networks. While individuals with PD can improve performance through repeated practice, the retention and generalization of learned motor behaviors often remain limited (Broeder et al., 2015).

Anodal tDCS applied over motor-related cortical areas, such as the dorsolateral prefrontal cortex (DLPFC), increases neuronal excitability and may facilitate long-term potentiation-like plastic changes. These neurophysiological effects potentially support the acquisition and stabilization of new motor skills when combined with physical training (Simpson & Mak, 2020).

5.4 Combining tDCS with Treadmill Gait Training in PD

Recent literature suggests that combining tDCS with treadmill gait training may offer synergistic benefits for individuals with PD. Broeder et al. (Broeder et al., 2015) concluded that tDCS can improve both motor and cognitive functioning in PwPD, noting that anodal tDCS, applied to increase cortical excitability, led to positive effects on various gait parameters in five out of seven studies. One of these studies specifically highlighted the added benefits of combining anodal tDCS with physical training, pointing at its potential as a valuable complement in neurorehabilitation.

Mechanistically, tDCS is thought to modulate neuronal activity across the basal ganglia-cortex-cerebellum circuitry, promoting dopamine release in motor-related cortical areas (Nguyen et al., 2024). Such neurochemical effects may facilitate improvements in motor execution and cognitive function during walking tasks. Supporting this, Frase et al. (Frase et al., 2021) demonstrated that repeated sessions of anodal tDCS can induce long-term plasticity in the human cortex, a key mechanism supporting motor learning.

Evidence also points to enhanced outcomes when tDCS is paired with exercise. Liu et al. (Liu et al., 2021) and Manenti et al. (Manenti et al., 2016) reported that the concurrent application of anodal tDCS with physiotherapy improved motor and cognitive functions in PwPD. However, diverse stimulation protocols, which often include differences in electrode montage, intensity, and cortical targets continue to pose challenges for generalizing results (Liu et al., 2021). While bi-hemispheric stimulation has been proposed as a cost-effective approach to support DT training and performance, current evidence remains inconclusive (Criminger et al., 2018; Swank et al., 2016).

5.5 Considerations and Challenges in tDCS Application

Despite its promise, the application of tDCS in PD rehabilitation requires careful consideration of several factors. Variability in study outcomes is influenced by differences in stimulation parameters, including electrode montage, current intensity, session duration, and stimulation site. Additionally, individual differences in anatomy, disease severity, and baseline cortical excitability may affect responsiveness to tDCS (Simpson & Mak, 2020).

Safety and tolerability are generally favorable, with mild side effects such as tingling, itching, and skin redness reported infrequently. However, the optimal protocols for achieving durable functional gains remain under investigation. There is also ongoing debate regarding the most effective cortical targets and timing of stimulation relative to training activities. For instance, simultaneous application during motor tasks may produce different outcomes than pre- or post-training stimulation (Broeder et al., 2015; Simpson & Mak, 2020).

Future research should focus on replicating and extending current methodologies to validate predictors of responsiveness, optimize stimulation protocols, and establish the mid- and long-term efficacy of tDCS as part of integrated rehabilitation strategies for PD.

Chapter 6. Justification and Research Aim

PD is a progressive neurodegenerative disorder with a multifaceted symptom profile, where gait dysfunction stands out as a major contributor to morbidity and loss of independence. While pharmacological therapies primarily target dopaminergic deficits, they show diminishing returns over time and fail to address key issues such as postural instability, FoG, and cognitive-motor interference (Mirelman et al., 2016; Poewe et al., 2017). Rehabilitation remains a cornerstone of management, yet its real-world efficacy is often constrained by inconsistent adherence, limited personalization, and a lack of ecologically valid training environments (Bloem et al., 2020).

Gait disturbance deficits are exacerbated under DT conditions, highlighting the need for interventions that integrate both motor and cognitive training components (Kelly et al., 2012). Given the chronic and multifactorial nature of PD, rehabilitation strategies must address neuroplastic mechanisms, motivational challenges, and relevance for real-life scenarios to promote sustained gait improvements.

6.1 The Case for Technology-Enhanced, Gamified Rehabilitation

VR systems, especially when combined with treadmill training, offer a controlled yet dynamic platform for practicing adaptive gait in scenarios that mirror real-world complexity. They allow for scalable modulation of task difficulty, continuous feedback, and increased training intensity in a safe environment, all of which are fundamental to neurorehabilitation (Dockx et al., 2016; Mirelman et al., 2016).

The addition of gamification could become particularly relevant for people with PD, who often experience apathy and reduced goal-directed behavior. By embedding rehabilitation in narrative contexts, visual performance tracking, and progressively challenging tasks, gamified VR can sustain attention, increase adherence, and improve training outcomes (Barry et al., 2014; Koivisto & Malik, 2021).

6.2 Rationale for the addition of tDCS

tDCS has shown promise in enhancing motor learning by modulating cortical excitability and promoting long-term potentiation-like mechanisms. These neurophysiological effects are particularly valuable in PD, where motor learning is often slow and retention poor due to compromised neural plasticity (Broeder et al., 2015; Simpson & Mak, 2020).

Thus, strong rationale exists for integrating tDCS into gait rehabilitation, especially when training involves cognitively challenging or attention-demanding conditions. As PD progresses, gait becomes increasingly reliant on executive control and compensatory cortical recruitment rather than automatic basal-ganglia-mediated processes (Yogev-Seligmann et al., 2008; Wu et al., 2015).

Stimulation of regions such as the primary motor cortex or dorsolateral prefrontal cortex may enhance the cognitive and motor mechanisms that support step regulation, dual-tasking, and adaptive locomotion, all domains commonly impaired in PD and closely linked to fall risk and mobility limitations.

The combination of tDCS with task-specific, technology-enhanced gait training may offer additional therapeutic value. Treadmill training provides repetitive, externally cued stepping that promotes rhythmicity and movement amplitude, whereas gamified virtual environments introduce motivational, visuospatial, and cognitive elements that further challenge motor control. tDCS may amplify the effects of these behavioral interventions by priming neural circuits for learning, increasing cortical excitability, and promoting long-term potentiation-like mechanisms (Nitsche & Paulus, 2000). This priming effect may increase the efficiency of error-based adaptation and enhance the integration of sensory information during gait. Such synergistic interactions are supported by emerging evidence showing that concurrent neuromodulation can potentiate motor and cognitive gains in populations with impaired cortical plasticity (Manenti et al., 2014).

Nevertheless, the application of tDCS in complex, multimodal rehabilitation contexts remains underexplored. Little is known about how neuromodulation interacts with the attentional, perceptual, and motivational demands imposed by immersive or gamified training environments. Understanding whether tDCS can augment gait rehabilitation under these enriched conditions, and identifying the mechanisms and patient profiles most likely to benefit, represents an important step toward more personalized and physiologically based therapeutic approaches for PD.

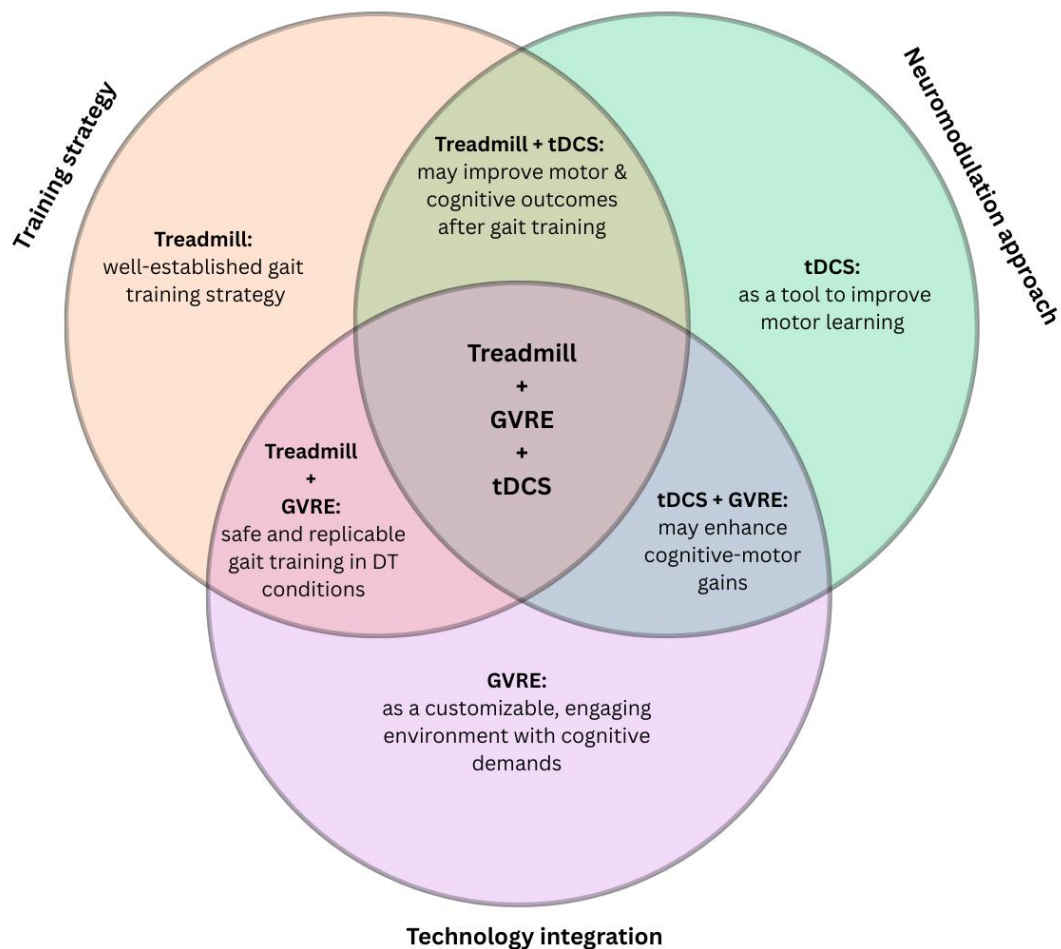


Figure 5. Conceptual framework for the integration of treadmill gait training, GVRE and tDCS in a Venn diagram format.

6.3 Theoretical and Clinical Relevance

The integration of VR, gamification, and tDCS represents a theoretically grounded and innovative approach to address the multifaceted needs of gait rehabilitation in PD. This multimodal strategy aligns with contemporary neurorehabilitation models emphasizing the interplay between motor control, cognitive function, sensory processing, and motivation (Aarsland et al., 2017; Allen et al., 2011). As PD progression leads to deficits automaticity, executive function and attentional resources, interventions that concurrently engage these concepts are increasingly important for meaningful gait improvement (Yogev-Seligmann et al., 2008; Wu et al., 2015). The present approach reflects emerging principles of precise and personalized rehabilitation, in which therapy is tailored to an individual’s functional profile, cognitive demands, and real-world movement challenges (Nguyen et al., 2024).

VR and gamification offer unique strengths by creating ecologically valid, immersive scenarios that replicate environmental and cognitive difficulties encountered in daily mobility. They enable controlled and safe exposure to dual-tasking, obstacle negotiation, visuospatial demands, and real-time feedback, thus stimulating cognitive–motor integration while maintaining patient engagement (Mirelman et al., 2011; 2016). These elements are particularly relevant in PD, where deficits in attention, visuospatial processing, and planning often contribute

to freezing of gait, instability, and increased fall risk. Gamification further enhances intrinsic motivation and adherence, which are well-known barriers in long-term rehabilitation.

The addition of tDCS complements these behavioral components by modulating neural excitability and potentially enhancing learning-related plasticity during task practice. By targeting cortical regions that support executive function, attentional modulation, or motor planning, tDCS may facilitate the neural mechanisms underlying adaptive gait behaviors (Aksu et al., 2022; Broeder et al., 2015; Simpson & Mak, 2020). In this context, neuromodulation is not conceptualized as a standalone therapy but as a mechanism to potentiate the effects of enriched, task-specific training; an approach increasingly relevant within the field of technology-based rehabilitation.

Clinically, this integrative framework offers the potential to refine rehabilitation practices by addressing limitations of conventional gait training, such as insufficient cognitive challenge, limited engagement, and reduced ecological validity. The ability to systematically adjust task complexity, sensory load, and motivational features while facilitating motor learning processes allows for adaptable progression tailored to individual capabilities and needs. If shown effective, such a paradigm could enhance rehabilitation outcomes, support the implementation of custom home-based or community-delivered digital interventions, and contribute to reducing the burden on healthcare systems by promoting more efficient and engaging therapy.

Ultimately, this thesis aims to contribute to a growing shift toward rehabilitation models that are immersive, adaptive, and tailored to the needs of people with PD. By leveraging the combined strengths of VR, gamification, and neuromodulation, it seeks to advance both theoretical understanding and clinical application of multidimensional interventions for PD, with the overarching goal of improving mobility, autonomy, and quality of life for those living with the condition.

Objectives

General objective

This thesis aimed to design and develop, as well as evaluate the feasibility and effectiveness of a Gamified Virtual Reality Environment (GVRE) combined with tDCS and treadmill training to improve gait performance and overall motor condition in individuals with PD.

Specific objectives

Specific objective I

To identify and classify the gamification elements and technologies used in motor rehabilitation in PD and to describe the justification behind the use of gamification and technology in this context

Specific objective II

To design, develop and evaluate the usability and acceptability of a treadmill rehabilitation program in a GVRE for people with PD

Specific objective III

To design a training protocol with which to evaluate the effects of the inclusion of a GVRE to a 6-week treadmill training program with anodal-tDCS in people with PD on gait parameters, clinical outcomes and executive functions; in comparison to a GVRE treadmill training program; and compared to a treadmill training as a control

Specific objective IV

To evaluate the effects of the inclusion of a GVRE to a 6-week treadmill training program with anodal-tDCS in people with PD on gait parameters, clinical outcomes, executive functions and participant experience and motivation; in comparison to a GVRE treadmill training program; and compared to a treadmill training as a control

Methodology



Methodology to address specific objectives I & II

- To identify and classify the gamification elements and technologies used in motor rehabilitation in PD and to describe the justification behind the use of gamification and technology in this context
- To design, develop and evaluate the usability and acceptability of a treadmill rehabilitation program in a GVRE for people with PD

To give answers to specific objectives I & II, a scoping review and a feasibility trial were designed. The scoping review was titled:

Gamification Integration in Technological Devices for Motor Rehabilitation in Parkinson's Disease: A Scoping Review

Study design:

A scoping review of intervention studies was conducted based on the Joanna Briggs Institute methodology for scoping reviews (Aromataris et al., 2020) and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) (Tricco et al., 2018) to ensure quality, transparency and reproducibility.

Search strategy:

The search strategy was developed and conducted by a librarian on November 23, 2023, across seven electronic databases: MEDLINE, EMBASE, Scopus, Cochrane, Web of Science, PsycINFO, and Epistemonikos. A combination of controlled vocabulary and free-text keywords was used to ensure retrieval of all potentially relevant studies. No systematic or scoping reviews on the specified topic were identified in the JBI Systematic Review Register, PROSPERO, or biomedical and nursing databases.

Inclusion and exclusion criteria:

All peer-reviewed articles and peer-reviewed conference papers published in English or Spanish were included. Grey literature sources were excluded to maintain methodological consistency, ensuring all included studies underwent formal peer evaluation and were fully accessible. To guide the eligibility criteria, the PCC framework was used, in which Population, Concept and Context (PCC) are defined to guide study selection. Population referred to people with PD, with no restrictions applied regarding specific sub-populations, gender, disease stage, or geographical location. The Concept covered intervention studies that described motor rehabilitation through technological solutions incorporating clearly identifiable gamification elements. Studies that used commercial video

games originally developed for entertainment were also included. No restrictions regarding Context or year of publication were established. Articles that met the selection criteria were incorporated without assessing their quality, as the objective of scoping reviews is to chart the pertinent works in a particular area and pinpoint areas lacking research (Aromataris et al., 2020).

Study selection:

All articles extracted from databases were imported to Covidence (Veritas Health Innovation, 2023) and checked for duplicates by using its duplicate detection system. Given the large volume of references obtained, the initial title and abstract screening was independently conducted by three reviewers rather than two, as initially proposed in the registered protocol. Any disagreements during this screening stage were resolved through consensus discussions involving all three reviewers. In the next step, full-text screening was independently performed by the same three reviewers, and inconsistencies were again resolved by consensus.

Data extraction and synthesis of results:

Data extraction of all included articles was conducted by one of the authors.

General study information such as location, sample size, age, disease duration, gender, year and study design were collected. Specific data pertinent to the review's objectives was also collected:

In order to identify and name the gamification elements found in each study, Marczewski's 52 Gamification Mechanics (Marczewski, 2017) nomenclature was used due to its clear terminology and ease of use. All gamification elements identified were then classified using Yu-kai Chou's Octalysis Framework (Chou, 2019) due to its focus on motivation and end-user interaction with the system. All gamification elements identified using Marczewski's framework were classified with the core drive they most effectively addressed.

Technological devices integrating gamification were classified based on the type of platform they were used with and based on which symptoms they intended to address.

Finally, a qualitative content analysis using an inductive approach was conducted to identify the justifications used by each study for the inclusion of gamification elements and technological devices for motor rehabilitation in PD (Hsieh & Shannon, 2005). Data from all included studies were coded and organized into categories, which were then clustered into broader themes with the support of a hierarchical tree diagram. Definitions were developed for each code, category, and subcategory. Two reviewers carried out the analysis independently and then discussed how to group codes, align interpretations, and resolve discrepancies.

Final themes were reviewed and refined through team-based triangulation to ensure consistency and credibility.

Following this review, and based on its gathered information, the design, development and feasibility testing of the GVRE was approached, which resulted in the following study:

A gamified virtual environment intervention for gait rehabilitation in Parkinson's Disease: co-creation and feasibility study

Intervention design and development:

The intervention consisted of a walking simulation in 3 different environments, which has a progressive increase in difficulty over time based on 5 different parameters: speed, visibility, path width, obstacles, and distractors.

In the first phase, a review of the available literature for technological solutions for the rehabilitation of gait and DT conditions in PD was performed.

In the second phase, the team of physiotherapists, nurses and computing scientists decided to develop an augmented reality treadmill set-up based on studies by Mirelman et al. (Mirelman et al., 2011, 2016). Participants walked while avoiding side-specific virtual obstacles by skipping over with the corresponding foot. Difficulty increased through increased walking duration, fog, narrowing paths, and environment-specific distractors. Three environments and related visual/auditory elements were validated for use in training

In the third phase, the software was refined using a User-Centered Design approach with feedback from experts and people with PD. Across multiple iterative sessions, PwPD tested the system while walking on the treadmill and were encouraged to comment on clarity of visual cues, perceived safety, cognitive effort, and comfort. PTs provided complementary feedback on clinical relevance, safety considerations, gait demands, and ease of supervision. This dual-perspective approach allowed the research team to detect usability issues early and adapt the design accordingly. The tracking system was upgraded to HTC Vive for better accuracy, and the interface was improved for customization and ease of use. Gamification elements were added to boost motivation, based on Self-Determination Theory (Deci & Ryan, 2008).

Study design and participants:

A single arm, one group, pre-post feasibility study was conducted. A total of eight participants were recruited, comprising four participants with PD and four physiotherapists. Participants with PD were aged 45–80, at H&Y Stage II–III, able to walk 10+ minutes unassisted, and had MMSE >24. Exclusion criteria included major cognitive, sensory, neurological, psychiatric, or cardiovascular issues, and prior brain surgery or DBS use. Sessions occurred at consistent times, with participants on regular medication, and were supervised by physiotherapists with diverse expertise.

tDCS was intentionally excluded from the feasibility study to avoid confounding early usability and safety assessments of the GVRE intervention. At that stage, the priority was to refine core elements of the system: real-time feedback, dual task scenarios, level progression and tolerability in relation to VR-induced symptoms, before introducing an additional neuromodulatory component. Moreover, since tDCS is already a clinically approved and well-established health device with a strong safety profile, additional feasibility testing of the device itself was not considered necessary. Instead, the focus was placed on ensuring that the newly developed GVRE and treadmill components were optimized and tolerable prior to integrating tDCS in the RCT phase.

Data collection:

Usability and acceptability were evaluated using a mixed methods approach, combining quantitative assessments with qualitative feedback.

Before the first session, individuals with PD completed clinical assessments:

- Montreal Cognitive Assessment for cognitive status (Nasreddine et al., 2005)
- MDS-UPDRS for disease severity (Goetz et al., 2008)
- Balance Evaluation Systems Test for balance (Horak et al., 2009)
- International Physical Activity Questionnaire for physical activity levels (Craig et al., 2003)
- H&Y for overall disease stage (Hoehn & Yahr, 1967)

Usability was evaluated through multiple tools completed by both physiotherapists and participants. These included:

- System Usability Scale for a 0-100 usability score (Del Rocio Sevilla-Gonzalez et al., 2020)
- Assistive Technology Usability Questionnaire for people with Neurological diseases for a usability score (Masbernat-Almenara et al., 2023)
- Simulator Sickness Questionnaire for nausea, sickness, disorientation, etc. (Campo Prieto et al., 2022)
- Independent Television Commission Sense of Presence Inventory for immersion perception (Lessiter et al., 2001)

Acceptability was assessed through participants' performance in the virtual environment. Additional feedback was gathered continuously using the "Thinking Aloud" technique combined with open-ended questions directed at both participants and physiotherapists.

Data analysis:

Quantitative data from the questionnaires were analyzed using measures of central tendency and dispersion. Qualitative data from participant feedback on acceptability was analyzed through inductive content analysis.

Ethical approval:

All participants provided signed informed consent. The study was approved by the ethics committee of Hospital Universitari Arnau de Vilanova (CEIC-2231) and complied with the Helsinki Declaration, the Oviedo Convention, and Spanish biomedical research regulations (Council of Europe, 1997; Law 14/2007, of July 3, on Biomedical Research, 2007; World Medical Association, 2013).

Methodology to address specific objective III

- To design a training protocol with which to evaluate the effects of the inclusion of a GVRE to a 6-week treadmill training program with anodal-tDCS in people with PD on gait parameters, clinical outcomes and executive functions; in comparison to a GVRE treadmill training program; and compared to a treadmill training as a control

In order to address specific objective III, a protocol for a randomized clinical trial was created, which resulted in the following article:

A treadmill training program in a gamified virtual reality environment combined with transcranial direct current stimulation in Parkinson's Disease: Study protocol for a randomized controlled trial

Study design:

This protocol proposes a single-blind, single center, three-arm RCT. This study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline for clinical trial protocols (Chan et al., 2013).

Participants:

A total of 78 participants will be recruited primarily through the Hospital Universitari Arnau de Vilanova in Lleida, as well as via neurologist referrals, local PD associations, flyers, and local media outreach.

Inclusion criteria will include:

- Age 50 or older
- Diagnosis of idiopathic PD
- Stage II–III on the H&Y scale during ON medication state
- Ability to walk independently for at least 10 minutes without stopping

Exclusion criteria will include:

- Cognitive decline (MMSE<23)
- Severe auditory or visual impairments
- Presence of other neurological or psychiatric disorders
- Cardiovascular conditions contraindicating physical activity
- History of brain surgery or use of a deep brain stimulation device

Participants requiring a change in medication during the RCT will be considered non-retention subjects.

Ethical approval:

All procedures had been approved by the ethical committee of Hospital Universitari Arnau de Vilanova (CEIC-2231), and both the Helsinki Declaration and the Oviedo Convention were to be followed, as well as Spanish regulations regarding Biomedical Research (Council of Europe, 1997; Law 14/2007, of July 3, on Biomedical Research, 2007; World Medical Association, 2013). This study is registered at Clinicaltrials.gov with code NCT05243394.

Intervention:

The intervention will last 6 weeks with 2 sessions per week (12 sessions total), each progressively increasing in duration and intensity. Three groups will be compared: (1) Treadmill + GVRE + anodal-tDCS, (2) Treadmill + GVRE, and (3) Treadmill only. Training would involve walking while avoiding virtual obstacles and interacting with gamified elements like a virtual dog, progress indicators, and level advancement. Difficulty will increase through obstacle frequency, distractors, visibility (e.g., fog, lighting), and narrower pathways. All sessions will be supervised by physiotherapists and monitored for safety and exertion. Group 1 will also receive 20 minutes of anodal-tDCS targeting the DLPFC.

Outcome measures:

The main outcome will be walking speed, measured during the Intermittent Shuttle Walking Test and under DT conditions. Secondary gait parameters in stride length, cadence, and variability will be recorded using inertial sensors during walking at five speeds and while performing three DT: mental tracking, verbal fluency, and motor. Executive functions will be assessed using computer-based Victoria Stroop and Go/No-Go tests. Clinical measures will include:

- MDS-UPDRS for disease severity (Goetz et al., 2008)
- H&Y for overall disease stage (Hoehn & Yahr, 1967)
- Parkinson's Disease Questionnaire 39 (PDQ39) for quality of life (Peto et al., 1995)
- MiniBest Test for balance (Horak et al., 2009)
- Falls Efficacy Scale–International for fear of falling (Delbaere et al., 2010)
- Montreal Cognitive Assessment for cognitive status (Nasreddine et al., 2005)

A semi-structured interview will assess treatment opinions and adherence.

Data collection and statistical analysis

Demographic data (age, sex, height, disease duration, most affected side) will be collected, and outcome measures will be recorded at baseline, post-treatment, and at 6-week follow-up. To ensure confidentiality, participants will be assigned randomized ID numbers, with personal data stored separately and securely. Statistical analysis will follow a blinded intention-to-treat approach with an alpha

level of 0.05. Descriptive statistics will be used for baseline comparisons, and data distribution will be tested for normality and homogeneity. Mixed methods regression will assess changes across groups and timepoints. Missing data will be handled via multiple imputation, and gait speed changes will be interpreted using thresholds for clinically meaningful differences.

Methodology to address specific objective IV

- To evaluate the effects of the inclusion of a GVRE to a 6-week treadmill training program with anodal-tDCS in people with PD on gait parameters, clinical outcomes, executive functions and participant experience and motivation; in comparison to a GVRE treadmill training program; and compared to a treadmill training as a control

To address specific objective IV, a mixed methods randomized clinical trial was carried out, which resulted in the following article:

A treadmill training program in a gamified virtual reality environment combined with transcranial direct current stimulation in Parkinson's Disease: Preliminary results for a mixed methods randomized controlled trial

Study Design

This study follows a mixed methods explanatory sequential design, beginning with a single-blind, single-center, three-arm, prospective RCT as the quantitative component, followed by a qualitative phase to further explore and explain the trial findings. This study adhered to the SPIRIT Guidelines (Chan et al., 2013).

Participants

A total of 23 participants were successfully recruited, primarily through flyers and the local PD Association. Additional recruitment was carried out via local news and word-of-mouth referrals.

Inclusion and Exclusion Criteria

Inclusion criteria included:

- Age 50 or older
- Diagnosis of idiopathic PD
- Stage II–III on the H&Y scale during ON medication state
- Ability to walk independently for at least 10 minutes without stopping

Exclusion criteria included:

- Cognitive decline (MMSE<23)
- Severe auditory or visual impairments
- Presence of other neurological or psychiatric disorders
- Cardiovascular conditions contraindicating physical activity
- History of brain surgery or use of a deep brain stimulation device

Participants who required a change in medication during the RCT were considered non-retained.

Ethical Approval

All procedures were approved by the ethics committee of Hospital Universitari Arnau de Vilanova (CEIC-2231). The study complied with the principles outlined in the Helsinki Declaration, the Oviedo Convention, and Spanish regulations on biomedical research (Council of Europe, 1997; Law 14/2007, of July 3, on Biomedical Research, 2007; World Medical Association, 2013). This study was registered at Clinicaltrials.gov with code NCT05243394.

Intervention

The intervention lasted for 6 weeks, with two sessions per week, totaling 12 sessions. Each session progressively increased in duration and intensity. Participants were assigned to one of three groups:

1. Treadmill training + GVRE + anodal tDCS
2. Treadmill training + GVRE
3. Treadmill training

All sessions involved treadmill walking and were supervised by physiotherapists experienced in PD and neurorehabilitation. The GVRE included virtual obstacles, a customizable dog avatar, and gamification elements such as score tracking and visual feedback. Difficulty was gradually increased using speed and obstacle increases, distractors, changes in visibility and narrowing path width. Group 1 also received 20 minutes of anodal-tDCS targeting the dorsolateral prefrontal cortex.

Outcome Measures

The primary outcome measure was walking speed, assessed during the Intermittent Shuttle Walking Test and under DT conditions. Secondary gait parameters, including stride length, cadence, and variability, were recorded using inertial sensors while participants walked at five different speeds and during three types of DT conditions (mental tracking, verbal fluency, and motor).

Executive function was evaluated using computer-based versions of the Victoria Stroop Test and the Go/No-Go Test, assessing inhibition, reaction time, and attention.

Additional clinical assessments included:

- MDS-UPDRS for motor symptom severity (Goetz et al., 2008)
- H&Y for disease staging (Hoehn & Yahr, 1967)
- PDQ-39 for quality of life (Peto et al., 1995)
- MiniBest Test for balance (Horak et al., 2009)
- FES-I for fear of falling (Delbaere et al., 2010)
- Montreal Cognitive Assessment for cognitive functioning (Nasreddine et al., 2005)

Individual semi-structured interviews were conducted to explore their perceptions and experiences. Of the 23 participants enrolled, 20 were interviewed; three could not participate due to varying reasons. The interview guide focused on participants' perceived changes in gait and mobility, both in routine and challenging environments (e.g., walking while multitasking or navigating obstacles), as well as the impact of the intervention on daily activities.

Additional themes included factors influencing adherence to the program and the evolution of participants' motivation over time. Interviewers also explored what aspects of the training were most engaging or discouraging, and how these influenced participants' willingness to continue physical activity beyond the study.

All interviews were conducted in a private setting by trained research staff, recorded with consent, and transcribed verbatim. The goal was to gain insight into the real-world relevance of the intervention and to identify facilitators or barriers to sustained engagement in mobility-related rehabilitation.

Data Collection and Statistical Analysis

Demographic data such as age, sex, height, disease duration, and most affected side were collected. Outcome data were recorded at three time points: baseline (T0), post-treatment (T1), and 6-week follow-up (T2). To protect confidentiality, participants were assigned randomized identification numbers, and all data were anonymized and stored securely.

Statistical analysis was conducted using a blinded, intention-to-treat approach. An alpha level of 0.05 was used for all significance testing. Descriptive statistics (frequencies, means, standard deviations, medians, and interquartile ranges) were used to summarize baseline characteristics. Normality and homogeneity were assessed using the Kolmogorov-Smirnov and Levene's tests, respectively.

A mixed-methods regression model was used to compare outcomes between groups and across timepoints. Freezing of gait was considered a confounding factor in the analysis. For non-normally distributed data, log transformation was applied. Missing data were addressed using multiple imputation by chained equations. Results were reported as estimated differences with 95% confidence intervals. Changes in gait speed were interpreted using established thresholds for clinical significance: small (0.06 m/s), moderate (0.14 m/s), and large (0.22 m/s), as defined by Hass et al. (Hass et al., 2014).

Articles

This doctoral thesis is presented as a compendium of four different scientific papers. In this section, each of the papers, three of which have been published in JCR-indexed journals, are presented:

Article I: Gamification Integration in Technological Devices for Motor Rehabilitation in Parkinson's Disease: A Scoping Review

Journal: JMIR Serious Games

Year: 2025

Article II: A gamified virtual environment intervention for gait rehabilitation in Parkinson's Disease: co-creation and feasibility study

Journal: Journal of NeuroEngineering and Rehabilitation

Year: 2024

Article III: A treadmill training program in a gamified virtual reality environment combined with transcranial direct current stimulation in Parkinson's Disease: Study protocol for a randomized controlled trial

Journal: PLoS ONE

Year: 2024

Article IV: A treadmill training program in a gamified virtual reality environment combined with transcranial direct current stimulation in Parkinson's Disease: Preliminary results of a mixed methods randomized controlled trial

Currently in manuscript form, pending submission to scientific journal.

Year: 2025

Discussion

Walking, especially when performed alongside concurrent tasks, is particularly challenging for individuals with PD and significantly increases the risk of falls and their associated consequences. The primary aim of this doctoral thesis was to design and develop, as well as evaluate the feasibility and effectiveness of a GVRE combined with tDCS and treadmill training to improve gait performance and overall motor condition in individuals with PD. The findings of this research offer valuable insights into the implementation of gait rehabilitation strategies, highlighting the potential of technology to create enriched training conditions and promote treatment adherence. Additionally, the results shed light on how a small cohort of participants responded to this novel rehabilitation model. These outcomes represent a meaningful step toward the development of next-generation gait rehabilitation tools that address the multifaceted challenges of PD by targeting motor, cognitive, and behavioral domains.

Objective I

Article I consisted of a scoping review of the literature, carried out to find the current trends in the use of technological interventions integrating gamification for the rehabilitation of motor symptoms in PD. This review reveals an experience predominantly centered on performance and participant feedback, with a clear dominance of gamification elements such as points and scoring, feedback mechanics, and progression systems. Through this deployment of elements, most interventions align with the Development & Accomplishment core drive of the Octalysis framework. These findings are consistent with the assertions of the framework's author (Chou, 2019), who notes that this particular core drive is the easiest to design for and implement, as well as the one that tends to receive the most attention from developers. Moreover, the prevalence of these elements is supported by the type of symptoms being targeted; primarily gait, balance, and functional mobility, which clearly benefit from real-time feedback mechanisms (Caudron et al., 2014).

Other core drives were sparsely represented, such as Loss & Avoidance, characterized by mechanics like time pressure and consequences that aim to introduce urgency and accountability into user interaction. The use of such elements in rehabilitation contexts for PD should be carefully considered, as previous studies suggest that different PD phenotypes may respond differently to reward-punishment systems (Van Nuland et al., 2020). Similarly, competition mechanics foster motivation and social interaction, contributing to long-term adherence. However, more intrinsically motivated pathways, such as those related to unpredictability and curiosity or ownership and possession, remain underutilized. Also noteworthy is the absence of more complex gamification elements, such as narratives or exploratory components, which underscores a gap in current design approaches.

In **Article I**, the included studies provided well-defined rationales for incorporating technology into their interventions. These justifications predominantly centered on established or anticipated therapeutic efficacy, the appeal of accessible modalities such as telerehabilitation, the capacity to create enriched and interactive training environments, enhanced safety, and the potential to foster more engaging and motivating rehabilitation experiences. However, only two out of 81 included studies specifically referred to the concept of gamification in their text, and none based their reasoning for using it on frameworks. Moreover, 37 out of the 81 included studies used commercial off-shelf video consoles and video games as the tools for their interventions. These findings highlight significant research gaps in the application of gamification to its full theoretical and practical potential within the rehabilitation of individuals with PD. Notably, there appears to be a marked dependence on commercially available video game consoles and software, such as the Nintendo Wii and Microsoft Kinect, that were originally developed for entertainment rather than therapeutic purposes. The widespread adoption of such platforms within rehabilitation settings presents a complex picture. On the one hand, the use of pre-existing, polished commercial products offer pragmatic advantages, including reduced development costs and high levels of user engagement due to their entertainment-oriented design. However, these systems are not specifically tailored to address the unique motor, cognitive, and sensory challenges faced by individuals with neurodegenerative conditions like PD. As such, they may fall short in meeting the particular therapeutic needs of this population.

Objective II

Article II demonstrated the feasibility of a treadmill-based gait rehabilitation program delivered through a GVRE for people with PD. The co-designed intervention was well received by both individuals with PD and physiotherapists, with high usability scores supporting the relevance of user-centered design in developing accessible and motivating neurorehabilitation tools (Deci & Ryan, 2008; Dopp et al., 2020). Participants highlighted the intervention's immersive and engaging qualities, particularly the naturalistic environments and narrative elements such as the "dog walking" task, which supported motivation and relatedness (Deci & Ryan, 2008). Physiotherapists also recognized the system's clinical potential, emphasizing its adaptability and safety. However, feedback from both groups identified areas for refinement. Although the harness increased participants' sense of safety, it also restricted natural movement and produced distracting noises during certain movements. This issue was resolved by adding rubber protections to eliminate metal-on-metal contact. Simulator sickness scores reached higher than expected values, but closer inspection revealed that the increase was largely driven by fatigue and sweating associated with the higher than intended physical intensity of the sessions, rather than by symptoms characteristic of VR-induced discomfort. This notion was also reinforced by the

fact that the sessions were conducted during a period of elevated ambient temperatures in Lleida, Spain, which likely contributed to this increased sweating and perceived exertion. This distinction strengthened our confidence that the GVRE setup itself did not produce meaningful cybersickness, and therefore the SSQ was not included in the RCT. Instead, symptoms were monitored by experienced physiotherapists throughout the intervention to ensure participant safety (Bimberg et al., 2020; Hara et al., 2018).

Performance data suggested that the progressive difficulty design was effective in challenging participants, but also revealed performance drops under conditions of limited visibility and increased obstacle frequency. This reflects prior findings that people with PD experience greater gait instability under DT or high-load conditions and supports the importance of adaptive progression mechanisms (Mirelman et al., 2011).

Qualitative feedback further highlighted the value of realistic, ecologically valid environments in enhancing engagement. Suggestions for improvement, such as saving calibration settings, diversifying stimuli, and personalizing feedback, point toward practical, user-informed modifications that could enhance both user experience and clinical applicability.

Objective III & IV

Articles III & IV delineated the mixed methods, RCT approach to evaluate the effects of the inclusion of a GVRE to a 6-week treadmill training program with anodal-tDCS in PD on gait parameters during Single and DT, clinical outcomes and executive functions as well as participant experience and motivation; in comparison to a GVRE treadmill training program; and compared to a treadmill training as a control. Approaching this study through a mixed methods lens allowed for the integration of quantitative measures such as kinematic and clinical outcomes and qualitative reports from participants, painting a comprehensive picture of the intervention's impact.

Across all intervention arms, traditional gait metrics (speed, cadence, stride length) exhibited expected DT decrements at baseline but showed no significant group-level improvements post-intervention, regardless of DT type. However, participants, particularly in the Treadmill+GVRE and Treadmill+GVRE+tDCS groups, reported perceived improvements in walking ease and confidence, suggesting early compensatory or attentional adaptations not reflected in objective metrics. This highlights the relevance of subjective mobility confidence as an independent rehabilitation outcome with clinical significance in PD (Morris et al., 2015). The observed increase in stride length–cadence coupling and intercept shifts in these groups suggest potential shifts toward more stable and adaptable gait patterns (Ambrus et al., 2019; Mehrholz et al., 2015).

While DT gait performance remained impaired, some cognitive outcomes showed delayed improvements, such as enhanced Go/No-Go accuracy in the combined group at follow-up, consistent with theories of time-dependent consolidation of tDCS effects (Aksu et al., 2022). Motor function (UPDRS-III) also improved post-intervention, especially in treadmill-based groups, with only the Treadmill+GVRE group maintaining gains at follow-up (Sánchez-Ferro et al., 2018). Motivational drivers were largely intrinsic, reinforced by the immersive and competence-based design of the gamified VR (Schootemeijer et al., 2020), while social support further sustained adherence (Kennedy et al., 2023). These findings underscore the importance of integrating subjective, motor, cognitive, and motivational dimensions in PD rehabilitation research.

Mechanisms and theoretical implications

As previously discussed, **Article I** highlights a dominant trend in motor rehabilitation for PD using technologies integrating gamification, which is characterized by feedback, scoring, and progressive difficulty. Rehabilitation of symptoms such as gait and balance appears to benefit from performance- and posture-based feedback, improving motor outcomes by providing users with timely and actionable information (Caudron et al., 2014; Subramanian & Levin, 2011). For individuals with PD, who often experience gait disturbances, elements that guide step adjustment during training and reward good performance are likely to be key in promoting effective and satisfying sessions. These mechanisms align closely with the principle of competence in Self-Determination Theory, which holds that individuals are more intrinsically motivated when they feel effective in their interactions with the environment (Deci & Ryan, 2008). When interventions integrate features that promote a sense of progress and mastery, they may better sustain user motivation, particularly in populations where apathy and low adherence are common, as is often the case in PD (den Brok et al., 2015). Complementing this, gamified systems that also support autonomy and relatedness, which form the other two core Self-Determination Theory needs, are likely to foster more meaningful engagement. Following this rationale, **Article II** evaluates an intervention that incorporates these principles within a User-Centered Design framework to deliver a personalized and ecologically valid gait rehabilitation experience for PD. The inclusion of feedback elements that guide users' steps, as well as scoring mechanisms and progressive difficulty, serve to support the sense of competence in individuals with PD, providing them with tools to improve their performance in an activity expected to transfer to real-life contexts, particularly under complex DT conditions (Mirelman et al., 2011).

In addition to promoting competence, the intervention introduces mechanisms to support relatedness and emotional resonance. The customizable dog avatar, which accompanies the user during training and visually reflects performance progress through animated behaviors, serves both as a motivational companion and a contextual cue embedded in a familiar and emotionally salient environment.

Similar emotionally engaging features have been shown to enhance user identification and long-term adherence in gamified health applications (Birk & Mandryk, 2018). This design decision reflects growing evidence that emotionally meaningful interactions within digital environments can influence user experience and perceived relevance (McCallum, 2012).

Furthermore, patient autonomy is supported through features that allow personalization of the training experience, including the avatar's name, appearance, and positioning. This sense of agency in configuring at least part of the training environment is essential for growing intrinsic motivation and has been shown to improve both engagement and perceived value of gamified interventions (Li et al., 2023). From a theoretical standpoint, the capacity to tailor the experience not only aligns with Self-Determination Theory but also contributes to ecological validity, a key factor in facilitating transfer of training to real-world mobility challenges (Holden, 2005).

In this context, and given the dopaminergic dysfunction in PD, gamified training may actively compensate for impaired reward processing mechanisms. The degeneration of nigrostriatal dopamine pathways in PD is known to reduce sensitivity to intrinsic reinforcement and prediction error signaling, impairing the capacity to learn from performance-based feedback (Frank et al., 2004). By integrating external feedback, reward cues, and progress indicators, gamified systems may stimulate dopaminergic circuits that are otherwise hypoactive, supporting both motor learning and motivation (Koepp et al., 1998). This is particularly relevant in this environment of reduced motivation and apathy in people with PD (den Brok et al., 2015; Lei et al., 2019), where gamification could act as a motivational lead.

Beyond the gamification layer, the overall intervention was conceived as a multicomponent strategy targeting complementary mechanisms of gait rehabilitation. Treadmill training provides rhythmic, externally cued stepping practice at sufficient intensity to drive motor adaptation (Kwakkel et al., 2007; Rochester et al., 2007). The GVRE builds on this foundation by embedding dual task demands, visual distractions and performance-related feedback into an ecologically meaningful context, thereby targeting cognitive–motor integration and attentional flexibility (Mirelman et al., 2011, 2016; Cano Porras et al., 2018). Finally, tDCS was incorporated with the aim of modulating cortical excitability in regions implicated in executive control and gait regulation, with prior work suggesting potential benefits for motor learning, executive function and dual tasking in PD and related populations (Broeder et al., 2015; Manenti et al., 2016; Liu et al., 2021). Conceptually, these three components were expected to operate synergistically: treadmill training as a motor substrate, the GVRE as a motivational and cognitive-motor component, and tDCS as a neuromodulatory improver of learning and attentional control.

Consistent with this theoretical rationale, qualitative results from **Article IV** highlighted the immersive and dynamic nature of VR as a key contributor to motivation, curiosity, and continued participation throughout the intervention. Participants also described the incremental difficulty increases and scoring system as valuable for performance monitoring and self-validation (Deci & Ryan, 2008). At the same time, these reports highlighted the need for careful individualized calibration: people with PD who are receiving dopaminergic therapy may show altered reward responsiveness or increased impulsivity under highly stimulating feedback loops (Voon et al., 2011), making the pacing and intensity of feedback crucial for both safety and efficacy.

While the theoretical foundation for incorporating reward-based or gamified interventions into motor rehabilitation is strong, particularly given their potential to engage dopaminergic pathways and enhance motivation, the mixed results observed in **Article III** and **Article IV** require cautious interpretation. After the 6-week intervention, no significant group-level changes in spatiotemporal gait metrics were observed across DT conditions. However, the transient reductions in cadence identified in the treadmill+GVRE+tDCS group raise important questions about how this gait parameter should be interpreted in PD. In people with PD, elevated cadence is often a compensatory strategy to offset reduced stride length and maintain walking speed relative to healthy controls. This heightened cadence tends to normalize during treadmill walking (Bello et al., 2014; Zanardi et al., 2021). Within this context, a post-intervention reduction in cadence may not necessarily indicate deterioration but could instead reflect a shift toward a more normalized and efficient gait pattern, particularly under DT conditions.

Further supporting this interpretation, participants in the Treadmill+GVRE+tDCS group exhibited a modest increase in the stride length–cadence slope at T1, indicative of improved capacity to scale stride length with cadence, a recognized marker of adaptive and efficient gait (Ambrus et al., 2019). The simultaneous decrease in the intercept suggests that participants adopted shorter steps for a given cadence, possibly reflecting a stability-oriented strategy during assessments (Bayle et al., 2016). These seemingly contradictory findings may indicate that participants developed greater adaptability, reflected in improved stride length–cadence scaling, while simultaneously adopting a more conservative default gait pattern to enhance stability during assessments. This interpretation is supported by participants' qualitative reports, relevantly in the tDCS groups, who consistently noted improvements in stride regulation, walking ease, and overall physical confidence.

Conversely, the significant increase in the intercept at T2 observed only in the treadmill+GVRE group suggests participants began taking longer strides without increasing cadence, aligning with findings on delayed improvements in stride length following similar interventions (Mehrholtz et al., 2015). However, the late

emergence of these changes diverges from most previous timelines, pointing at the need for cautious interpretation (Mirelman et al., 2013).

Further exploring findings from **Article IV**, it's clear that despite the inclusion of cognitive demands, particularly in the GVRE and tDCS conditions, DT gait performance did not significantly improve, remaining consistently impaired across groups. This outcome stands in notable contrast to previous studies suggesting that tDCS can enhance DT performance in individuals with PD (H. Lee et al., 2024). Several factors may explain this discrepancy, including the study's limited sample size, the relatively low symptom severity, and the high physical activity levels of participants, all of which may have reduced the sensitivity to detect change or introduced ceiling effects in this cohort. Similarly, Stroop task outcomes did not demonstrate consistent cognitive gains, though a temporary increase in response time was observed at T1 in the Treadmill+GVRE group. As this effect dissipated by T2, it is likely explained by transient factors such as task unfamiliarity, fatigue, or early cognitive adjustment, rather than sustained cognitive decline.

In contrast, the Go/No-Go task revealed a significant improvement in inhibitory control at T2 in the Treadmill+GVRE+tDCS group. This delayed effect aligns with evidence suggesting that cognitive benefits from tDCS may emerge gradually (Aksu et al., 2022). Interestingly, this improvement occurred without parallel gains in DT gait, supporting the view that motor and cognitive systems may respond differently to neuromodulation in PD (Schabrun et al., 2016). Participant reports of increased attentional focus and anticipatory stride adjustments further suggest enhanced cognitive engagement in walking, even in the absence of changes in conventional DT metrics.

While quantitative gait metrics remained largely unchanged, clinical motor assessments revealed meaningful trends. Both the treadmill+GVRE and treadmill+GVRE+tDCS groups showed improvements on the UPDRS-III at T1 that approached or exceeded the MCID (Sánchez-Ferro et al., 2018), though only the GVRE group maintained these gains at follow-up. The treadmill-only group exhibited gradual but significant motor improvements by T2, underscoring the enduring value of aerobic training in PD management (Zhen et al., 2022).

Balance also improved across all groups, with MiniBESTest scores showing statistically significant but modest gains. Although mean changes fell below the MCID threshold (Godi et al., 2020), this may reflect a ceiling effect as previously stated due to the cohort's high physical activity and low baseline impairment. Participants' reports of enhanced self-monitoring and cautious gait regulation suggest that interventions may have fostered greater cognitive-motor awareness and self-regulation, aligning with established self-management strategies critical for maintaining independence in PD (Tuijt et al., 2020).

Comparison with previous studies

The scoping review presented in **Article I** painted the landscape of gamification integrated in technological interventions for motor rehabilitation in PD. While prior reviews have examined VR or exergaming interventions more broadly, few have isolated gamification as a design strategy and systematically explored its specific applications and characteristics in PD rehabilitation. For instance, Barry et al. (Barry et al., 2014) provided a foundational review of exergaming in PD, but the emphasis was largely on hardware types and clinical outcomes rather than motivational design elements. In contrast, our review highlighted the mechanistic role of gamification features, such as feedback, scoring, adaptive difficulty, and progression, and address how these may be relevant in the context of motivational deficits common in PD.

Kwon et al. (Kwon et al., 2023) conducted a meta-analysis showing that VR-based rehabilitation significantly improves balance in people with PD, though effects on other outcomes were not statistically significant. While their work focused on clinical measurements, **Article I** adds complementary value by emphasizing gamification features as potential drivers of useful feedback, engagement and adherence, which are underexplored in outcome-focused reviews about PD.

Some reviews have addressed gamification in broader neurorehabilitation contexts (Lumsden et al., 2016; Primack et al., 2012), but few tailored their inclusion criteria to account for PD-specific motor and cognitive impairments, or the implications of dopaminergic dysfunction on feedback sensitivity and reward processing. This narrower focus in **Article I** allowed a closer look at the unique demands and design considerations for this population, such as the importance of calibrating reward mechanisms and addressing DT challenges through design. In this sense, this review complements existing literature by not only cataloguing intervention types, but by proposing design priorities grounded in theory and PD-specific challenges, such as apathy, fatigue, and altered motor learning profiles. It also identifies gaps, such as the lack of customization to the needs of neurorehabilitation and scarce use of framework-based design, which helped inform the development of the subsequent feasibility intervention described in **Article II**.

The intervention presented in this thesis aligns with prior research on VR and gamified rehabilitation in PD but also extends the field in several important ways. Earlier studies, such as Mirelman et al. (2011) (Mirelman et al., 2011), demonstrated that treadmill training augmented with virtual reality can improve gait parameters and reduce fall risk in people with PD, particularly under complex conditions. However, their systems typically lacked personalized or emotionally resonant features. By incorporating gamified elements grounded in Self-Determination Theory and developed through user-centered design, our

intervention addresses both physical and motivational barriers to engagement. Other prior studies have also shown that feedback mechanisms and real-time challenges can enhance motor learning. For example, Barry et al. (2014) (Barry et al., 2014) found that visual and auditory cues during treadmill walking improved gait performance in PD. **Article II**'s findings build on this by embedding such cues within a game-like framework that provides narrative context and a sense of progression, potentially sustaining engagement over longer periods.

Unlike many VR rehabilitation tools that use generic task structures, the present intervention includes emotionally engaging components, such as a dog avatar and customizable features that may enhance relatedness and autonomy. Birk and Mandryk (2018) (Birk & Mandryk, 2018) showed that personalization and avatar-based systems can enhance user engagement in digital health contexts, but few studies have applied this principle directly to neurorehabilitation in PD.

Importantly, while some studies have demonstrated the feasibility of combining VR and DT training (Eggenberger et al., 2016), few have systematically integrated DT components into a gamified VR platform that allows for iterative difficulty adjustment. This adaptive feature may be critical for maximizing both challenge and success, both factors linked to motor learning and retention (Nieuwboer et al., 2009a).

When placed in the context of comparable treadmill+GVRE+tDCS interventions, the outcomes of **Article IV** appear relatively modest. Prior studies using treadmill and tDCS combinations have demonstrated clear, positive interactions, showing enhanced gait and motor outcomes in people with PD (Na et al., 2022). Likewise, foundational work such as that of Mirelman et al. (Mirelman et al., 2016), with larger samples and strong methodological design, has reported significant improvements in gait parameters following similar multimodal interventions; outcomes that **Article IV** did not replicate. However, it is important to note that other studies with comparable limitations, including reduced sample sizes and shorter training durations, have reported similarly modest or inconclusive results (Pisano et al., 2024). These findings suggest that more robust protocols and larger-scale trials may be necessary to fully realize the potential of such combined interventions, and that current results, while informative, require further refinement and replication to guide clinical application.

Finally, unlike studies focused solely on performance metrics, the present work captures user experience, engagement feedback and insights from personal interviews, which have been underreported in prior trials. This mixed-methods approach aligns with important calls in rehabilitation science to consider effective and motivational outcomes as integral to intervention success (Levac et al., 2016).

Strengths and limitations

This doctoral thesis makes significant contributions to the field of PD rehabilitation through a multi-method investigation of interventions deploying gamification, combining a scoping review with the development, feasibility assessment and clinical testing of a GVRE. One of its key strengths lies in the comprehensive synthesis of existing literature in **Article I**, which analyzed 81 studies and identified 453 gamification elements, revealing a widespread experience reliant on feedback, scoring and difficulty increases, as well as a notable absence of theoretical, framework-based justification for gamification. This review sets a crucial foundation for more deliberate gamification design by exposing current gaps in the field.

The development and feasibility testing of the GVRE in **Article II** further strengthen the thesis by adopting a User-Centered Design process. Involving people with PD and physiotherapists ensured clinical relevance and alignment with end-user preferences. High usability scores and positive qualitative feedback validated the system's relevance, particularly the preference for naturalistic environments and adaptive features, which addressed limitations commonly found in commercially available exergames. Importantly, the GVRE was developed with theoretical grounding in Self-Determination Theory, directly addressing the conceptual void identified in **Article I** and aligning gamification elements with PD-specific rehabilitation goals.

Methodologically, the thesis benefits from its use of mixed methods approaches (Tovin & Wormley, 2023) in **Article I**, **Article II** and **Article IV**, integrating quantitative data such as clinical assessments or obstacle-dodging performance with qualitative methodologies, including collecting user feedback on training experience, comfort or difficulty perception, as well as author rationale for the development of their interventions. More specifically regarding **Article IV**, studying this multifaceted, complex intervention through the lens of an explanatory sequential mixed-methods design provided a highly relevant multidimensional perspective. High adherence rates and strong participant motivation across **Article II** and **Article IV** further support the intervention's feasibility and acceptability, with gamification elements likely boosting engagement, in line with evidence on motivation-enhancing technologies in older and neurologically affected populations. Finally, the combination of clinical, cognitive, kinematic, and qualitative assessments enabled a comprehensive evaluation of both motor and cognitive-motor effects.

Despite these strengths, several limitations must be acknowledged when assessing the generalizability and impact of the findings. In **Article I**, an initial title and abstract screening was conducted due to the large number of retrieved studies. While three reviewers were involved in resolving disagreements, this step still carries the inherent risk of inadvertently excluding relevant literature.

Additionally, the review was limited by its search date, meaning that studies published afterward were not included. Grey literature was also excluded, potentially omitting unconventional or practice-based insights, and only studies in English or Spanish were considered, narrowing the cultural and geographic diversity of the evidence base. Furthermore, the review did not systematically evaluate the usability, accessibility, or adaptability of the interventions, as these criteria were not part of the original data extraction framework. While these are key considerations for the successful implementation of tools integrating gamification in PD populations, they remain underexplored. Another limitation relates to the identification of gamification elements: although efforts were made to analyze both published manuscripts and supplementary online sources, some commercial or custom-designed software lacked sufficient documentation. This may have led to an incomplete accounting of all relevant gamification mechanics.

Article II's feasibility testing was carried out over only three sessions, which is insufficient to allow people with PD to achieve the kind of physiological or motor adaptations that would occur with a longer training program. This short duration may have influenced participant feedback, particularly concerning aspects like training periodization, rest scheduling, and perceptions of fatigue and exertion. Furthermore, there was no control over participants' physical activity outside of the intervention sessions, which could have affected performance and introduced variability into the results. The ITC-SOPI questionnaire, used to assess user experience, does not currently have a validated Spanish version; therefore, the authors conducted an in-house translation, which was later reviewed by a professional translator. Nonetheless, the possibility of semantic bias remains, and the resulting data should be interpreted with caution. Additionally, while the GVRE included DT stimuli focusing on cognitive load, obstacle management, and reduced reaction time through visual impairments and distractors, it did not incorporate decision-making elements or changes in direction. These features could have offered a more dynamic and engaging experience, as well as better mimic real-world challenges faced by individuals with PD.

Finally, **Article IV** also presents several limitations that should be considered when interpreting the findings. The small sample size ($n=23$), typical of preliminary trials, significantly reduced statistical power, particularly for detecting changes in variable domains like executive function and DT performance. Additionally, participants had relatively high physical activity levels and mild-to-moderate disease severity, which likely led to ceiling effects in gait, balance, and cognitive outcomes, limiting the ability to detect clinically meaningful improvements; a challenge previously noted in similar high-functioning PD cohorts (Barry et al., 2014). Subjective feedback reinforced this, as participants with lower baseline activity reported more noticeable benefits. The short intervention duration (six weeks) may also have been insufficient to induce sustained neuroplastic changes, with both objective results and participant

reflections suggesting limited time for meaningful adaptation. Lastly, while qualitative interviews enriched the interpretation of intervention effects, the lack of real-world mobility or ecological DT assessments constrains conclusions about practical impact. Future research would benefit from longer interventions, stratified recruitment, and the use of wearables or ecological momentary assessment tools to capture behavior in everyday contexts (Bougea, 2025).

Clinical and research implications

The integration of gamification into technological rehabilitation for individuals with PD presents an emerging frontier in neurorehabilitation. While promising, this evolving domain still lacks systematic theoretical application and robust empirical validation. Clinically, the use of gamified environments in rehabilitation aims to counteract two central barriers in PD management: the progressive motor decline and poor long-term adherence to therapy, often exacerbated by apathy and depression (Chaudhuri et al., 2006; Schapira et al., 2017). Gamification elements, particularly those grounded in feedback, progression, and challenge, leverage motivational psychology to enhance user engagement and performance (Deci & Ryan, 2008). The clinical rationale for combining VR and gamification is further strengthened by the unique demands of DT gait training. DT walking exacerbates gait variability and increases fall risk in PD patients (Yogev-Seligmann et al., 2008). VR-based treadmill environments allow precise manipulation of training environments, creating controlled, safe, and replicable DT scenarios. Studies suggest that training under these conditions can improve gait performance as well as executive function, reducing the likelihood of freezing and falls (Mirelman et al., 2011). The ability to simulate such environments safely within a clinical or home-based setting offers great translational potential for long-term, personalized care.

However, despite its promise, the implementation of gamification in PD rehabilitation is often superficial. Many studies emphasize mechanics like points and levels without clearly articulating their theoretical grounding or linking them to behavioral outcomes. This lack of framework adherence undermines reproducibility and hinders the systematic evaluation of gamification's added value (Sardi et al., 2017). For example, while frameworks like Chou's Octalysis (Chou, 2019) or Marczewski's mechanics (Marczewski, 2017) offer structured approaches to game design, their adoption in clinical research remains limited. Without theoretical foundation, gamification risks becoming a buzzword rather than a robust intervention strategy.

From a research perspective, several gaps remain. First, there is minimal work isolating the effects of gamification itself. Most current interventions combine game-like elements with an underlying rehabilitative activity, such as treadmill walking, making it difficult to determine whether improvements are due to the gamification layer, the technological component or the physical exercise itself

(Koivisto & Hamari, 2019). This calls for controlled, sequenced designs capable of disaggregating these components.

Second, usability and acceptability remain central to intervention success. Studies have shown that older adults with PD often experience technology-related anxiety and cognitive fatigue, which can interfere with uptake (Nawaz et al., 2016). Implementing user-centered design, wherein patients and clinicians co-develop solutions, has proven effective in increasing both satisfaction and efficacy in neurorehabilitation tools (Jankowski et al., 2017). Incorporating this methodology into the development of gamified systems ensures that interventions are not only technologically sound but also aligned with patients' functional and psychological needs.

The findings from **Article IV** offer several meaningful implications for both clinical practice and future research in PD rehabilitation. Clinically, the high adherence rates and positive subjective responses highlight the feasibility and acceptability of integrating GVRE and tDCS into treadmill-based training. These results support growing evidence that engaging, motivationally rich interventions can enhance participation and perceived benefits, even when traditional metrics show limited change (Dockx et al., 2016; Schootemeijer et al., 2020). The intervention's success in promoting gait confidence, attentional engagement, and self-monitoring suggests its potential as a supportive tool for enhancing self-management and mitigating fall risk, particularly among patients with reduced baseline activity or higher severity at the beginning of training (Morris et al., 2015; Tuijt et al., 2020).

From a research perspective, this study underscores the importance of adopting multimodal assessment frameworks that include not only clinical and kinematic outcomes but also subjective experience and cognitive-motor strategies. The dissociation between perceived and measured improvements reinforces the need for outcome measures that capture real-world functional impact, such as ecological momentary assessments or wearable sensors to evaluate mobility in daily life (Bougea, 2025). Additionally, the limited effect of GVRE and tDCS on DT gait in this high-functioning cohort points to the necessity of targeted recruitment strategies, including participants with greater impairment or cognitive-motor interference, where neurostimulation effects may be more pronounced (Aksu et al., 2022; S. A. Lee & Kim, 2021). Finally, given the delayed cognitive effects and the attenuation of motor gains without continued stimulation, future studies should explore longer intervention periods and booster sessions to assess the durability of outcomes and the optimal dosage for combined interventions.

Lastly, the expanding interest in home-based rehabilitation and telerehabilitation highlights the importance of accessibility. Portable, low-cost solutions, such as tablet-based exergames or motion sensors, can simplify access, especially for those in rural or under-resourced areas. However, rigorous validation of these

systems is necessary to ensure safety, particularly given PD patients' balance impairments and risk of falls.

Conclusions

Gamification is a widely adopted strategy in PD rehabilitation, predominantly shaped by performance-driven experiences and feedback mechanisms, with nearly half of existing studies leveraging commercial video game consoles. Despite this prevalence, the field lacks a structured, framework-based design approach, and remains conceptually narrow in its use of gamification elements, highlighting the need for more theoretically grounded, diversified applications to fully explore its rehabilitative potential

A custom-made GVRE combined with treadmill training is a feasible and user-accepted modality for DT gait rehabilitation in people with PD, offering a replicable and adaptable platform that balances clinical relevance with end-user engagement.

Preliminary results demonstrate that combining treadmill training with a GVRE and tDCS is a feasible and well-tolerated approach in people with PD, particularly effective in enhancing subjective gait confidence and cognitive-motor awareness. However, the lack of consistent objective improvements, especially in gait parameters and DT performance, indicates the need for protocol refinement, longer intervention periods, larger sample sizes and outcome measures that better reflect everyday functional mobility.

These findings underscore the potential of multimodal, cognitively engaging rehabilitation strategies to support self-management and sustained motivation in PD. Future research should emphasize stratified participant selection, integration of ecological monitoring tools, and investigation into the long-term efficacy of combined treadmill, VR, and neuromodulation therapies to further understand them and optimize their impact.

References

- Aarsland, D., Creese, B., Politis, M., Chaudhuri, K. R., Ffytche, D. H., Weintraub, D., & Ballard, C. (2017). Cognitive decline in Parkinson disease. *Nature Reviews. Neurology*, *13*(4), 217. <https://doi.org/10.1038/NRNEUROL.2017.27>
- Aksu, S., Uslu, A., İşçen, P., Tülay, E. E., Barham, H., Soyata, A. Z., Demirtas-Tatlidede, A., Yıldız, G. B., Bilgiç, B., Hanağası, H., Woods, A. J., Karamürsel, S., & Uyar, F. A. (2022). Does transcranial direct current stimulation enhance cognitive performance in Parkinson's disease mild cognitive impairment? An event-related potentials and neuropsychological assessment study. *Neurological Sciences*, *43*(6), 4029–4044. <https://doi.org/10.1007/S10072-022-06020-Z>,
- Alfieri, F. M., da Silva Dias, C., de Oliveira, N. C., & Battistella, L. R. (2022). Gamification in Musculoskeletal Rehabilitation. *Current Reviews in Musculoskeletal Medicine*, *15*(6), 629. <https://doi.org/10.1007/S12178-022-09797-W>
- Allen, N. E., Sherrington, C., Paul, S. S., & Canning, C. G. (2011). Balance and falls in Parkinson's disease: A meta-analysis of the effect of exercise and motor training. *Movement Disorders*, *26*(9), 1605–1615. <https://doi.org/10.1002/MDS.23790>,
- Ambrus, M., Sanchez, J. A., & Fernandez-del-Olmo, M. (2019). Walking on a treadmill improves the stride length-cadence relationship in individuals with Parkinson's disease. *Gait and Posture*, *68*, 136–140. <https://doi.org/10.1016/j.gaitpost.2018.11.025>
- Aromataris, Edoardo., Munn, Zachary., & Joanna Briggs Institute. (2020). *JBI manual for evidence synthesis*. Joanna Briggs Institute.
- Azulay, J. P., Mesure, S., Amblard, B., Blin, O., Sangla, I., & Pouget, J. (1999). Visual control of locomotion in Parkinson's disease. *Brain*, *122*(1), 111–120. <https://doi.org/10.1093/BRAIN/122.1.111>,
- Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). NON-INVASIVE MAGNETIC STIMULATION OF HUMAN MOTOR CORTEX. *The Lancet*, *325*(8437), 1106–1107. [https://doi.org/10.1016/S0140-6736\(85\)92413-4](https://doi.org/10.1016/S0140-6736(85)92413-4)
- Barry, G., Galna, B., & Rochester, L. (2014). The role of exergaming in Parkinson's disease rehabilitation: A systematic review of the evidence. *Journal of NeuroEngineering and Rehabilitation*, *11*(1), 1–10. <https://doi.org/10.1186/1743-0003-11-33/TABLES/4>
- Bayle, N., Patel, A. S., Crisan, D., Guo, L. J., Hutin, E., Weisz, D. J., Moore, S. T., & Gracies, J. M. (2016). Contribution of Step Length to Increase Walking and Turning Speed as a Marker of Parkinson's Disease Progression. *PLOS ONE*, *11*(4), e0152469. <https://doi.org/10.1371/JOURNAL.PONE.0152469>

- Bello, O., Sánchez, J. A., Vazquez-Santos, C., & Fernandez-Del-Olmo, M. (2014). Spatiotemporal parameters of gait during treadmill and overground walking in Parkinson's disease. *Journal of Parkinson's Disease*, 4(1), 33–36. <https://doi.org/10.3233/JPD-130251>,
- Berardelli, A., Rothwell, J. C., Thompson, P. D., & Hallett, M. (2001). Pathophysiology of bradykinesia in parkinson's disease. *Brain*, 124(11), 2131–2146. <https://doi.org/10.1093/BRAIN/124.11.2131>,
- Bimberg, P., Weissker, T., & Kulik, A. (2020). On the Usage of the Simulator Sickness Questionnaire for Virtual Reality Research. *2020 IEEE Conference on Virtual Reality and 3D User Interfaces Abstracts and Workshops (VRW)*, 464–467. <https://doi.org/10.1080/10447318.2017.1286767>
- Birk, M. V., & Mandryk, R. L. (2018). Combating attrition in digital self-improvement programs using avatar customization. *Conference on Human Factors in Computing Systems - Proceedings, 2018-April*. <https://doi.org/10.1145/3173574.3174234>
- Blauwendraat, C., Nalls, M. A., & Singleton, A. B. (2020). The genetic architecture of Parkinson's disease. *The Lancet Neurology*, 19(2), 170–178. [https://doi.org/10.1016/S1474-4422\(19\)30287-X](https://doi.org/10.1016/S1474-4422(19)30287-X)
- Bloem, B. R., Grimbergen, Y. A. M., Cramer, M., Willemsen, M., & Zwinderman, A. H. (2001). Prospective assessment of falls in Parkinson's disease. *Journal of Neurology*, 248(11), 950–958. <https://doi.org/10.1007/S004150170047/METRICS>
- Bloem, B. R., Hausdorff, J. M., Visser, J. E., & Giladi, N. (2004). Falls and freezing of Gait in Parkinson's disease: A review of two interconnected, episodic phenomena. In *Movement Disorders* (Vol. 19, Issue 8, pp. 871–884). <https://doi.org/10.1002/mds.20115>
- Bloem, B. R., Henderson, E. J., Dorsey, E. R., Okun, M. S., Okubadejo, N., Chan, P., Andrejack, J., Darweesh, S. K. L., & Munneke, M. (2020). Integrated and patient-centred management of Parkinson's disease: a network model for reshaping chronic neurological care. *The Lancet Neurology*, 19(7), 623–634. [https://doi.org/10.1016/S1474-4422\(20\)30064-8](https://doi.org/10.1016/S1474-4422(20)30064-8)
- Bloem, B. R., Okun, M. S., & Klein, C. (2021). Parkinson's disease. *The Lancet*, 397(10291), 2284–2303. [https://doi.org/10.1016/S0140-6736\(21\)00218-X](https://doi.org/10.1016/S0140-6736(21)00218-X)
- Bougea, A. (2025). Application of Wearable Sensors in Parkinson's Disease: State of the Art. *Journal of Sensor and Actuator Networks 2025, Vol. 14, Page 23*, 14(2), 23. <https://doi.org/10.3390/JSAN14020023>

- Bowen, D. J., Kreuter, M., Spring, B., Cofta-Woerpel, L., Linnan, L., Weiner, D., Bakken, S., Kaplan, C. P., Squiers, L., Fabrizio, C., & Fernandez, M. (2009). How We Design Feasibility Studies. *American Journal of Preventive Medicine*, 36(5), 452. <https://doi.org/10.1016/J.AMEPRE.2009.02.002>
- Braak, H., Del Tredici, K., Rüb, U., De Vos, R. A. I., Jansen Steur, E. N. H., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging*, 24(2), 197–211. [https://doi.org/10.1016/S0197-4580\(02\)00065-9](https://doi.org/10.1016/S0197-4580(02)00065-9)
- Broeder, S., Nackaerts, E., Heremans, E., Vervoort, G., Meesen, R., Verheyden, G., & Nieuwboer, A. (2015). Transcranial direct current stimulation in Parkinson's disease: Neurophysiological mechanisms and behavioral effects. In *Neuroscience and Biobehavioral Reviews* (Vol. 57, pp. 105–117). Elsevier Ltd. <https://doi.org/10.1016/j.neubiorev.2015.08.010>
- Buch, E. R., Santarnecchi, E., Antal, A., Born, J., Celnik, P. A., Classen, J., Gerloff, C., Hallett, M., Hummel, F. C., Nitsche, M. A., Pascual-Leone, A., Paulus, W. J., Reis, J., Robertson, E. M., Rothwell, J. C., Sandrini, M., Schambra, H. M., Wassermann, E. M., Ziemann, U., & Cohen, L. G. (2017). Effects of tDCS on motor learning and memory formation: A consensus and critical position paper. *Clinical Neurophysiology*, 128(4), 589–603. <https://doi.org/10.1016/j.clinph.2017.01.004>
- Calcaterra, V., Vandoni, M., Marin, L., Carnevale Pellino, V., Rossi, V., Gatti, A., Patanè, P., Cavallo, C., Re, F., Albanese, I., Silvestri, D., De Nunzio, A., & Zuccotti, G. (2023). Exergames to Limit Weight Gain and to Fight Sedentarism in Children and Adolescents with Obesity. *Children*, 10(6), 928. <https://doi.org/10.3390/CHILDREN10060928>
- Campo Prieto, P., Rodríguez Fuentes, G., & Cancela Carral, J. M. (2022). Traducción y adaptación transcultural al español del Simulator Sickness Questionnaire. *Retos: Nuevas Tendencias En Educación Física, Deporte y Recreación*, ISSN 1579-1726, ISSN-e 1988-2041, N.º. 43, 2022, Págs. 503-509, 43(43), 503–509. <https://dialnet.unirioja.es/servlet/articulo?codigo=8058611&info=resumen&idioma=ENG>
- Carod-Artal, F. J., Vargas, A. P., & Martinez-Martin, P. (2007). Determinants of quality of life in Brazilian patients with Parkinson's disease. *Movement Disorders*, 22(10), 1408–1415. <https://doi.org/10.1002/MDS.21408>,
- Caudron, S., Guerraz, M., Eusebio, A., Gros, J. P., Azulay, J. P., & Vaugoyeau, M. (2014). Evaluation of a visual biofeedback on the postural control in Parkinson's disease. *Neurophysiologie Clinique/Clinical Neurophysiology*, 44(1), 77–86. <https://doi.org/10.1016/J.NEUCLI.2013.10.134>

- Chan, A. W., Tetzlaff, J. M., Altman, D. G., Laupacis, A., Gøtzsche, P. C., Krleža-Jerić, K., Hróbjartsson, A., Mann, H., Dickersin, K., Berlin, J. A., Doré, C. J., Parulekar, W. R., Summerskill, W. S. M., Groves, T., Schulz, K. F., Sox, H. C., Rockhold, F. W., Rennie, D., & Moher, D. (2013). SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Annals of Internal Medicine*, 158(3), 200. <https://doi.org/10.7326/0003-4819-158-3-201302050-00583>
- Chaudhuri, K. R., Healy, D. G., & Schapira, A. H. V. (2006). Non-motor symptoms of Parkinson's disease: Diagnosis and management. *Lancet Neurology*, 5(3), 235–245. [https://doi.org/10.1016/S1474-4422\(06\)70373-8/ASSET/71F8F9A5-00E0-4BE1-83A9-8D9D73D5F77C/MAIN.ASSETS/GR1.JPG](https://doi.org/10.1016/S1474-4422(06)70373-8/ASSET/71F8F9A5-00E0-4BE1-83A9-8D9D73D5F77C/MAIN.ASSETS/GR1.JPG)
- Chaudhuri, K. R., & Schapira, A. H. (2009). Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurology*, 8(5), 464–474. [https://doi.org/10.1016/S1474-4422\(09\)70068-7](https://doi.org/10.1016/S1474-4422(09)70068-7)
- Chen, Z., Li, G., & Liu, J. (2020). Autonomic dysfunction in Parkinson's disease: Implications for pathophysiology, diagnosis, and treatment. *Neurobiology of Disease*, 134, 104700. <https://doi.org/10.1016/J.NBD.2019.104700>
- Chou, Y. (2019). *Actionable gamification: Beyond points, badges, and leaderboards*. Packt Publishing Ltd.
- Council of Europe. (1997). Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. [ETS No. 164].
- Craig, C. L., Marshall, A. L., Sjöström, M., Bauman, A. E., Booth, M. L., Ainsworth, B. E., Pratt, M., Ekelund, U., Yngve, A., Sallis, J. F., & Oja, P. (2003). International physical activity questionnaire: 12-Country reliability and validity. *Medicine and Science in Sports and Exercise*, 35(8), 1381–1395. <https://doi.org/10.1249/01.MSS.0000078924.61453.FB>
- Criminger, C., Swank, C., Almutairi, S., & Mehta, J. (2018). Transcranial direct current stimulation plus concurrent activity may influence task prioritization during walking in people with Parkinson's disease – initial findings. *Journal of Parkinsonism and Restless Legs Syndrome, Volume 8*, 25–32. <https://doi.org/10.2147/jprls.s161740>
- Deci, E. L., & Ryan, R. M. (2008). *Self-Determination Theory: A Macrotheory of Human Motivation, Development, and Health*. <https://doi.org/10.1037/a0012801>
- Del Din, S., Godfrey, A., Mazzà, C., Lord, S., & Rochester, L. (2016). Free-living monitoring of Parkinson's disease: Lessons from the field. *Movement Disorders*, 31(9), 1293–1313.

<https://doi.org/10.1002/MDS.26718>;SUBPAGE:STRING:ABSTRACT;WEBSITE:WEBSITE:MOVEMENTDISORDERS;JOURNAL:JOURNAL:15318257;REQUESTEDJOURNAL:JOURNAL:15318257;WGROUPE:STRING:PUBLIC ATION

Del Rocio Sevilla-Gonzalez, M., Loaeza, L. M., Lazaro-Carrera, L. S., Ramirez, B. B., Rodríguez, A. V., Peralta-Pedrero, M. L., & Almeda-Valdes, P. (2020). Spanish Version of the System Usability Scale for the Assessment of Electronic Tools: Development and Validation. *JMIR Human Factors*, 7(4). <https://doi.org/10.2196/21161>

Delbaere, K., Close, J. C. T., Mikolaizak, A. S., Sachdev, P. S., Brodaty, H., & Lord, S. R. (2010). The Falls Efficacy Scale International (FES-I). A comprehensive longitudinal validation study. *Age and Ageing*, 39(2), 210–216. <https://doi.org/10.1093/AGEING/AFP225>

den Brok, M. G. H. E., van Dalen, J. W., van Gool, W. A., Moll van Charante, E. P., de Bie, R. M. A., & Richard, E. (2015). Apathy in Parkinson's disease: A systematic review and meta-analysis. *Movement Disorders : Official Journal of the Movement Disorder Society*, 30(6), 759–769. <https://doi.org/10.1002/MDS.26208>

Deterding, S., Khaled, R., Nacke, L. E., & Dixon, D. (2011). Gamification: Toward a Definition. *Conference: CHI 2011 Gamification Workshop Proceedings*.

Dockx, K., Bekkers, E., Van den Bergh, V., Ginis, P., Rochester, L., Hausdorff, J., Mirelman, A., & Nieuwboer, A. (2016). Virtual reality for rehabilitation in Parkinson's disease. *The Cochrane Database of Systematic Reviews*, 12(12). <https://doi.org/10.1002/14651858.CD010760.PUB2>

Dopp, A. R., Parisi, K. E., Munson, S. A., & Lyon, A. R. (2020). Aligning implementation and user-centered design strategies to enhance the impact of health services: results from a concept mapping study. *Implementation Science Communications*, 1(1), 1–13. <https://doi.org/10.1186/S43058-020-00020-W/TABLES/2>

Dorsey, E., Elbaz, A., Nichols, E., Abd-Allah, F., Abdelalim, A., Adsuar, J. C., Ansha, M. G., Brayne, C., Choi, J. Y. J., Collado-Mateo, D., Dahodwala, N., Do, H. P., Edessa, D., Endres, M., Fereshtehnejad, S. M., Foreman, K. J., Gankpe, F. G., Gupta, R., Hankey, G. J., ... Murray, C. J. L. (2018). Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet. Neurology*, 17(11), 939. [https://doi.org/10.1016/S1474-4422\(18\)30295-3](https://doi.org/10.1016/S1474-4422(18)30295-3)

- Duan, Z., & Zhang, C. (2024). Transcranial direct current stimulation for Parkinson's disease: systematic review and meta-analysis of motor and cognitive effects. *Npj Parkinson's Disease*, *10*(1), 1–14. <https://doi.org/10.1038/S41531-024-00821-Z>;SUBJMETA=1718,2778,308,346,375,617,692;KWRD=PARKINSON
- Eggenberger, P., Wolf, M., Schumann, M., & de Bruin, E. D. (2016). Exergame and balance training modulate prefrontal brain activity during walking and enhance executive function in older adults. *Frontiers in Aging Neuroscience*, *8*(APR), 186959. <https://doi.org/10.3389/FNAGI.2016.00066/BIBTEX>
- Ellis, T., Boudreau, J. K., Deangelis, T. R., Brown, L. E., Cavanaugh, J. T., Earhart, G. M., Ford, M. P., Foreman, K. B., & Dibble, L. E. (2013). *Barriers to Exercise in People With Parkinson Disease*. <https://academic.oup.com/ptj/article/93/5/628/2735346>
- Ellis, T., & Rochester, L. (2018). Mobilizing Parkinson's disease: The future of exercise. *Journal of Parkinson's Disease*, *8*(s1), S95–S100. <https://doi.org/10.3233/JPD-181489>,
- Espay, A. J., Brundin, P., & Lang, A. E. (2017). Precision medicine for disease modification in Parkinson disease. *Nature Reviews Neurology*, *13*(2), 119–126. <https://doi.org/10.1038/NRNEURO.2016.196>,
- Fasano, A., Canning, C. G., Hausdorff, J. M., Lord, S., & Rochester, L. (2017). Falls in Parkinson's disease: A complex and evolving picture. *Movement Disorders*, *32*(11), 1524–1536. <https://doi.org/10.1002/MDS.27195>,
- Feigin, V. L., Krishnamurthi, R. V., Theadom, A. M., Abajobir, A. A., Mishra, S. R., Ahmed, M. B., Abate, K. H., Mengistie, M. A., Wakayo, T., Abd-Allah, F., Abdulle, A. M., Abera, S. F., Mohammed, K. E., Abyu, G. Y., Asgedom, S. W., Atey, T. M., Betsu, B. D., Mezgebe, H. B., Tuem, K. B., ... Zaki, M. E. (2017). Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet. Neurology*, *16*(11), 877–897. [https://doi.org/10.1016/S1474-4422\(17\)30299-5](https://doi.org/10.1016/S1474-4422(17)30299-5)
- Fereshtehnejad, S. M., Zeighami, Y., Dagher, A., & Postuma, R. B. (2017). Clinical criteria for subtyping Parkinson's disease: Biomarkers and longitudinal progression. *Brain*, *140*(7), 1959–1976. <https://doi.org/10.1093/BRAIN/AWX118>,
- Foster, E. R., Bedekar, M., & Tickle-Degnen, L. (2014). Systematic review of the effectiveness of occupational therapy-related interventions for people with parkinsons disease. *American Journal of Occupational Therapy*, *68*(1), 39–49. <https://doi.org/10.5014/AJOT.2014.008706>,

- Fox, S. H., Katzenschlager, R., Lim, S. Y., Barton, B., de Bie, R. M. A., Seppi, K., Coelho, M., & Sampaio, C. (2018). International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. *Movement Disorders, 33*(8), 1248–1266. <https://doi.org/10.1002/MDS.27372>;WEBSITE:WEBSITE:MOVEMENTDISORDERS;JOURNAL:JOURNAL:15318257;REQUESTEDJOURNAL:JOURNAL:15318257;WGROUPE:STRING:PUBLICATION
- Frank, M. J., Seeberger, L. C., & O'Reilly, R. C. (2004). By carrot or by stick: Cognitive reinforcement learning in Parkinsonism. *Science, 306*(5703), 1940–1943. <https://doi.org/10.1126/SCIENCE.1102941>,
- Frase, L., Mertens, L., Krahl, A., Bhatia, K., Feige, B., Heinrich, S. P., Vestring, S., Nissen, C., Domschke, K., Bach, M., & Normann, C. (2021). Transcranial direct current stimulation induces long-term potentiation-like plasticity in the human visual cortex. *Translational Psychiatry, 11*, 17. <https://doi.org/10.1038/s41398-020-01134-4>
- GBD 2019 Diseases and Injuries Collaborators. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet, 396*(10258), 1204–1222. [https://doi.org/10.1016/S0140-6736\(20\)30925-9](https://doi.org/10.1016/S0140-6736(20)30925-9),
- Gellner, C., Buchem, I., & Müller, J. (2021). Application of the octalysis framework to gamification designs for the elderly. *Proceedings of the European Conference on Games-Based Learning, 2021-September*, 260–267. <https://doi.org/10.34190/GBL.21.022>
- Gillies, G. E., Pienaar, I. S., Vohra, S., & Qamhawi, Z. (2014). Sex differences in Parkinson's disease. *Frontiers in Neuroendocrinology, 35*(3), 370. <https://doi.org/10.1016/J.YFRNE.2014.02.002>
- Ginis, P., Heremans, E., Ferrari, A., Bekkers, E. M. J., Canning, C. G., & Nieuwboer, A. (2017). External input for gait in people with Parkinson's disease with and without freezing of gait: One size does not fit all. *Journal of Neurology, 264*(7), 1488–1496. <https://doi.org/10.1007/S00415-017-8552-6>,
- Goble, D. J., Cone, B. L., & Fling, B. W. (2014). Using the Wii Fit as a tool for balance assessment and neurorehabilitation: the first half decade of "Wii-search." *Journal of NeuroEngineering and Rehabilitation, 11*(1), 12. <https://doi.org/10.1186/1743-0003-11-12>
- Godi, M., Arcolin, I., Giardini, M., Corna, S., & Schieppati, M. (2020). Responsiveness and minimal clinically important difference of the Mini-

- BESTest in patients with Parkinson's disease. *Gait and Posture*, *80*, 14–19.
<https://doi.org/10.1016/j.gaitpost.2020.05.004>
- Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Nyenhuis, D., ... Zweig, R. M. (2008). Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders*, *23*(15), 2129–2170.
<https://doi.org/10.1002/MDS.22340>,
- Grillner, S., & El Manira, A. (2020). Current principles of motor control, with special reference to vertebrate locomotion. *Physiological Reviews*, *100*(1), 271–320. <https://doi.org/10.1152/PHYSREV.00015.2019>,
- Hamari, J., Koivisto, J., & Sarsa, H. (2014). Does gamification work? - A literature review of empirical studies on gamification. *Proceedings of the Annual Hawaii International Conference on System Sciences*, 3025–3034.
<https://doi.org/10.1109/HICSS.2014.377>
- Hara, M., Kitamura, T., Murakawa, Y., Shimba, K., Yamaguchi, S., & Tamaki, M. (2018). Safety and Feasibility of Dual task Rehabilitation Program for Body Trunk Balance Using Virtual Reality and Three-dimensional Tracking Technologies. *Progress in Rehabilitation Medicine*, *3*(0), n/a.
<https://doi.org/10.2490/PRM.20180016>
- Hariz, M., & Blomstedt, P. (2022). Deep brain stimulation for Parkinson's disease. *Journal of Internal Medicine*, *292*(5), 764.
<https://doi.org/10.1111/JOIM.13541>
- Hass, C. J., Bishop, M., Moscovich, M., Stegemöller, E. L., Skinner, J., Malaty, I. A., Shukla, A. W., McFarland, N., & Okun, M. S. (2014). Defining the clinically meaningful difference in gait speed in persons with Parkinson disease. *Journal of Neurologic Physical Therapy*, *38*(4), 233–238.
<https://doi.org/10.1097/NPT.0000000000000055>
- Hausdorff, J., Balash, J., & Giladi, N. (2003). Effects of cognitive challenge on gait variability in patients with Parkinson's disease. *Journal of Geriatric Psychiatry and Neurology*, *16*(1), 53–58.
<https://doi.org/10.1177/0891988702250580>
- Hausdorff, J. M., Schaafsma, J. D., Balash, Y., Bartels, A. L., Gurevich, T., & Giladi, N. (2003). Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. *Experimental Brain Research*, *149*(2), 187–194. <https://doi.org/10.1007/S00221-002-1354-8/METRICS>
- Heilig, M. L. (1961). *Sensorama simulator*.

- Heinzel, S., Berg, D., Gasser, T., Chen, H., Yao, C., & Postuma, R. B. (2019). Update of the MDS research criteria for prodromal Parkinson's disease. *Movement Disorders*, *34*(10), 1464–1470. <https://doi.org/10.1002/MDS.27802>,
- Hely, M. A., Morris, J. G. L., Reid, W. G. J., & Trafficante, R. (2005). Sydney Multicenter Study of Parkinson's disease: Non-L-dopa-responsive problems dominate at 15 years. *Movement Disorders*, *20*(2), 190–199. <https://doi.org/10.1002/MDS.20324>,
- Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: Onset, progression, and mortality. *Neurology*, *17*(5), 427–442. <https://doi.org/10.1212/WNL.17.5.427>
- Holden, M. K. (2005). Virtual environments for motor rehabilitation: Review. *Cyberpsychology and Behavior*, *8*(3), 187–211. <https://doi.org/10.1089/CPB.2005.8.187>,
- Horak, F. B., Dimitrova, D., & Nutt, J. G. (2005). Direction-specific postural instability in subjects with Parkinson's disease. *Experimental Neurology*, *193*(2), 504–521. <https://doi.org/10.1016/j.expneurol.2004.12.008>
- Horak, F. B., Wrisley, D. M., & Frank, J. (2009). The Balance Evaluation Systems Test (BESTest) to Differentiate Balance Deficits. *Physical Therapy*, *89*(5), 484. <https://doi.org/10.2522/PTJ.20080071>
- Hsieh, H. F., & Shannon, S. E. (2005). Three approaches to qualitative content analysis. *Qualitative Health Research*, *15*(9), 1277–1288. <https://doi.org/10.1177/1049732305276687>
- Hu, C. H., Lai, Y. R., Huang, C. C., Lien, C. Y., Chen, Y. S., Yu, C. C., Lee, S. Y., Lin, W. C., Cheng, B. C., Chiu, W. C., Chiang, Y. F., Kung, C. F., & Lu, C. H. (2024). Exploring the role of anticipatory postural adjustment duration within APA2 subphase as a potential mediator between clinical disease severity and fall risk in Parkinson's disease. *Frontiers in Aging Neuroscience*, *16*, 1354387. <https://doi.org/10.3389/FNAGI.2024.1354387/BIBTEX>
- Huotari, K., & Hamari, J. (2012). Redefining gamification. *Proceedings of the IADIS International Conference Interfaces and Human Computer Interaction 2012, IHCI 2012, Proceedings of the IADIS International Conference Game and Entertainment Technologies 2012*, 227–231. <https://doi.org/10.1145/2393132.2393137>
- Iranzo, A., Tolosa, E., Gelpi, E., Molinuevo, J. L., Valldeoriola, F., Serradell, M., Sanchez-Valle, R., Vilaseca, I., Lomeña, F., Vilas, D., LLadó, A., Gaig, C., & Santamaria, J. (2013). Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: An observational cohort study. *The Lancet Neurology*, *12*(5), 443–453.

[https://doi.org/10.1016/S1474-4422\(13\)70056-5/ATTACHMENT/83F9B14C-E7FE-4263-8DA5-612A71C978E1/MMC1.PDF](https://doi.org/10.1016/S1474-4422(13)70056-5/ATTACHMENT/83F9B14C-E7FE-4263-8DA5-612A71C978E1/MMC1.PDF)

- Jankovic, J. (2008). Parkinson's disease: clinical features and diagnosis. *Journal of Neurology, Neurosurgery, and Psychiatry*, 79(4), 368–376. <https://doi.org/10.1136/JNNP.2007.131045>
- Jankowski, N., Schönijahn, L., Kreitlow, A., Götze, E., & Wahl, M. (2017). A user-centered design approach in the development of rehabilitation devices after stroke. *IEEE International Conference on Rehabilitation Robotics, 2017*, 965–970. <https://doi.org/10.1109/ICORR.2017.8009374>,
- Kalia, L. V., & Lang, A. E. (2015). Parkinson's disease. *The Lancet*, 386(9996), 896–912. [https://doi.org/10.1016/S0140-6736\(14\)61393-3](https://doi.org/10.1016/S0140-6736(14)61393-3)
- Kelly, V. E., Eusterbrock, A. J., & Shumway-Cook, A. (2012). A Review of Dual task Walking Deficits in People with Parkinson's Disease: Motor and Cognitive Contributions, Mechanisms, and Clinical Implications. *Parkinson's Disease, 2012*. <https://doi.org/10.1155/2012/918719>
- Keus, S. H. J., Munneke, M., Nijkrake, M. J., Kwakkel, G., & Bloem, B. R. (2009). Physical therapy in Parkinson's disease: Evolution and future challenges. In *Movement Disorders* (Vol. 24, Issue 1, pp. 1–14). <https://doi.org/10.1002/mds.22141>
- Khobkhun, F., Hollands, K., Hollands, M., & Ajjimaporn, A. (2020). Effectiveness of exercise-based rehabilitation for the treatment of axial rigidity in people with Parkinson's disease: A Scoping Review. *Physical Therapy Reviews*, 25(4), 283–291. <https://doi.org/10.1080/10833196.2020.1816127>
- Kluger, B. M., Herlofson, K., Chou, K. L., Lou, J. S., Goetz, C. G., Lang, A. E., Weintraub, D., & Friedman, J. (2016). Parkinson's disease-related fatigue: A case definition and recommendations for clinical research. *Movement Disorders*, 31(5), 625–631. <https://doi.org/10.1002/MDS.26511>
- Koepp, M. J., Gunn, R. N., Lawrence, A. D., Cunningham, V. J., Dagher, A., Jones, T., Brooks, O. J., Bench, C. J., & Grasby, P. M. (1998). Evidence for striatal dopamine release during a video game. *Nature*, 393(6682), 266–268. <https://doi.org/10.1038/30498>,
- Koivisto, J., & Hamari, J. (2019). The rise of motivational information systems: A review of gamification research. *International Journal of Information Management*, 45, 191–210. <https://doi.org/10.1016/J.IJINFOMGT.2018.10.013>

- Koivisto, J., & Malik, A. (2021). Gamification for Older Adults: A Systematic Literature Review. *The Gerontologist*, 61(7), e360–e372. <https://doi.org/10.1093/GERONT/GNAA047>
- Kouli, A., Torsney, K. M., & Kuan, W.-L. (2018). Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis. *Parkinson's Disease: Pathogenesis and Clinical Aspects*, 3–26. <https://doi.org/10.15586/CODONPUBLICATIONS.PARKINSONSDISEASE.2018.CH1>
- Kwakkel, G., de Goede, C. J. T., & van Wegen, E. E. H. (2007). Impact of physical therapy for Parkinson's disease: A critical review of the literature. *Parkinsonism and Related Disorders*, 13(SUPPL. 3). [https://doi.org/10.1016/S1353-8020\(08\)70053-1](https://doi.org/10.1016/S1353-8020(08)70053-1)
- Kwon, S. H., Park, J. K., & Koh, Y. H. (2023). A systematic review and meta-analysis on the effect of virtual reality-based rehabilitation for people with Parkinson's disease. *Journal of NeuroEngineering and Rehabilitation*, 20(1), 1–14. <https://doi.org/10.1186/S12984-023-01219-3/FIGURES/7>
- Lanier, J., & Biocca, F. (1992). An Insider's View of the Future of Virtual Reality. *Journal of Communication*, 42(4), 150–172. <https://doi.org/10.1111/J.1460-2466.1992.TB00816.X;WGROU:STRING:PUBLICATION>
- Laver, K. E., Lange, B., George, S., Deutsch, J. E., Saposnik, G., & Crotty, M. (2017). Virtual reality for stroke rehabilitation. *Cochrane Database of Systematic Reviews*, 2017(11). <https://doi.org/10.1002/14651858.CD008349.PUB4>,
- Law 14/2007, of July 3, on Biomedical Research, Official State Gazette (Boletín Oficial del Estado) 28826 (2007).
- Lee, H., Choi, B. J., & Kang, N. (2024). Non-invasive brain stimulation enhances motor and cognitive performances during dual tasks in patients with Parkinson's disease: a systematic review and meta-analysis. *Journal of NeuroEngineering and Rehabilitation*, 21(1), 1–16. <https://doi.org/10.1186/S12984-024-01505-8;TYPE=ARTICLE;KWRD=PARKINSON'S>
- Lee, S. A., & Kim, M. K. (2021). The Effect of Transcranial Direct Current Stimulation Combined with Visual Cueing Training on Motor Function, Balance, and Gait Ability of Patients with Parkinson's Disease. *Medicina (Kaunas, Lithuania)*, 57(11). <https://doi.org/10.3390/MEDICINA57111146>
- Lefaucheur, J. P., Antal, A., Ayache, S. S., Benninger, D. H., Brunelin, J., Cogiamanian, F., Cotelli, M., De Ridder, D., Ferrucci, R., Langguth, B., Marangolo, P., Mylius, V., Nitsche, M. A., Padberg, F., Palm, U., Poulet, E., Priori, A., Rossi, S., Sackellmann, M., ... Paulus, W. (2017). Evidence-

based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical Neurophysiology*, 128(1), 56–92.
<https://doi.org/10.1016/J.CLINPH.2016.10.087>

Lei, C., Sunzi, K., Dai, F., Liu, X., Wang, Y., Zhang, B., He, L., & Ju, M. (2019). Effects of virtual reality rehabilitation training on gait and balance in patients with Parkinson's disease: A systematic review. *PLoS ONE*, 14(11).
<https://doi.org/10.1371/JOURNAL.PONE.0224819>

Leite Silva, A. B. R., Gonçalves de Oliveira, R. W., Diógenes, G. P., de Castro Aguiar, M. F., Sallem, C. C., Lima, M. P. P., de Albuquerque Filho, L. B., Peixoto de Medeiros, S. D., Penido de Mendonça, L. L., de Santiago Filho, P. C., Nones, D. P., da Silva Cardoso, P. M. M., Ribas, M. Z., Galvão, S. L., Gomes, G. F., Bezerra de Menezes, A. R., dos Santos, N. L., Mororó, V. M., Duarte, F. S., & dos Santos, J. C. C. (2023). Premotor, nonmotor and motor symptoms of Parkinson's Disease: A new clinical state of the art. *Ageing Research Reviews*, 84, 101834.
<https://doi.org/10.1016/J.ARR.2022.101834>

Lessiter, J., Freeman, J., Keogh, E., & Davidoff, J. (2001). A cross-media presence questionnaire: The ITC-sense of presence inventory. *Presence: Teleoperators and Virtual Environments*, 10(3), 282–297.
<https://doi.org/10.1162/105474601300343612>

Levac, D., Glegg, S. M. N., Sveistrup, H., Colquhoun, H., Miller, P. A., Finestone, H., DePaul, V., Harris, J. E., & Velikonja, D. (2016). A knowledge translation intervention to enhance clinical application of a virtual reality system in stroke rehabilitation. *BMC Health Services Research*, 16(1), 1–11. <https://doi.org/10.1186/S12913-016-1807-6/FIGURES/5>

Li, M., Ma, S., & Shi, Y. (2023). Examining the effectiveness of gamification as a tool promoting teaching and learning in educational settings: a meta-analysis. *Frontiers in Psychology*, 14, 1253549.
<https://doi.org/10.3389/FPSYG.2023.1253549/BIBTEX>

Lipsmeier, F., Taylor, K. I., Kilchenmann, T., Wolf, D., Scotland, A., Schjodt-Eriksen, J., Cheng, W. Y., Fernandez-Garcia, I., Siebourg-Polster, J., Jin, L., Soto, J., Verselis, L., Boess, F., Koller, M., Grundman, M., Monsch, A. U., Postuma, R. B., Ghosh, A., Kremer, T., ... Lindemann, M. (2018). Evaluation of smartphone-based testing to generate exploratory outcome measures in a phase 1 Parkinson's disease clinical trial. *Movement Disorders*, 33(8), 1287–1297.
<https://doi.org/10.1002/MDS.27376;WGROU:STRING:PUBLICATION>

Liu, X., Liu, H., Liu, Z., Rao, J., Wang, J., Wang, P., Gong, X., & Wen, Y. (2021). Transcranial Direct Current Stimulation for Parkinson's Disease: A

- Systematic Review and Meta-Analysis. *Frontiers in Aging Neuroscience*, 13, 691. <https://doi.org/10.3389/FNAGI.2021.746797/BIBTEX>
- Lumsden, J., Edwards, E. A., Lawrence, N. S., Coyle, D., & Munafò, M. R. (2016). Gamification of cognitive assessment and cognitive training: A systematic review of applications and efficacy. *JMIR Serious Games*, 4(2). <https://doi.org/10.2196/GAMES.5888>,
- Maillet, A., Pollak, P., & Debû, B. (2012). Imaging gait disorders in parkinsonism: a review. *Journal of Neurology, Neurosurgery & Psychiatry*, 83(10), 986–993. <https://doi.org/10.1136/JNNP-2012-302461>
- Mak, M. K., Wong-Yu, I. S., Shen, X., & Chung, C. L. (2017). Long-term effects of exercise and physical therapy in people with Parkinson disease. *Nature Reviews Neurology*, 13(11), 689–703. <https://doi.org/10.1038/nrneuro.2017.128>
- Mak, M. K. Y., & Pang, M. Y. C. (2009). Fear of falling is independently associated with recurrent falls in patients with Parkinson's disease: A 1-year prospective study. *Journal of Neurology*, 256(10), 1689–1695. <https://doi.org/10.1007/S00415-009-5184-5>,
- Manenti, R., Brambilla, M., Benussi, A., Rosini, S., Cobelli, C., Ferrari, C., Petesi, M., Orizio, I., Padovani, A., Borroni, B., & Cotelli, M. (2016). Mild cognitive impairment in Parkinson's disease is improved by transcranial direct current stimulation combined with physical therapy. *Movement Disorders*, 31(5), 715–724. <https://doi.org/10.1002/MDS.26561>
- Marczewski, A. (2017, April 3). *The Periodic Table Of Gamification Elements - Gamified UK - #Gamification Expert*. Gamified.Uk. <https://www.gamified.uk/2017/04/03/periodic-table-gamification-elements/>
- Marras, C., Canning, C. G., & Goldman, S. M. (2019). Environment, lifestyle, and Parkinson's disease: Implications for prevention in the next decade. *Movement Disorders*, 34(6), 801–811. <https://doi.org/10.1002/MDS.27720>,
- Martínez-Martín, P., Rodríguez-Blázquez, C., Forjaz, M. J., Álvarez-Sánchez, M., Arakaki, T., Bergareche-Yarza, A., Chade, A., Garretto, N., Gershanik, O., Kurtis, M. M., Martínez-Castrillo, J. C., Mendoza-Rodríguez, A., Moore, H. P., Rodríguez-Violante, M., Singer, C., Tilley, B. C., Huang, J., Stebbins, G. T., & Goetz, C. G. (2014). Relationship between the MDS-UPDRS domains and the health-related quality of life of Parkinson's disease patients. *European Journal of Neurology*, 21(3), 519–524. <https://doi.org/10.1111/ENE.12349>
- Martinez-Martin, P., Rodriguez-Blazquez, C., Kurtis, M. M., & Chaudhuri, K. R. (2011). The impact of non-motor symptoms on health-related quality of life

- of patients with Parkinson's disease. *Movement Disorders*, 26(3), 399–406.
<https://doi.org/10.1002/MDS.23462>
- Masbernat-Almenara, M., Rubi-Carnacea, F., Opisso, E., Duarte-Oller, E., Medina-Casanovas, J., & Valenzuela-Pascual, F. (2023). Developing an assistive technology usability questionnaire for people with neurological diseases. *PLOS ONE*, 18(1), e0281197.
<https://doi.org/10.1371/JOURNAL.PONE.0281197>
- McCallum, S. (2012). Gamification and serious games for personalized health. *Studies in Health Technology and Informatics*, 177, 85–96.
<https://doi.org/10.3233/978-1-61499-069-7-85>
- Mehrholz, J., Friis, R., Kugler, J., Twork, S., Storch, A., & Pohl, M. (2009). Treadmill training for patients with Parkinson's disease. *Cochrane Database of Systematic Reviews*, 2.
<https://doi.org/10.1002/14651858.CD007830>
- Mehrholz, J., Kugler, J., Storch, A., Pohl, M., Elsner, B., & Hirsch, K. (2015). Treadmill training for patients with Parkinson's disease. *Cochrane Database of Systematic Reviews*.
<https://doi.org/10.1002/14651858.cd007830.pub3>
- Mehrholz, J., Thomas, S., & Elsner, B. (2017). Treadmill training and body weight support for walking after stroke. *Cochrane Database of Systematic Reviews*, 2017(8). <https://doi.org/10.1002/14651858.CD002840.PUB4>,
- Milgram, P., & Kishino, F. (1994). A Taxonomy of Mixed Reality Visual Displays. *IEICE Transactions on Information and Systems*, 1321–1329.
https://www.researchgate.net/publication/231514051_A_Taxonomy_of_Mixed_Reality_Visual_Displays
- Mirelman, A., Bonato, P., Camicioli, R., Ellis, T. D., Giladi, N., Hamilton, J. L., Hass, C. J., Hausdorff, J. M., Pelosin, E., & Almeida, Q. J. (2019). Gait impairments in Parkinson's disease. *The Lancet Neurology*, 18(7), 697–708. [https://doi.org/10.1016/S1474-4422\(19\)30044-4](https://doi.org/10.1016/S1474-4422(19)30044-4)
- Mirelman, A., Maidan, I., Herman, T., Deutsch, J., Giladi, N., & Hausdorff, J. (2011). Virtual reality for gait training: can it induce motor learning to enhance complex walking and reduce fall risk in patients with Parkinson's disease? *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 66(2), 234–240.
<https://doi.org/10.1093/GERONA/GLQ201>
- Mirelman, A., Rochester, L., Maidan, I., Del Din, S., Alcock, L., Nieuwhof, F., Rikkert, M. O., Bloem, B. R., Pelosin, E., Avanzino, L., Abbruzzese, G., Dockx, K., Bekkers, E., Giladi, N., Nieuwboer, A., & Hausdorff, J. M. (2016). Addition of a non-immersive virtual reality component to treadmill training to

- reduce fall risk in older adults (V-TIME): a randomised controlled trial. *The Lancet*, 388(10050), 1170–1182. [https://doi.org/10.1016/S0140-6736\(16\)31325-3](https://doi.org/10.1016/S0140-6736(16)31325-3)
- Mirelman, A., Rochester, L., Reelick, M., Nieuwhof, F., Pelosin, E., Abbruzzese, G., Dockx, K., Nieuwboer, A., & Hausdorff, J. (2013). V-TIME: a treadmill training program augmented by virtual reality to decrease fall risk in older adults: study design of a randomized controlled trial. *BMC Neurology*, 13. <https://doi.org/10.1186/1471-2377-13-15>
- Mohanty, S., & Christopher B, P. (2023). A bibliometric analysis of the use of the Gamification Octalysis Framework in training: evidence from Web of Science. *Humanities and Social Sciences Communications*, 10(1), 1–14. <https://doi.org/10.1057/S41599-023-02243-3>;SUBJMETA=4000,4001,4014;KWRD=BUSINESS+AND+MANAGEMENT
- Morris, M. E., Huxham, F., McGinley, J., Dodd, K., & Iansek, R. (2001). The biomechanics and motor control of gait in Parkinson disease. *Clinical Biomechanics*, 16(6), 459–470. [https://doi.org/10.1016/S0268-0033\(01\)00035-3](https://doi.org/10.1016/S0268-0033(01)00035-3)/ASSET/DBAB9FD8-412A-4215-9BD2-D90C3DAEE25F/MAIN.ASSETS/GR5.SML
- Morris, M. E., Martin, C. L., & Schenkman, M. L. (2010). Striding out with Parkinson disease: Evidence-based physical therapy for gait disorders. *Physical Therapy*, 90(2), 280–288. <https://doi.org/10.2522/PTJ.20090091>,
- Morris, M. E., Menz, H. B., McGinley, J. L., Watts, J. J., Huxham, F. E., Murphy, A. T., Danoudis, M. E., & Iansek, R. (2015). A Randomized Controlled Trial to Reduce Falls in People with Parkinson's Disease. *Neurorehabilitation and Neural Repair*, 29(8), 777–785. <https://doi.org/10.1177/1545968314565511>/ASSET/45BD5B81-5F31-47FE-968F-7BAA565730D3/ASSETS/IMAGES/LARGE/10.1177_1545968314565511-FIG1.JPG
- Müller, B., Assmus, J., Herlofson, K., Larsen, J. P., & Tysnes, O. B. (2013). Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease. *Parkinsonism and Related Disorders*, 19(11), 1027–1032. <https://doi.org/10.1016/J.PARKRELDIS.2013.07.010>,
- Na, Y., Kim, J., Lee, S. H., Kim, J., Lee, J., Shin, S. Y., Chang, W. H., Cho, J. W., & Kim, Y. H. (2022). Multichannel Transcranial Direct Current Stimulation Combined With Treadmill Gait Training in Patients With Parkinson's Disease: A Pilot Study. *Frontiers in Neurology*, 13, 804206. <https://doi.org/10.3389/FNEUR.2022.804206>/BIBTEX

- Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. <https://doi.org/10.1111/j.1532-5415.2005.53221.x>
- Nawaz, A., Skjæret, N., Helbostad, J. L., Vereijken, B., Boulton, E., & Svanaes, D. (2016). Usability and acceptability of balance exergames in older adults: A scoping review. *Health Informatics Journal*, *22*(4), 911–931. <https://doi.org/10.1177/1460458215598638>
- Nguyen, T. X. D., Mai, P. T., Chang, Y. J., & Hsieh, T. H. (2024). Effects of transcranial direct current stimulation alone and in combination with rehabilitation therapies on gait and balance among individuals with Parkinson's disease: a systematic review and meta-analysis. *Journal of NeuroEngineering and Rehabilitation*, *21*(1), 1–19. <https://doi.org/10.1186/S12984-024-01311-2/METRICS>
- Nieuwboer, A., & Giladi, N. (2013). Characterizing freezing of gait in Parkinson's disease: Models of an episodic phenomenon. *Movement Disorders*, *28*(11), 1509–1519. <https://doi.org/10.1002/MDS.25683;WGROU:STRING:PUBLICATION>
- Nieuwboer, A., Rochester, L., Müncks, L., & Swinnen, S. P. (2009a). Motor learning in Parkinson's disease: limitations and potential for rehabilitation. *Parkinsonism and Related Disorders*, *15*(SUPPL. 3). [https://doi.org/10.1016/S1353-8020\(09\)70781-3](https://doi.org/10.1016/S1353-8020(09)70781-3)
- Nieuwboer, A., Rochester, L., Müncks, L., & Swinnen, S. P. (2009b). Motor learning in Parkinson's disease: limitations and potential for rehabilitation. *Parkinsonism & Related Disorders*, *15*(SUPPL. 3), S53–S58. [https://doi.org/10.1016/S1353-8020\(09\)70781-3](https://doi.org/10.1016/S1353-8020(09)70781-3)
- Nieuwboer, A., Rochester, L., Müncks, L., & Swinnen, S. P. (2009c). Motor learning in Parkinson's disease: limitations and potential for rehabilitation. *Parkinsonism and Related Disorders*, *15*(SUPPL. 3). [https://doi.org/10.1016/S1353-8020\(09\)70781-3](https://doi.org/10.1016/S1353-8020(09)70781-3)
- Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology*, *527*(Pt 3), 633. <https://doi.org/10.1111/J.1469-7793.2000.T01-1-00633.X>
- Nonnekes, J., Timmer, M. H. M., de Vries, N. M., Rascol, O., Helmich, R. C., & Bloem, B. R. (2016). Unmasking levodopa resistance in Parkinson's disease. *Movement Disorders*, *31*(11), 1602–1609. <https://doi.org/10.1002/MDS.26712>,

- Nutt, J. G., Bloem, B. R., Giladi, N., Hallett, M., Horak, F. B., & Nieuwboer, A. (2011). Freezing of gait: moving forward on a mysterious clinical phenomenon. *The Lancet Neurology*, *10*(8), 734–744. [https://doi.org/10.1016/S1474-4422\(11\)70143-0](https://doi.org/10.1016/S1474-4422(11)70143-0)
- Obeso, J. A., Rodríguez-Oroz, M. C., Benitez-Temino, B., Blesa, F. J., Guridi, J., Marin, C., & Rodriguez, M. (2008). Functional organization of the basal ganglia: Therapeutic implications for Parkinson's disease. *Movement Disorders*, *23*(SUPPL. 3). <https://doi.org/10.1002/MDS.22062>,
- Olanow, C. W., Watts, R. L., & Koller, W. C. (2001). An algorithm (decision tree) for the management of Parkinson's disease (2001): Treatment guidelines. *Neurology*, *56*(11 SUPPL. 5). https://doi.org/10.1212/WNL.56.SUPPL_5.S1,
- Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H. U., & Jönsson, B. (2012). The economic cost of brain disorders in Europe. *European Journal of Neurology*, *19*(1), 155–162. <https://doi.org/10.1111/J.1468-1331.2011.03590.X>,
- Peto, V., Jenkinson, C., Fitzpatrick, R., & Greenhall, R. (1995). The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. *Quality of Life Research*, *4*(3), 241–248. <https://doi.org/10.1007/BF02260863>
- Petzinger, G. M., Fisher, B. E., McEwen, S., Beeler, J. A., Walsh, J. P., & Jakowec, M. W. (2013). Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. *The Lancet Neurology*, *12*(7), 716–726. [https://doi.org/10.1016/S1474-4422\(13\)70123-6](https://doi.org/10.1016/S1474-4422(13)70123-6)
- Pickering, R. M., Grimbergen, Y. A. M., Rigney, U., Ashburn, A., Mazibrada, G., Wood, B., Gray, P., Kerr, G., & Bloem, B. R. (2007). A meta-analysis of six prospective studies of falling in Parkinson's disease. *Movement Disorders*, *22*(13), 1892–1900. <https://doi.org/10.1002/MDS.21598>,
- Pisano, F., Mellace, D., Fugatti, A., Aiello, E. N., Diotti, S., Curti, B., Giust, A., Marfoli, A., Perin, C., De Sandi, A., Alimonti, D., Priori, A., & Ferrucci, R. (2024). Cerebellar tDCS combined with augmented reality treadmill for freezing of gait in Parkinson's disease: a randomized controlled trial. *Journal of NeuroEngineering and Rehabilitation*, *21*(1), 1–13. <https://doi.org/10.1186/S12984-024-01457-Z/FIGURES/3>
- Plotnik, M., Giladi, N., & Hausdorff, J. M. (2007). A new measure for quantifying the bilateral coordination of human gait: Effects of aging and Parkinson's disease. *Experimental Brain Research*, *181*(4), 561–570. <https://doi.org/10.1007/S00221-007-0955-7/FIGURES/4>

- Poewe, W., & Mahlknecht, P. (2020). Pharmacologic Treatment of Motor Symptoms Associated with Parkinson Disease. In *Neurologic Clinics* (Vol. 38, Issue 2, pp. 255–267). W.B. Saunders.
<https://doi.org/10.1016/j.ncl.2019.12.002>
- Poewe, W., Seppi, K., Tanner, C. M., Halliday, G. M., Brundin, P., Volkman, J., Schrag, A. E., & Lang, A. E. (2017). Parkinson disease. *Nature Reviews Disease Primers*, 3(1), 1–21.
<https://doi.org/10.1038/NRDP.2017.13;SUBJMETA=1718,346,365,375,692,699;KWRD=MOVEMENT+DISORDERS,NEURODEGENERATIVE+DISEASES,PARKINSON>
- Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A. E., Halliday, G., Goetz, C. G., Gasser, T., Dubois, B., Chan, P., Bloem, B. R., Adler, C. H., & Deuschl, G. (2015). MDS clinical diagnostic criteria for Parkinson's disease. *Movement Disorders*, 30(12), 1591–1601. <https://doi.org/10.1002/MDS.26424>,
- Postuma, R. B., Iranzo, A., Hu, M., Högl, B., Boeve, B. F., Manni, R., Oertel, W. H., Arnulf, I., Ferini-Strambi, L., Puligheddu, M., Antelmi, E., Cohen De Cock, V., Arnaldi, D., Mollenhauer, B., Videnovic, A., Sonka, K., Jung, K. Y., Kunz, D., Dauvilliers, Y., ... Pelletier, A. (2019). Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: A multicentre study. *Brain*, 142(3), 744–759.
<https://doi.org/10.1093/BRAIN/AWZ030>,
- Pozzi, N. G., Canessa, A., Palmisano, C., Brumberg, J., Steigerwald, F., Reich, M. M., Minafra, B., Pacchetti, C., Pezzoli, G., Volkman, J., & Isaias, I. U. (2019). Freezing of gait in Parkinson's disease reflects a sudden derangement of locomotor network dynamics. *Brain*, 142(7), 2037–2050.
<https://doi.org/10.1093/BRAIN/AWZ141>,
- Primack, B. A., Carroll, M. V., McNamara, M., Klem, M. Lou, King, B., Rich, M., Chan, C. W., & Nayak, S. (2012). Role of Video Games in Improving Health-Related Outcomes: A Systematic Review. *American Journal of Preventive Medicine*, 42(6), 630.
<https://doi.org/10.1016/J.AMEPRE.2012.02.023>
- Pringsheim, T., Jette, N., Frolkis, A., & Steeves, T. D. L. (2014). The prevalence of Parkinson's disease: A systematic review and meta-analysis. *Movement Disorders*, 29(13), 1583–1590. <https://doi.org/10.1002/MDS.25945>,
- Rizvi, A., Bell, K., Yang, D., Montenegro, M. P., Kim, H., Bao, S., Wright, D. L., Buchanan, J. J., & Lei, Y. (2023). Effects of transcranial direct current stimulation over human motor cortex on cognitive-motor and sensory-motor functions. *Scientific Reports*, 13(1), 1–12. <https://doi.org/10.1038/S41598-023-48070->

Z;SUBJMETA=2632,2811,378,477,631;KWRD=HUMAN+BEHAVIOUR,MO
TOR+CONTROL

- Rizzo, A., Lange, B., Suma, E. A., & Bolas, M. (2011). Virtual reality and interactive digital game technology: New tools to address obesity and diabetes. *Journal of Diabetes Science and Technology*, 5(2), 256–264. <https://doi.org/10.1177/193229681100500209>,
- Rocha, P. A., Porfírio, G. M., Ferraz, H. B., & Trevisani, V. F. M. (2014). Effects of external cues on gait parameters of Parkinson's disease patients: A systematic review. *Clinical Neurology and Neurosurgery*, 124, 127–134. <https://doi.org/10.1016/J.CLINEURO.2014.06.026>
- Rochester, L., Galna, B., Lord, S., & Burn, D. (2014). The nature of dual task interference during gait in incident Parkinson's disease. *Neuroscience*, 265, 83–94. <https://doi.org/10.1016/j.neuroscience.2014.01.041>
- Rochester, L., Nieuwboer, A., Baker, K., Hetherington, V., Willems, A. M., Chavret, F., Kwakkel, G., Van Wegen, E., Lim, I., & Jones, D. (2007). The attentional cost of external rhythmical cues and their impact on gait in Parkinson's disease: Effect of cue modality and task complexity. *Journal of Neural Transmission*, 114(10), 1243–1248. <https://doi.org/10.1007/S00702-007-0756-Y>,
- Rosenthal, E., Brennan, L., Xie, S., Hurtig, H., Milber, J., Weintraub, D., Karlawish, J., & Siderowf, A. (2010). Association between cognition and function in patients with Parkinson disease with and without dementia. *Movement Disorders*, 25(9), 1170–1176. <https://doi.org/10.1002/MDS.23073>,
- Rothbaum, B. O., Hodges, L. F., Ready, D., Graap, K., & Alarcon, R. D. (2001). Virtual reality exposure therapy for Vietnam veterans with posttraumatic stress disorder. *Journal of Clinical Psychiatry*, 62(8), 617–622. <https://doi.org/10.4088/JCP.V62N0808>,
- Sánchez-Ferro, Á., Matarazzo, M., Martínez-Martín, P., Martínez-Ávila, J. C., Gómez de la Cámara, A., Giancardo, L., Arroyo Gallego, T., Montero, P., Puertas-Martín, V., Obeso, I., Butterworth, I., Mendoza, C. S., Catalán, M. J., Molina, J. A., Bermejo-Pareja, F., Martínez-Castrillo, J. C., López-Manzanares, L., Alonso-Cánovas, A., Herreros Rodríguez, J., & Gray, M. (2018). Minimal Clinically Important Difference for UPDRS-III in Daily Practice. *Movement Disorders Clinical Practice*, 5(4), 448. <https://doi.org/10.1002/MDC3.12632>
- Sardi, L., Idri, A., & Fernández-Alemán, J. L. (2017). A systematic review of gamification in e-Health. *Journal of Biomedical Informatics*, 71, 31–48. <https://doi.org/10.1016/J.JBI.2017.05.011>

- Schabrun, S. M., Lamont, R. M., & Brauer, S. G. (2016). Transcranial direct current stimulation to enhance dual task gait training in Parkinson's disease: A pilot RCT. *PLoS ONE*, *11*(6).
<https://doi.org/10.1371/journal.pone.0158497>
- Schapira, A. H. V., Chaudhuri, K. R., & Jenner, P. (2017). Non-motor features of Parkinson disease. *Nature Reviews Neuroscience* *2017 18:7*, *18*(7), 435–450. <https://doi.org/10.1038/nrn.2017.62>
- Schoneburg, B., Mancini, M., Horak, F., & Nutt, J. G. (2013). Framework for understanding balance dysfunction in Parkinson's disease. *Movement Disorders*, *28*(11), 1474–1482.
<https://doi.org/10.1002/MDS.25613;CSUBTYPE:STRING:SPECIAL;PAGE:STRING:ARTICLE/CHAPTER>
- Schootemeijer, S., Van Der Kolk, N. M., Ellis, T., Mirelman, A., Nieuwboer, A., Nieuwhof, F., Schwarzschild, M. A., De Vries, N. M., & Bloem, B. R. (2020). Barriers and Motivators to Engage in Exercise for Persons with Parkinson's Disease. In *Journal of Parkinson's Disease* (Vol. 10, Issue 4, pp. 1293–1299). IOS Press BV. <https://doi.org/10.3233/JPD-202247>
- Simpson, M. W., & Mak, M. (2020). The effect of transcranial direct current stimulation on upper limb motor performance in Parkinson's disease: a systematic review. *Journal of Neurology*, *267*(12), 3479–3488.
<https://doi.org/10.1007/S00415-019-09385-Y>,
- Strouwen, C., Molenaar, E. A. L. M., Keus, S. H. J., Münks, L., Heremans, E., Vandenberghe, W., Bloem, B. R., & Nieuwboer, A. (2016). Are factors related to dual task performance in people with Parkinson's disease dependent on the type of dual task? *Parkinsonism & Related Disorders*, *23*, 23–30. <https://doi.org/10.1016/J.PARKRELDIS.2015.11.020>
- Subramanian, S. K., & Levin, M. F. (2011). Viewing medium affects arm motor performance in 3D virtual environments. *Journal of NeuroEngineering and Rehabilitation*, *8*(1), 1–9. <https://doi.org/10.1186/1743-0003-8-36/FIGURES/4>
- Swank, C., Mehta, J., & Criminger, C. (2016). Transcranial direct current stimulation lessens dual task cost in people with Parkinson's disease. *Neuroscience Letters*, *626*, 1–5.
<https://doi.org/10.1016/j.neulet.2016.05.010>
- Takakusaki, K. (2017). Functional Neuroanatomy for Posture and Gait Control. *Journal of Movement Disorders*, *10*(1), 1–17.
<https://doi.org/10.14802/JMD.16062>
- Thaut, M. H., McIntosh, G. C., Rice, R. R., Miller, R. A., Rathbun, J., & Brault, J. M. (1996). Rhythmic auditory stimulation in gait training for Parkinson's

- disease patients. *Movement Disorders*, 11(2), 193–200.
<https://doi.org/10.1002/MDS.870110213>,
- Thenganatt, M. A., & Jankovic, J. (2014). Parkinson Disease Subtypes. *JAMA Neurology*, 71(4), 499–504.
<https://doi.org/10.1001/JAMANEUROL.2013.6233>
- Titova, N., Padmakumar, C., Lewis, S. J. G., & Chaudhuri, K. R. (2017). Parkinson's: a syndrome rather than a disease? *Journal of Neural Transmission*, 124(8), 907–914. <https://doi.org/10.1007/S00702-016-1667-6/FIGURES/6>
- Tomlinson, C., Patel, S., Meek, C., Herd, C., Clarke, C., Stowe, R., Shah, L., Sackley, C., Deane, K., Wheatley, K., & Ives, N. (2012). Physiotherapy intervention in Parkinson's disease: systematic review and meta-analysis. *BMJ (Clinical Research Ed.)*, 345(7872).
<https://doi.org/10.1136/BMJ.E5004>
- Tovin, M. M., & Wormley, M. E. (2023). Systematic Development of Standards for Mixed Methods Reporting in Rehabilitation Health Sciences Research. *Physical Therapy*, 103(11). <https://doi.org/10.1093/PTJ/PZAD084>,
- Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., ... Straus, S. E. (2018). PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. In *Annals of Internal Medicine* (Vol. 169, Issue 7, pp. 467–473). American College of Physicians.
<https://doi.org/10.7326/M18-0850>
- Tuijt, R., Tan, A., Armstrong, M., Pigott, J., Read, J., Davies, N., Walters, K., & Schrag, A. (2020). Self-Management Components as Experienced by People with Parkinson's Disease and Their Carers: A Systematic Review and Synthesis of the Qualitative Literature. *Parkinson's Disease*, 2020(1), 8857385. <https://doi.org/10.1155/2020/8857385>
- Tysnes, O. B., & Storstein, A. (2017). Epidemiology of Parkinson's disease. *Journal of Neural Transmission*, 124(8), 901–905.
<https://doi.org/10.1007/S00702-017-1686-Y>
- Van Nuland, A. J., Helmich, R. C., Dirkx, M. F., Zach, H., Toni, I., Cools, R., & Den Ouden, H. E. M. (2020). Effects of dopamine on reinforcement learning in Parkinson's disease depend on motor phenotype. *Brain*, 143(11), 3422. <https://doi.org/10.1093/BRAIN/AWAA335>
- Veritas Health Innovation. (2023). *Covidence systematic review software*. Available at www.covidence.org.

- Voon, V., Sohr, M., Lang, A. E., Potenza, M. N., Siderowf, A. D., Whetteckey, J., Weintraub, D., Wunderlich, G. R., & Stacy, M. (2011). Impulse control disorders in parkinson disease: A multicenter case-control study. *Annals of Neurology*, 69(6), 986–996. <https://doi.org/10.1002/ANA.22356>,
- Weber, P., Grönwald, L., & Ludwig, T. (2022). Reflection on the Octalysis framework as a design and evaluation tool. *6th International GamiFIN Conference 2022 (GamiFIN 2022)*. https://www.researchgate.net/publication/361054198_Reflection_on_the_Octalysis_framework_as_a_design_and_evaluation_tool
- Weintraub, D., Koester, J., Potenza, M. N., Siderowf, A. D., Stacy, M., Voon, V., Whetteckey, J., Wunderlich, G. R., & Lang, A. E. (2010). Impulse Control Disorders in Parkinson Disease: A Cross-Sectional Study of 3090 Patients. *Archives of Neurology*, 67(5), 589–595. <https://doi.org/10.1001/ARCHNEUROL.2010.65>
- Werbach, K., & Hunter, D. (2012). For the Win: How Game Thinking Can Revolutionize Your Business - Kevin Werbach, Dan Hunter - Google Libros. In *Wharton Digital Press*. Wharton Digital Press.
- Wooten, G. F., Currie, L. J., Bovbjerg, V. E., Lee, J. K., & Patrie, J. (2004). Are men at greater risk for Parkinson's disease than women? *Journal of Neurology, Neurosurgery, and Psychiatry*, 75(4), 637. <https://doi.org/10.1136/JNNP.2003.020982>
- World Medical Association. (2013). World Medical Association Declaration of Helsinki ethical principles for medical research involving human subjects. *JAMA: Journal of the American Medical Association*, 310(20), 2191–2194.
- Wu, T., Hallett, M., & Chan, P. (2015). Motor automaticity in Parkinson's disease. *Neurobiology of Disease*, 82, 226. <https://doi.org/10.1016/J.NBD.2015.06.014>
- Yang, W., Hamilton, J. L., Kopil, C., Beck, J. C., Tanner, C. M., Albin, R. L., Ray Dorsey, E., Dahodwala, N., Cintina, I., Hogan, P., & Thompson, T. (2020). Current and projected future economic burden of Parkinson's disease in the U.S. *Npj Parkinson's Disease*, 6(1), 1–9. <https://doi.org/10.1038/S41531-020-0117-1>;SUBJMETA=375,3934,692,699,700;KWRD=HEALTH+CARE+ECONOMICS,NEUROLOGICAL+DISORDERS
- Yogev-Seligmann, G., Hausdorff, J. M., & Giladi, N. (2008). The role of executive function and attention in gait. In *Movement Disorders* (Vol. 23, Issue 3, pp. 329–342). *Mov Disord*. <https://doi.org/10.1002/mds.21720>
- Zanardi, A. P. J., da Silva, E. S., Costa, R. R., Passos-Monteiro, E., dos Santos, I. O., Krueh, L. F. M., & Peyré-Tartaruga, L. A. (2021). Gait parameters of

Parkinson's disease compared with healthy controls: a systematic review and meta-analysis. *Scientific Reports*, 11(1), 752.
<https://doi.org/10.1038/S41598-020-80768-2>

Zhen, K., Zhang, S., Tao, X., Li, G., Lv, Y., & Yu, L. (2022). A systematic review and meta-analysis on effects of aerobic exercise in people with Parkinson's disease. *Npj Parkinson's Disease*, 8(1), 1–12.
<https://doi.org/10.1038/S41531-022-00418-4>;SUBJMETA=1718,375,692,699,700,784;KWRD=PARKINSON