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Neural substrates of rehabilitation of gait and balance disorders in Parkinson's disease with freezing of gait using video games

Anna Skrzatek

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Presented and defended publicly by

Anna SKRZATEK

**Neural substrates of rehabilitation of gait and balance disorders in
Parkinson’s disease with freezing of gait using video games**

*Les substrats neuronaux des effets de la rééducation des troubles de la marche
et de l’équilibre dans la maladie de Parkinson avec freezing de la marche à
travers les jeux vidéo*

Directed by Pr Marie-Laure WELTER

Co-Directed by Dr Eric BARDINET

Defended the 29/09/2023 in front of the jury composed of:

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Co-Director:	Dr Eric BARDINET	Sorbonne University
President:	Pr Stéphane LEHERICY	Sorbonne University

“The term ‘holistic’ refers to my conviction that what we are concerned with here is the fundamental interconnectedness of all things. [...] I see the solution to each problem as being detectable in the pattern and web of the whole. The connections between causes and effects are often much more subtle and complex than we with our rough and ready understanding of the physical world might naturally suppose, Mrs Rawlinson. Let me give you an example. If you go to an acupuncturist with toothache, he sticks a needle instead into your thigh. Do you know why he does that, Mrs Rawlinson? No, neither do I, Mrs Rawlinson, but we intend to find out.”

Douglas Adams,
“Dirk Gently’s Hollistic Detective Agency”

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Contributions

I declare that this manuscript entitled “Neural substrates of gait and balance in Parkinson’s disease with freezing of gait using video games” is the result of my personal work. It contains the works related to the PARKGAME II project including clinical, gait and neuroimaging research data from a collaborative work.

The recruitment and clinical evaluations were performed by Pr Marie-Laure Welter. Clinical scales and electrophysiological data acquisition was done by Dijana Nuic, with help of Sophien Mehdi, Claire Olivier and Saoussen Cherif. Clinical data were then processed by Anais Herve.

The gait recording data processing was principally done by Dijana Nuic and Saoussen Cherif. With help from Claire Olivier, I performed the processing and created the scripts for the intra-individual variability analysis.

Neuroimaging data was acquired at the CENIR platform at ICM with help of Stephanie Anastacio, Melanie Didier, Celine Homo, Christine Sung, Frederique Humbert, and Patrice Marion. I pre-processed the images with help of Benoit Beranger and analysed them with help of Cecile Gallea and Francois-Xavier Lejeune.

The development of VR-rehabilitation tools was performed in collaboration with the society GENIOUS Healthcare. Dijana Nuic was in charge to develop the rehabilitation program and user guides for patients.

Abstract

Gait is a complex and dynamic phenomenon based on efficient and functional inter-communication between diverse brain structures. It implies motor control mechanisms going from automatisms and postural reflexes to planning, initiation, and execution of volitional motor actions, including gait maintenance and adaptation. In Parkinson's disease (PD) dopaminergic neurodegeneration in the nigrostriatal pathway induces a disturbance among cortico-subcortical pathways. In consequence, patients lose motor automatisms and postural control which manifests, among other signs, as gait disorders and postural instability. With disease progression, other brain regions are impacted, specifically the frontal regions and the mesencephalic locomotor region, as well as the cerebellum. It comes with the appearance of the freezing of gait (FOG) and the falls. These signs are little, or not at all, alleviated by the dopamine replacement treatment or the deep brain stimulation. Therefore, the multimodal rehabilitation remains the only efficient therapeutic tool, provided that it is adapted to patient's handicap while proposing relatively high training intensity and regularity in time. Recently, adding virtual reality (VR) to the rehabilitation has made it possible to increase its intensity, transfer, and patients' motivation, but also to offer a home-based rehabilitation tool. The goal of this research was to study the clinical and neurobiological (via MRI) effects of the home-based training on 50 PD patients with FOG and/or falls, using a video game conceived specifically for them ("Toap Run"), in a randomized controlled trial. As means to do it, patients undertook 18 home-based training sessions spread over 6-9 weeks, with duration from 15 (1st session) to 45 minutes (last session). Two groups followed the training, one with real movement execution (active group), and one playing with the computer keyboard (control group). Active training has induced a decrease in the severity of gait disorders and postural instability, along with alterations of functional connectivity among sensorimotor, cerebellar and cortico-subcortical networks. Inversely, in the control group the training with the game didn't result in a decrease in the severity of gait disorders and postural instability. Among these patients, functional connectivity changes were less extensive, with alterations in subcortico-cerebellar pathways. These data are in favour of using the innovative approaches, such as the adapted video games aiming at gait disorders reduction in PD, in line with neurobiological effects. However, obtained in small cohorts this work needs to be replicated in bigger samples, and compared to other rehabilitation techniques to better adapt the existing therapeutics to each patient's individual needs.

Résumé

La marche est un phénomène complexe et dynamique qui demande la communication efficace et fonctionnelle de diverses structures cérébrales. Elle implique les mécanismes du contrôle moteur allant des automatismes et réflexes posturaux à la planification, l'initiation, et l'exécution des mouvements volontaires y compris leur maintien et leur adaptation. Lors de la maladie de Parkinson (MP), dégénérescence des neurones dopaminergiques de la voie nigrostriatale induit des dysfonctionnements au sein des voies cortico-sous-corticales. Ceci a pour conséquence une perte des automatismes moteurs et du contrôle postural se manifestant, entre autres, par des troubles de la marche et une instabilité posturale. Avec l'évolution de la maladie, d'autres régions cérébrales sont touchées, en particulier les régions frontales et la région locomotrice mésencéphalique, mais aussi le cervelet, avec l'apparition d'un freezing de la marche (freezing of gait-FOG) et des chutes. Ces signes ne sont pas ou peu améliorés par le traitement dopaminergique ou la stimulation cérébrale profonde. La rééducation multimodale reste le seul outil thérapeutique efficace, à condition qu'elle soit adaptée au handicap du patient, tout en proposant une relative haute intensité de l'entraînement et maintenue dans le temps. Récemment, l'ajout de la réalité virtuelle (RV) à la rééducation a permis d'augmenter son intensité, son transfert, et la motivation des patients, tout en permettant de proposer une prise en charge à distance. L'objectif de ce travail de recherche était d'étudier les effets cliniques et neurobiologiques (par IRM) d'un entraînement réalisé à domicile chez 50 patients avec MP ayant un FOG et/ou des chutes, par l'utilisation d'un jeu vidéo spécifiquement élaboré pour ces patients (« Toap Run »), dans une étude contrôlée randomisée. Pour cela, les patients ont réalisé 18 séances à domicile répartis sur 6-9 semaines, d'une durée de 15 (1ère séance) à 45 minutes (dernière séance). Deux groupes se sont ainsi entraînés avec des mouvements (groupe actif) ou en jouant sur le clavier de l'ordinateur (groupe contrôle). L'entraînement actif a permis une réduction de la sévérité des troubles de la marche et de l'instabilité posturale avec une modification de la connectivité fonctionnelle au sein des réseaux sensorimoteurs, cérébelleux et cortico-sous-corticaux. Inversement, au sein du groupe contrôle, le jeu n'a pas permis d'induire de réduction de la sévérité des troubles de la marche et de l'instabilité posturale. Chez ces patients, les modifications de la connectivité fonctionnelle étaient moindres avec des modulations au sein des voies ganglions de la base-cervelet. Ces données sont en faveur de l'utilisation de ces approches innovantes que sont les jeux vidéo adaptés, pour réduire les troubles de la marche des patients avec MP, en lien avec des effets neurobiologiques. Obtenus sur de petites cohortes, ces travaux nécessitent d'être répliqués dans un plus grand échantillon,

et en comparaison à d'autres techniques de rééducation pour mieux adapter la prise en charge aux besoins de chaque patient individuel.

List of Abbreviations

A

- ACC Anterior Cingulate Cortex
- AOT Action Observation Therapy
- APA Anticipatory Postural Adjustments

B

- BOLD Blood Oxygenation Level Dependent (signal)

C

- CgS Cingulate Sulcus
- CL Central Lateral Nucleus
- CLR Cerebellar Locomotor Region
- CN Cuneiform Nucleus
- CoM Centre of Mass
- CoP Centre of Pressure
- CPG Central Pattern Generators
- CT Computed Tomography

D

- DBS Deep Brain Stimulation
- DLPFC/dlPFC Dorsolateral Prefrontal Cortex
- dMRF dorsal Medial Reticular Formation
- DN Dentate Nucleus
- DOPA/L-DOPA
- DPFC Dorsal Prefrontal Cortex
- DS Double Stance

E

- EEG Electroencephalography
- EMG Electromyography

F

- FAB Frontal Assessment Battery
- FC Functional Connectivity
- FDG Flurodeoxyglucose
- FEF Frontal Eye Fields
- fMRI functional Magnetic Resonance Imaging
- fNIRS functional Near Infra-Red Spectroscopy
- FOG Freezing Of Gait
- FOG-Q freezing of gait questionnaire

G

- GABA Gamma Aminobutyric Acid
- GABS Gait And Balance Scale
- GP Globus Pallidus
- GPe Globus Pallidus externus
- GPi Globus Pallidus internus
- GM Grey Matter

I

- IO Inferior Olive
- iRBD idiopathic Rapid Eye Movement Behaviour Disorder

L

- LC Locus Coeruleus
- LED Light-Emitting Diodes
- LFP Local Field potential

M

- M1 Primary Motor Cortex
- MBN/NBM Meynert basal nucleus
- MCI Mild Cognitive Impairment
- MLR Mesencephalic Locomotor Region

- MOCA/MoCA Montreal Cognitive Assessment
 - MPTP 1-methyl-4-phenyl-1,2,3,6-tetrahydrophindole
 - MRI Magnetic Resonance Imaging
- N**
- NA Nucleus Accumbens
 - NIBS Non-Invasive Brain Stimulation
 - NRTP Nucleus Reticularis Tegmenti Pontis
- O**
- OFC Orbito-Frontal Cortex
- P**
- PD Parkinson's Disease
 - PET Positron Emission Tomography
 - PFC Prefrontal Cortex
 - PIGD Postural Instability and Gait Disorders
 - PM Premotor cortex
 - PMd Premotor dorsal
 - PMv Premotor ventral
 - PPC Posterior Parietal Cortex
 - PPN Pedunculopontine Nucleus
 - PRF Pontal Reticular Formation
 - PSP Progressive Supranuclear Palsy
- Q**
- QOL Quality Of Life
- R**
- REM Rapid Eye Movement
 - RN Raphe Nucleus
- rTMS repeated Transcranial Magnetic Stimulation
- S**
- S1 Primary Sensory Cortex
 - SLR Subthalamic Locomotor Region
 - SMA Supplementary Motor Area
 - SMAp Supplementary Motor Area posterior
 - SNc Substantia Nigra pars compacta
 - SNr Substantia Nigra pars reticulata
 - STN Subthalamic Nucleus
 - SWST Stand-Walk-Sit test
 - tDCS transcranial Direct Current Stimulation
- T**
- TMT Trail Making Test
 - TUG Timed Up and Go
 - TT Treadmill Training
- U**
- UPDRS Unified Parkinson's Disease Rating Scale
 - UPDRS III motor Unified Parkinson's Disease Rate Scale
- V**
- VLo Ventral Lateral Nucleus pars oralis
 - vmPFC ventromedial Prefrontal Cortex
 - vMRF ventral Medial Reticular Formation
 - VPLo Ventral Posterior Lateral Nucleus pars oralis

- VR Virtual Reality
- VIM Ventral Intermediate Nucleus

W

- WM White Matter

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Introduction

Parkinson's Disease (PD) is a neurodegenerative disorder characterised by a progressive death of dopaminergic neurons starting in Substantia Nigra pars compacta (SNc; (Bazelon et al., 1967; Ehringer & Hornykiewicz, 1960; D. D. Song & Haber, 2000)). It provokes an important impairment in cortico-basal ganglia networks, resulting in complex motor, cognitive and limbic alterations. The three main symptoms hallmarking the disease are: tremor, rigidity and hypokinesia. Although the dopaminergic replacement medication and/or deep brain stimulation (DBS) of subthalamic nucleus (STN) help alleviate the latter, the disease progresses to the loss of motor automaticity, which tends to resist to treatment in the long term (Muller et al., 2019; Smulders et al., 2016). One of its main manifestations are gait disorders present already in early disease and evolving to seriously restraining the everyday life functional mobility. Moreover, with the disease progression, patients further develop postural instability, related to alterations in other brain regions such as frontal cortex, mesencephalic locomotor region (MLR), and the cerebellum (Peterson & Horak, 2016). The more PD advances, the more patients experience freezing of gait (FOG), characterized by a sudden arrest of gait or motor blockade of few seconds (Bloem et al., 2004; Giladi & Nieuwboer, 2008), and falls. This condition leads to serious injuries, loss of autonomy, and therefore loss of quality of life, fear of falling, depression and, eventually, death (Moore et al., 2007; Okuma et al., 2018). The appearance of postural instability and gait disturbances marks the severity and the diminished life expectancy - independently from the Hoehn-Yahr score, nor disease duration (Nutt et al., 2011; Peterson & Horak, 2016). Yet despite that 60% of patients are affected by severe FOG after 6-10 years of disease duration (Ebersbach et al., 2013), its understanding is still very limited. In fact, FOG comes and goes in situations of high stress and increased complexity, like discovering new environments, or in narrow passages. Given the heterogeneity and episodic nature of its occurrences, it is also considered the main factor for falls and comorbidities. Although FOG perceptual, emotional, and cognitive triggers have been identified, and theoretical models have been proposed, the common mechanisms underlying them haven't been clearly confirmed in humans (Bardakan et al., 2022; Ehgoetz Martens, Hall, et al., 2018; Marquez et al., 2020). In consequence, FOG remains the symptom difficult to address through classical PD therapeutics.

As mentioned, regular dopaminergic replacement treatment and/or STN-DBS have less effect on gait and balance disorders than on other symptoms, and, according to recent studies, may even become detrimental as to provoke more FOG episodes or dyskinesias in case of

dopaminergic treatment (Espay et al., 2018; Fabbrini et al., 2007; Ferraye et al., 2008; Yamada et al., 2008). Therefore, given the inefficiency of dopamine-related treatments, other experimental treatments aimed at exploring cholinergic and noradrenergic pathways suggested as additionally altered in PD with PIGD. Indeed, the malfunction of extranigral non-dopaminergic pathways, and specifically a degeneration of cholinergic neurons in the MLR, and alterations of noradrenergic system have been consistently reported (Ehringer & Hornykiewicz, 1960; Karachi, Grabli, Bernard, Tande, et al., 2010; R. Morris et al., 2019; Rochester et al., 2012; Taylor et al., 2022). Nevertheless, anticholinesterasic or methylphenidate drug (Chung et al., 2010; Moreau et al., 2012) and surgical pedunculopontine nucleus (PPN) low frequency stimulation treatments targeting these two pathways have shown unclear and disappointing results (Bourilhon et al., 2022; Ferraye et al., 2010).

To date, only the intensive and regular multimodal rehabilitation seems to alleviate PIGD in PD provided it is targeted and patient oriented (Abbruzzese et al., 2016; Ferrazzoli et al., 2018, 2020). Hence, rehabilitation programs focusing on gait and balance are widely used in clinical practice. They result in an increase in gait velocity, first step length and anteroposterior anticipatory adjustments (APA) size, along with a decrease of postural instability (Tomlinson et al., 2013). The intensity and the duration of the training seem the principal conditions that need to be fulfilled to reach satisfying results, yet scientific evidence for choosing the optimal rehabilitation protocol is still lacking (Mak et al., 2017; Tomlinson et al., 2012, 2013). Moreover, numerous techniques are being tested to assure patients' adherence (Ferrazzoli et al., 2018, 2020). In the last decade researchers proposed using the emerging field of virtual reality (VR) as means to combine different elements of existing techniques. However, we lack in understanding of how these interventions impact the brain mechanics, what are the observed effects in terms of neural mechanisms, and how they are linked to clinical measures. The main rationale of this thesis is to attempt answering these questions, specifically in frame of the rehabilitation with custom made video games for PIGD in PD.

In the first chapter I will introduce the bases of gait and posture control and the mechanisms underlying effective motor control in healthy individuals. Second chapter will focus on the neural mechanisms observed in PD patients with gait and balance disorders with FOG and falls, in order to identify disease-induced changes that the rehabilitation could act upon. Thirdly, I will try to review the existing methods of rehabilitation available for patients, their efficiency, and limitations. Highlight will be put on VR-enhanced training as the last

emerging method showing promising results so far. And finally, I will aim at introducing brain structures/networks suggested as underlying clinical changes induced by multimodal rehabilitation techniques. We will advocate that sources seem divergent and inexhaustive, as means to introduce our project in detail. Hence, the remaining manuscript will be divided in two studies: 1) “Home-based exergaming to treat gait and balance disorders in patients with Parkinson’s Disease: a phase II randomized controlled trial” and 2) “Neural mechanisms of home-based rehabilitation using serious games to treat freezing of gait in patients with Parkinson’s Disease”. The submitted articles present our protocol, used methods and results obtained with related discussions. I will end this work by a global discussion and conclusion.

State of the art

Chapter 1: Gait and balance control in humans

Mobility represents a basis for goal-oriented and exploration behaviours ruling our lives on every evolutionary level. Indeed, we move to find food, to hunt, to flee the predators, to find a mate and reproduce. To put it simply, we move to interact with our environment. Movement, and thus motor control, is at the centre of our survival, with a special role of gait and balance as elementary functions supporting it. Moreover, these functions are particularly intertwined in mammals – there is no effective gait without balance, and there is no balance without postural control. Therefore, while studying gait, we address a multilayer system implying a remarkable complexity between static and dynamic postural control, and between automated and intentional motor control systems. In this chapter I will introduce biomechanical and neural processes involved in an “isolated” and “integrated” gait condition. The first one refers to simple walking, as we measure it in clinical context, meanwhile the latter corresponds to real-life conditions integrating multi-tasking and the dynamic nature of our environment.

1.1 “Isolated” gait and balance mechanisms

1.1.1 Biomechanical perspective: from static to dynamic postural control

A. Biomechanical bases of balance

Posture may be defined as a maintained position of a body, or of its segment. Human body has a potential of an uncounted number of different postures, although they are all dependent on internal and external physical forces. In a standing position, we speak of the force of one’s mass, opposed to ground reaction force. The first one is applied to the centre of mass (CoM), situated vertically to the ankles at the level of hips. The second one acts on the centre of foot pressure (CoP), which, in a static position, can be confounded with the CoM. In silent standing, balance on this level is defined as the cancelling out of these two forces (Hamaoui, 2018; Nuic, 2020). Indeed, in order to maintain a posture, tonic muscle contractions must oppose the gravity forces on the same axis plane, thereby stabilising all body segment positions (Ivanenko & Gurfinkel, 2018). This continuous effort is observed as perpetual, short and slow displacements of the CoM in the antero-posterior axis around the ankles (D. Winter et al., 1990; D. A. Winter & Eng, 1995; Collomb-Clerc & Welter, 2015). The area of these displacements

is called a support polygon, and its limits define how far we can displace our CoM in the mediolateral axis without falling.

This brings us to balance, which, in the most simplistic way, can be described as the process of holding a stable upright posture, despite the interfering forces. Given the complexity of balance as a process, Horak and colleagues (Horak et al., 2009; Vercauysse, 2012) proposed a model defining six domains affecting it - both in maintaining a static posture (stability limits, biomechanical constraints, postural responses, sensory orientation), and in initiating gait (anticipatory postural adjustments, stability in gait). Accordingly, the fore-mentioned mechanisms of posture control need to be deployed and altered for maintaining the balance in different situations.

As previously explained, balance in standing is constrained by limited displacement range, linked to interacting physical forces and possible planes of segment's anatomical freedom. In the same manner, in case of a new external force applied to our CoM, a change in force direction or a new sensory stimulus from our body (pain, dizziness), we can experience balance disruptions and need to adapt our posture (i.e., body tilt, compensatory steps) as means to efficiently avoid falling (Vercauysse, 2012). These automated adaptations can also be considered as a transformation from static to dynamic posture control, like the one needed in voluntary movement initiation. Yet, it is important to note that volitional movement schemes are slightly different from those of the automated postural responses.

B. Dynamic balance: gait initiation and gait cycle

In fact, the muscular contraction and the initiated movement create a transitory posture and balance disruption, illustrated by a decoupling of CoM and CoP displacements (Bouisset & Do, 2008; Couillandre et al., 2000; Nuic, 2020). As a result, the opposing physical forces are not equal anymore and their product provokes a propulsion of the body in the opposite direction. In biomechanics we can clearly identify different postural adjustments preceding and following the movement (Bouisset, 1991; Bouisset & Do, 2008; Yiou et al., 2012), although in the case of gait, we will specifically dwell on the anticipatory postural adjustments (APA).

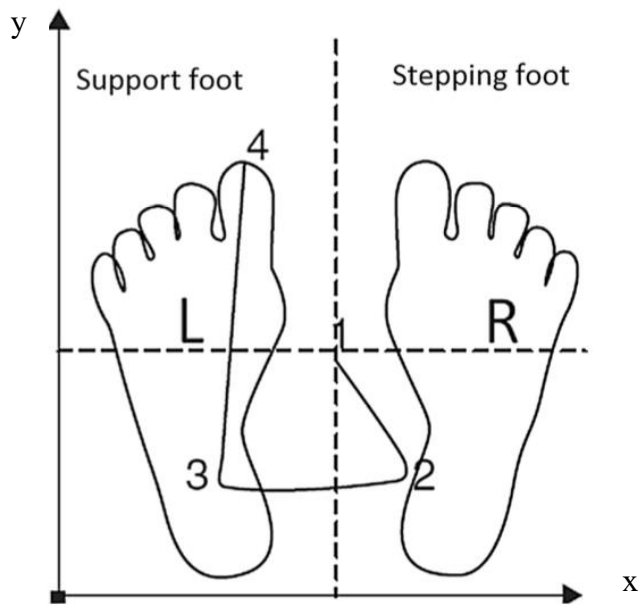


Figure 1-1: Scheme of the Centre of Pressure (CoP) displacements in mediolateral (x) - anteroposterior (y) axes during the Anticipatory Postural Adjustments (APA) in gait initiation.

The displacement starts at Centre of Mass (CoM; 1), and shifts backwards through the swing leg's heel (R), and laterally towards the heel of the stance leg (L; 2-3). Finally, the CoP is propelled forward (4), definitely unloading the swing leg (R) and allowing to lift the heel off the ground.

Adapted from Maslivec et al., 2020.

Indeed, before starting a movement we must assure our balance at all times. It means that before lifting the swing leg, one should first reduce the support basis and transfer it to the stance leg. Indeed, the APAs consist of moving the CoP backward towards the swing leg, then towards the heel of the stance leg, and finally its tip, thereby fully liberating the swing leg from any supportive function (Figure 1-1, Maslivec et al., 2020). In this manner the CoM is transferred forward, giving the propulsion needed for the movement. Hence, the APA end at the event of lifting the swing leg's heel from the ground and make the gait execution possible. Naturally, they are also predictive of gait characteristics – APA size in the antero-posterior axis conditions the length of the first step and

its velocity, meanwhile the medio-lateral displacement is linked with the size of the support polygon during gait (Caderby et al., 2014; Nuic, 2020; Yiou et al., 2017).

We can then observe the swing phase, characterised by CoM fall forward, until the posterior leg muscles don't start to slow it down, just before the ground reaction forces break the fall of the swing leg (Hase & Stein, 1998). The latter takes the role of the support leg, moving the CoP to its heel, and then under the foot tip, making the stance leg become a swing leg in the next step. This process is then repeated as long as one continues to progress (Azulay et al., 2009; Chastan et al., 2009; Collomb-Clerc & Welter, 2015; Nuic, 2020). However, given the specificity of the preparation phase, only the first step is considered as gait initiation. The steps executed after that fall under the phase of gait cycle.

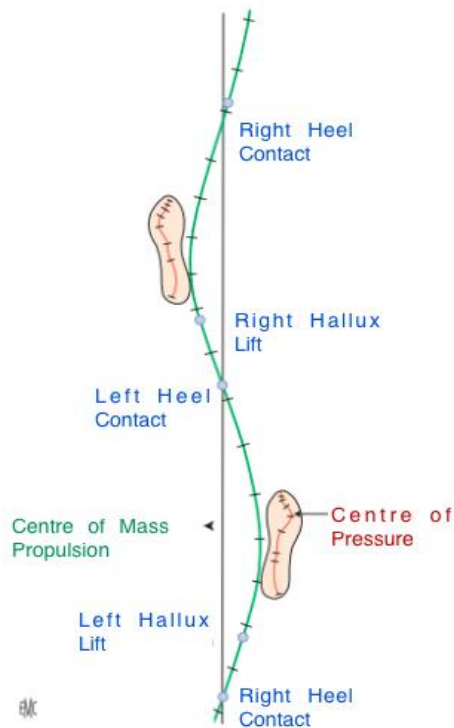


Figure 1-2: Scheme of the gait cycle.

Displacement of the centre of pressure (CoP; in red) and the centre of mass (CoM; in green) during the gait cycle along the antero-posterior axis. Gait moments (in blue) start with the Right Heel Contact after the gait initiation, followed by the Left Hallux Lift and the Left Heel Contact during the left leg swing phase. The gait cycle finishes by the Right Hallux Lift to come back to the Right Heel Contact.

Adapted from Azulay et al., 2009, courtesy of D.Nuic.

It is noteworthy that the balance conserving mechanisms during the gait cycle are more nuanced than during its initiation. The reason for that is the constant movement of CoP and CoM, as you can see on the Figure 1-2. It shows the conservation of the CoM inside the support polygon and on the inside border of the stance foot, albeit demanding dynamic control of its changing velocity and position (Azulay et al., 2009). Muscle contractions must be activated in alternation with respect to gravitational forces, in order to keep moving forward the CoM (Lepers & Breniere, 1995; Nuic, 2020).

The cycle is usually defined between the first swing leg's contact with the ground and the subsequent contact of the same foot (Carcreff et al., 2016). In between we can distinguish the alternating swing and stance phases of both feet, with a transitory double stance (DS) period, when the mass is transferred from one foot to the other, and so when both feet touch the ground at the same time (**Figure 1-1**, Azulay et al., 2009; Nuic, 2020). In normal condition, the stance phase represents about 60% of the cycle, with only 10% of the cycle corresponding to the DS. The remaining 40% of the cycle is the swinging phase (Azulay et al., 2009; Carcreff et al., 2016).

In humans, all these interacting biomechanical processes of postural control and balance are most of the time subconscious and automatised, even though they are modulable when needed, and adapted according to voluntary movement initiation. This equilibrium between automatised and volitional control is inherent to the neural networks underlying the postural control and locomotion.

1.1.2 Neural perspective: from automated to voluntary motor control systems

A. Anatomical bases of locomotion

Locomotion is supported by a large, interconnected circuitry involving different levels of nervous system, including spinal cord, brainstem, basal ganglia, thalamus, cerebral cortex, and cerebellum (Takakusaki, 2017; Takakusaki et al., 2003a, 2008). In a very general manner, posture is maintained constantly by spinal nervous reflexes, which themselves are dependent on inputs from sensory and vestibular system. Meanwhile, when initiating movement, the information coming from the premotor and motor cortex is transferred through thalamo-spinal tract and coordinated via spinocerebellar and cerebellothalamic tract. All input information is

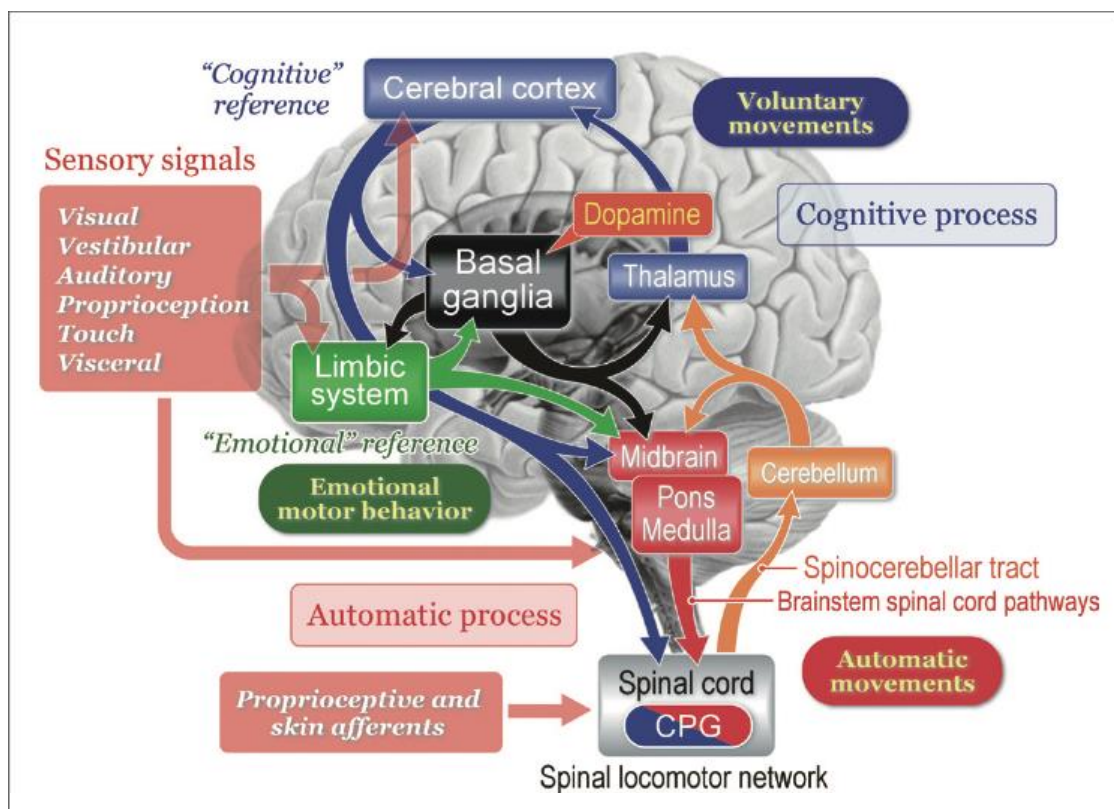


Figure 1-3: Brain networks involved in postural control.

The postural control is executed at multiple levels starting with afferent signals from visual, vestibular, auditory, proprioceptive, and visceral receptors. These signals contribute to creating an integrative image of one's body in the surrounding space in order to make reaction (emotional motor behaviour) and interaction (voluntary movements) possible. The information is further filtered by the cortico-subcortical loops (cerebral cortex, basal ganglia, thalamus) and modulated through the spinocerebellar and cerebellothalamic pathways. Automatic processes are assured at all times by the postural reflexes (brain stem, spinal cord), while cognitive postural control is necessary for motor learning.

Takakusaki et al., 2017

filtered, and outputs modulated accordingly by basal ganglia: responsible for “fight or flight” behaviour, as well as for goal-directed behaviours.

When we get more into details, we remark that all involved structures are interconnected through parallel mechanisms of multi-level motor control (Figure 1-3, Takakusaki, 2017). Usually, we separate these systems into four groups of neural circuits: descending motor commands, basal ganglia, cerebellum, and motoneuron-related (Figure 1-4; Grabli et al., 2012; Purves et al., 2004). In fact, derived from animal electrophysiology and human functional imaging, we observe parallelly the cortical efferent projections directly to the spinal interneuron groups, and the indirect cortical projections through basal ganglia and brainstem locomotion centres. The cerebellum participates indirectly through its bidirectional communication with the cortex, the basal ganglia, and the brainstem. Particularly noteworthy are the independent direct loops between cortico-subcortical, cortico-cerebellar, ponto-subcortical, ponto-cerebellar structures, and indirect loops between cortico-pontine, cortico-spinal, and subcortico-cerebellar regions.

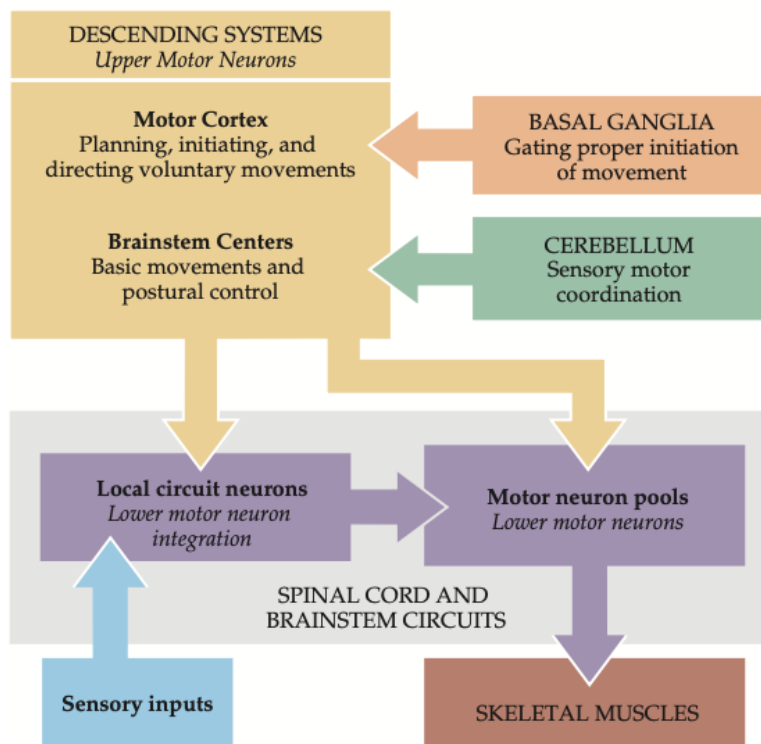


Figure 1-4: Overall organisation of the motor control brain structures separated into four subsystems.

Organisation of the neural systems of the motor control in 1) cortical paths and brainstem centres descending towards 2) local spinal circuits which are modulated by 3) the basal ganglia and 4) the cerebellum.

Purves et al., 2004

In this manuscript I would like to present a less localizationist perspective on networks underlying effective gait and balance. I will argue that the activity of locomotion circuits is distributed along clear functional and hierarchical axis. As a matter of fact, according to the literature (Grabli et al., 2012; Purves et al., 2004; Takakusaki, 2017) we can distinguish a clear

hierarchy with 1) higher order mechanisms involving cognitive resources, in order to prepare, execute, and learn motor behaviours in different situations; 2) those modulating the effective motor commands, assuring adapted behavioural responses to unexpected inputs (internal and/or external), and participating in creation of motor automatisms; 3) and finally those more elementary, lower order neural organisations responsible for motor execution, reflexes and background activity in posture maintenance. In line, I would like to focus on a continuum from the statical posture maintenance, through volitional movement and its execution, to the skill automatization. In this part I will start by presenting the smallest building blocks of gait and balance control, such as the fully autonomous musculoskeletal and peripheral nervous system. Then, I will dwell on higher order mechanisms involved in motor planning, initiation, and activation of the forementioned elementary circuits. And finally, I will end by presenting the modulation mechanisms responsible for motor adaptation and learning.

B. Gait and posture: lower order processing

At the automatised level, the mechanisms of multisensory integration in proprioception, conveying the information from the peripheral nervous system seems to be an evident starting point for all motor command. Indeed, as means to execute the most efficient and precise movement one must first identify the position of all body segments in space, relative to the surroundings and to each other. These afferent signals from auditory, visual, vestibular, and visceral systems allow to create an internal representation of our body in the surrounding space. It is further integrated in the posterior parietal cortex and transferred to the supplementary motor area (SMA) for higher order processing - necessary to adjust the motor plan and movement parameters accordingly. Thus, fully functional proprioception is necessary for motor control, movement, and interaction with the world.

Among the proprioceptive signals, the muscular tonus is of particular importance in posture regulation. As a matter of fact, it is transmitted directly to the spinal cord, where the **spinal interneurons** regulate the transitory tension in all skeletal muscles. These **spinal reflexes** make it possible to hold different positions of each body segment, but they are also essential to preserve our body from any harm: including falls, fractures, etc. In case any of the muscular sensory receptors detect pain or pressure, they send an excitatory impulse to the spinal cord, thereby activating the interneurons acting on the motoneurons, causing a reflexive contraction (Sherrington, 1906). Nevertheless, in the absence of any afferent or efferent

somatosensory signals, postural and gait-like musculoskeletal patterns can be elicited and modulated through stimulation of the midbrain.

Indeed, Takakusaki and colleagues (2016) have demonstrated activation of the dorso-medial part of **pontomedullary reticular formation** during muscular atonia and the ventromedial part during hypertonus, present in reflex standing in decerebrated cats. In fact, the animal models studied in-vitro (Cazalets et al., 1992; Grillner & Wallen, 1985) and in-vivo (Hagglund et al., 2010) confirm the autonomy of these circuits, showing a synchronised activity of muscle groups, axially alternating, without any supraspinal control (Takakusaki et al., 2003b, 2004) both for postural control and gait-like movement.

It is particularly striking during gait, because we can observe sequential and organised activations of excitatory and inhibitory ponto-spinal interneurons acting on motoneurons of antagonist and agonist muscle groups. This rhythmical activity was shown to be controlled by **central pattern generators (CPG)**, which are principally situated in the **medulla and pons of the brainstem** (T. G. Brown, 1914; MacKay-Lyons, 2002). CPG ensure the coordination between limbs and the spatio-temporal patterns of firing in associated muscle groups, related to automatic spinal reflexes (Drew et al., 2004). Moreover, Hinsey, Ranson, and McNattin (1930) have shown that sectioning the forebrain at the precollicular-premamillary level in cats doesn't stop them from "eliciting locomotion with well-coordinated postural control" (Takakusaki, 2017). While, when the section is done between precolliculus and post-mammillary axis, electrical or chemical stimulation of lateral mesencephalic locomotor region (MLR) provokes locomotion. The more intense is the stimulation, the higher is the resulting pace (Shik & Orlovsky, 1976). This highlights the major modulatory role of the midbrain structures. These results were equally corroborated in other animal species like lampreys, salamanders, rats, rabbits, and guinea pigs (Ryczko & Dubuc, 2017), therefore bringing to light the hierarchy of the automatised posture and gait control processes. Despite that the CPG have only been demonstrated in animal studies, identical alternating patterns of grouped muscular activation during gait and posture have been identified in human gait – specifically in the cervical-lumbar spinal region (Hinneken et al., 2018). These data clearly suggest similar neuronal organisation among animal species for locomotion.

C. Higher order motor control systems

As previously introduced, sensory, vestibular, and visceral information is integrated in cortical structures in order to create a representation of one's body in space – necessary to further plan and execute movements. As one can imagine, and as already explained, motor initiation isn't restrained to a simple motor command. It demands preparation and/or planning, as means to execute a precise movement using an optimal amount of resources. In case of gait and balance control, sensory information is integrated and used to prepare possible motor commands adequately. The information is transferred from the posterior-parietal cortex, where the body scheme is continuously communicated to the SMA, responsible for motor planning. When one wants to initiate the movement, motor intention is sent from the prefrontal cortex to the SMA, and so, through the cortico-reticular and reticulospinal tracts, needed APA are executed (Figure 1-5; Takakusaki, 2017). Finally, SMA communicates the following motor

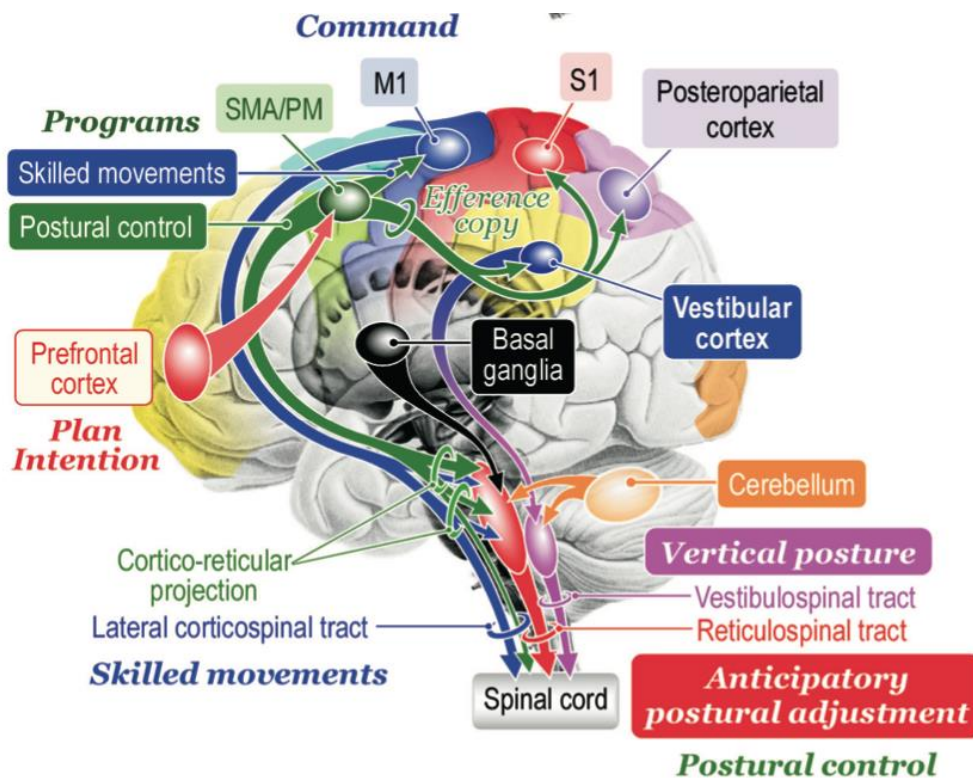


Figure 1-5: Brain mechanisms of motor command initiation.

The goals, intentions, and motor plans are sent from the prefrontal cortex to the premotor regions (SMA) which transfers a copy of the future action to the primary sensory (S1), vestibular, and posterior parietal regions. SMA further stimulates the cortico-reticular projection thereby triggering the anticipatory postural adjustments (APA). Once the movement is well learnt and goal directed, the motor programs from the SMA are sent to the primary motor cortex (M1) responsible for generating movement through cortico-spinal tracts. All these processes are modulated by the basal ganglia, the cerebellum, and the vestibular cortex.

Takakusaki, 2017

schemes to be executed to the primary motor cortex (M1). When the latter is activated, it sends the motor command through the cortico-spinal tract (Figure 1-5; Takakusaki, 2017).

Once the movement is initiated, the dynamic control from the higher order control systems is only needed in case of unexpected events. Hence, the afferent signals from visual, proprioceptive, and vestibular systems update regularly the body scheme, help us judge our balance and our capacity to move, thereby requiring an adaptation of the posture and of motor planning for the upcoming movement if needed. These visuomotor cognitive processes involve posterior parietal cortex, cerebellum, and basal ganglia, and seem necessary for accurate and dynamic motor control (Takakusaki et al., 2008).

Simultaneously, sensory information is transmitted to the hippocampus responsible for spatial memory, as well as short-term memory, making it possible to choose and update the trajectory correspondingly to the identified obstacles (Figure 1-6; Takakusaki, 2017). These mechanisms also contribute to the motor learning by creating associations between different sensory stimuli and related motor schemes, as well as to the creation of a mental map of the surroundings that will be stocked for future (McVea & Pearson, 2006, 2007; Takakusaki et al., 2008). Indeed, the long-term memory is equally important while planning a trajectory, be it for distance differences, or for difficult, painful, or emotional memories related to a place (Chun & Jiang, 2003; Galvez-Marquez et al., 2022).

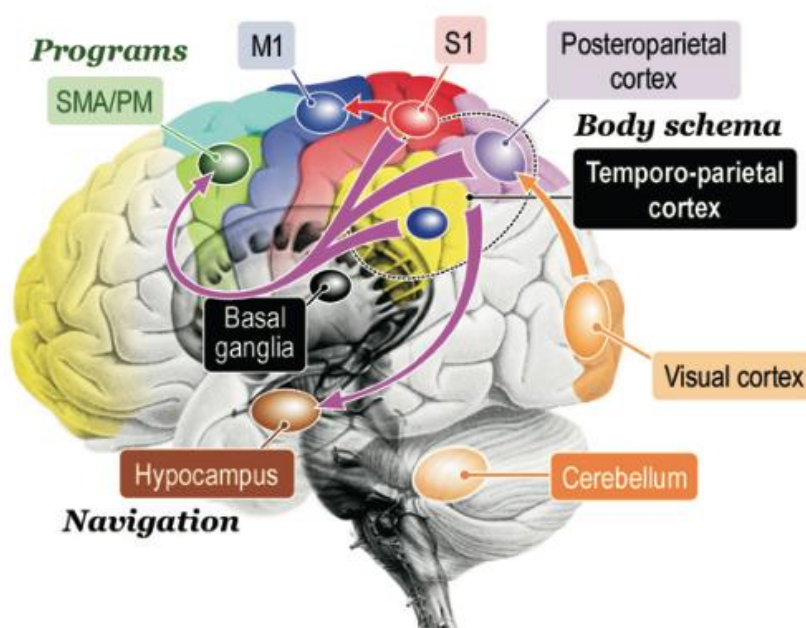


Figure 1-6: Transfer of bodily information for motor planning and adaptation.

The body schema is the result of the integration of sensory, vestibular, and visual information in the temporo-parietal cortex. They are further transmitted to the SMA for motor planning adaptation, and to the hippocampus for spatial navigation of future behaviours.

Takakusaki, 2017

Overall, this hierarchical and bi-directional communication between motor, sensory, modulatory, and cortical regions permits the muscles to react to eventual sudden changes in the gravitational force, the ground structure, or other external/internal factors demanding an adapted motor behaviour (MacKay-Lyons, 2002). Executive functions and cognitive resources are even more recruited in real-life conditions of a dynamically changing environment.

D. Modulatory control systems (Midbrain, Basal Ganglia, Cerebellum)

As mentioned, while suggesting the independence of the spinal reflexes from the sensory inputs and the cortical control, the importance of the **midbrain nuclei, basal ganglia and cerebellum as modulators** of this spontaneous and volitional activity has been highlighted and demonstrated. In the literature (Bardakan et al., 2022; Bohnen & Jahn, 2013) we distinguish three main modulator regions at this middle-level of control: **the cerebellar locomotor region (CLR), the subthalamic locomotor region (SLR) and the mesencephalic locomotor region (MLR)**. In fact, the electrical stimulation of the MLR and of the SLR have respectively induced gait initiation and normal gait pattern (Takakusaki, 2017). The stimulation of the CLR led to coordinated quadrupedal gait pattern and when stimulated repeatedly to increased tonic muscle activities in the neck, lumbar back, fore and hind-limb extensors (Asanome et al., 1998; Mori et al., 1999). In the following part we will take a closer look at each region separately, to better understand how their activity and interaction give the possibility to control, adapt, and change the movement through inputs from the higher order processing and their outputs to the CPG.

- Midbrain modulators

The MLR was first identified in cats (Shik et al., 1969) as inducing rhythmic, coordinated stepping movements when electrically stimulated. MLR is composed of the **pedunculopontine nucleus (PPN)** and the **cuneiform nucleus (CN)**. Both nuclei are located in the reticular mesencephalic formation, and composed of GABAergic and glutamatergic neurons, the difference between them is marked by the presence of cholinergic neurons in the PPN pars compacta (Mesulam et al., 1989; Olszewski & Baxter, 1954).

Interestingly, studies in cats and rodents have shown the complementary roles of each nucleus: the PPN being more involved in the **tonus control** and the CN more responsible of **regulation of the pace** (Grätsch et al., 2019; Takakusaki et al., 2003b, 2016). The latter is supposedly a response to “fight or flight” type of stimuli, given a structural connectivity of the

CN with the limbic areas of the basal ganglia and of thalamus, and with amygdala (A.-S. Rolland et al., 2011; Sébille et al., 2017a; Veazey & Severin, 1980). Moreover, low frequency (20-60 Hz) electrical stimulation of PPN, as well as repeated stimulation of the CN provokes locomotion movements in decerebrate animals and alert cats (Takakusaki et al., 2003b, 2016), while repeated stimulation of PPN provokes postural atonia (Takakusaki et al., 2003b, 2004). According to Maloney and colleagues (1999, 2000), as well as other evidence from pathological models discussed further, these structures seem to be a part of a bigger modulatory system.

Indeed, in primates PPN receives input from sensorimotor, associative, and limbic anatomo-functional territories of basal ganglia, cortex and cerebellum (Jenkinson et al., n.d.; Lavoie & Parent, 1994; Sébille et al., 2017). The majority of cortical projections come from premotor cortices, which suggests its participation in motor planning and initiation – as

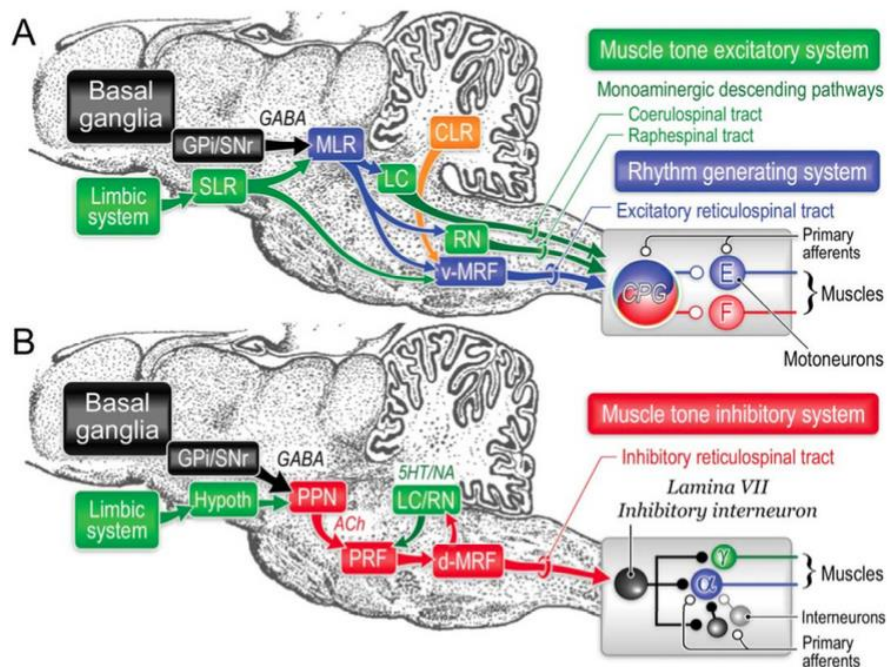


Figure 1-7: Pedunculopontine Nucleus (PPN) and Cuneiform Nucleus (CuN) control scheme in cats.

A. CuN (here MLR) pathways of muscle tonus activation and locomotor rhythm generation via the reticulospinal tract in ventro-medial reticular formation (vMRF). Afferent pathways from the basal ganglia and parallel projections from the subthalamic and the cerebellar locomotor regions (SLR & CLR), and from locus coeruleus (LC) and raphe nuclei (RN) are equally represented. **B.** Muscular tonus inhibitory pathways from PPN via pontal (PRF) and dorsomedial (d-MRF) reticular formation.

Takakusaki, 2013

forementioned. In addition, PPN sends efferent outputs to the reticulospinal tract, locus coeruleus, and raphe nucleus, as well as afferent outputs to the thalamus, pallidum, STN, and SNc (Figure 1-7; Jenkinson et al., 2009; Takakusaki, 2013, 2017; Takakusaki et al., 2016). The

excitatory action of the cholinergic neurons of PPN generates an inhibitory impulse of the reticulospinal neurons to the motoneurons controlling the locomotion (Takakusaki et al., 2004, 2016), and thus a possible movement arrest (Grabli et al., 2013; Karachi, Grabli, Bernard, Tandé, et al., 2010). Meanwhile, the activation of noradrenergic coeruleo-spinal and coeruleo-cerebellar excitatory tracts is linked to the autonomic regulation and postural reflexes. The serotonergic raphe-spinal neurons seem to influence the timing of muscular discharges and their pattern (Grabli et al., 2012; Timmann & Horak, 1997). Therefore, the less they are excited, the less accurate is the timing of muscular antagonist activation pattern (Dunbar et al., 2010; Grabli et al., 2012).

Ever since, PPN has been proven active in humans during real and imaginary gait, suggesting its supplementary contribution to motor planning (Jahn et al., 2008; B. Lau et al., 2015; Marchal et al., 2019; Tattersall et al., 2014). All these data suggests that MLR nuclei are implicated in complex gait and posture control, beyond the purely motor mechanisms. Their communication loop with basal ganglia is to be particularly highlighted.

- **Subcortical modulators**

Precisely, when we focus on subcortical structures one must first remember that they contain important nuclei implicated in reinforcement learning (Schultz et al., 1997), action-result associative learning (Balleine & O'Doherty, 2010), selection of context-adapted choice in case of competing demands (Redgrave et al., 1999), decision making (Cavanagh et al., 2012; Frank et al., 2007; Jahanshahi, Obeso, Rothwell, et al., 2015), and finally, motor control and initiation (DeLong et al., 1984).

Basal ganglia are composed of the striatum, the pallidum (external and internal parts), the substantia nigra (SN) and the STN. Striatum is one of the main entries to the basal ganglia circuit: be it for the thalamus, the amygdala, the globus pallidus externus (GPe), the serotonergic raphe nucleus (RN), the cholinergic PPN, or for the various cortical regions ranging from prefrontal, through motor, to parietal regions (Dudman & Krakauer, 2016a; Joel & Weiner, 1994; Nambu, 2011). It is anatomically divided in dorsal part (caudate nucleus and putamen) and ventral part (nucleus accumbens), meanwhile its functional territories are distributed depending on the efferent cortical and subcortical projections it receives (Javanshahi et al., 2015). Three separate functional loops have been proposed: sensorimotor, associative,

and limbic ones (Figure 1-8; Alexander et al., 1986; Draganski et al., 2008; Jahanshahi et al., 2015).

According to studies in immunohistology (Karachi et al., 2002) and imagery (Lehéricy, Ducros, et al., 2004; Lehéricy et al., 2005) in humans, the STN, the globus pallidus internus (GPi), and the SNr structures show topological rostro-caudal organisation of these functional territories. Yet it is noteworthy that these territories are partly overlapping, hence they are implicated in different degrees in all functional loops (Figure 1-8; Haber, 2003; Haynes & Haber, 2013; Joel & Weiner, 1994, 1997; McFarland & Haber, 2002).

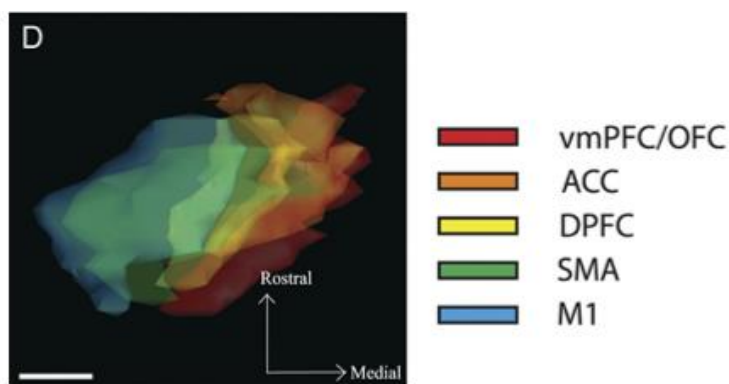


Figure 1-8: Axial view of the overlapping dense projections from different functional cortical regions on the subthalamic nucleus (STN) in primates.

Projections to the STN from cognitive-associative (vmPFC/OFC, ACC, DPFC) and motor regions (SMA, M1)

Haynes & Haber, 2013

As presented on the Figure 1-9, striatal GABAergic neurons have two direct projections to basal ganglia outputs: the fore-mentioned SN pars reticulata (SNr), and the globus pallidus internus (GPi), both acting on the thalamus and the superior colliculi through the GABAergic projections themselves. Overall, these striato-pallido-nigral projections have an excitatory effect on their final outputs, which corresponds to what is called **the direct pathway**. Inhibiting the basal ganglia output structures, is equivalent to loosening of the brakes on the other structures' activity, for they act principally as an inhibitor of the motor commands from the cortex (Albin et al., 1989; Alexander & Crutcher, 1990). Moreover, **the indirect pathway** from the striatum consists of the GABAergic projections to the globus pallidus externus (GPe), thereby disinhibiting the STN. STN is therefore excited, and through its glutamatergic projections induces an excitation of the output structures. The indirect pathway has a major role in stopping the ongoing and/or inappropriate movements - the higher is its activation, the higher stimulation of the SNr and GPi. The balance between both pathways is assured by SN pars compacta (SNc) projections to the striatum - depending on type of the targeted neuroreceptor, D1 or D2, the dopamine will either activate the direct or indirect pathway, respectively (Gerfen et al., 1990). Nevertheless, one must keep in mind that this modulation it is not purely

dichotomic. Indeed, both pathways seem to be activated during movement initiation, movement arrest, and behavioural sequence initiation (Cui et al., 2013; Jin et al., 2014; Schultz, 2013).

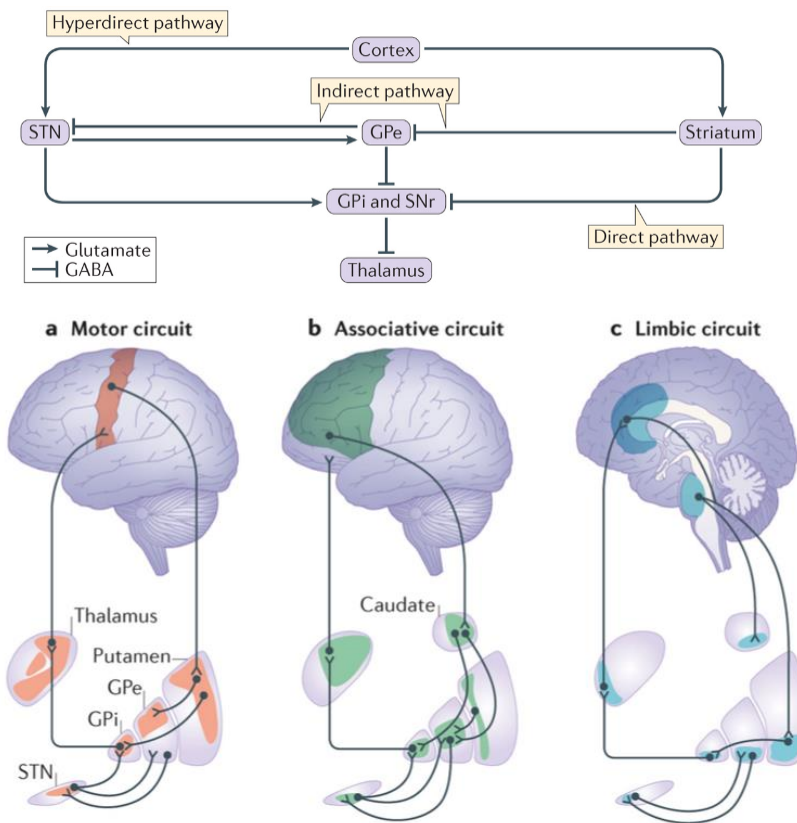


Figure 1-9: Models of the functional organisation of the basal ganglia.

Graph presents direct, indirect, and hyperdirect pathways of cortico-thalamic communication via the basal ganglia inputs: striatum (caudate, putamen) and subthalamic nucleus (STN), which further inhibit (GABA) or activate (Glutamate) the globus pallidus externus (GPe) and internal (GPi), substantia nigra pars reticulata (SNr) and thereby the thalamus.

a-c. The schematic models of the functional cortico-subcortical loops. Motor, associative, and limbic regions are present in all basal-thalamic structures.

Jahanshahi et al., 2015

Obviously, the striatum doesn't limit its influence to the subcortical output, but also reaches the cortico-thalamic loops (Alexander, 1994; Alexander et al., 1986; Alexander & Crutcher, 1990). In fact, the information coming from the peripheral systems integrated in the SMA is further processed and filtered by the striatum (Mink & Thach, 1991; Waldschmidt & Ashby, 2011) before being sent to the primary motor cortex (M1). According to Kable & Glimcher (2009), striatum would proceed to an evaluation of the outcomes of each possible movement before the motor scheme choice, and to their re-evaluation once the action is executed, in order to assign specific stimuli to specific motor schemes, and finally to their outcomes. This specialisation and motor scheme filtering is achieved through dopaminergic neurons activity – dopamine acting as a reward when a movement has a successful outcome and keeping this positive valence association for the future motor scheme choices (Ruff & Fehr, 2014; Schultz, 2013). In fact, motor affordances, that is the preference, and hence the activation, of the right motor scheme in a given context, are a result of successful reinforcement &

associative learning through dopamine liberation (Ernst & Paulus, 2005; Schultz, 2002). This cortico-nigrostriatal loop also assures the reinforcement of circuits often used together – making the skill automatization possible (Schultz, 2013). Pessiglione and colleagues (2003, 2004, 2005) have shown that in case of dopamine depletion in non-human primates, after learning a reach-target task, when an obstacle is placed between the individual and the target, the adjustment of movement is never retained between trials, with a movement trajectory impairment.

Once filtered, the descending signals can be further modulated through non-dopaminergic centres (MLR, cerebellum), which then communicate back with the basal ganglia, and with the circuits involved in direct control of automatised motor mechanisms. In fact, it is important to remind that SNr is involved in modulation of MLR activity, as well as directly in muscle tone and locomotion modulation. GABAergic projections to the PPN and the CN create a passage for tonic inhibitory signals from the basal ganglia (Menard et al., 2007; Takakusaki et al., 2003b). Therefore, SNr stimulation is known to increase muscular tonus, lengthen the time to initiate the movement, and the gait cycle duration, thereby decreasing the effects of PPN and CN activations (Takakusaki et al., 2003b).

Beside the direct and indirect pathways, the literature describes also an even faster inhibitory tract demonstrated in primates, that is **the hyperdirect pathway** – excitatory projections coming from the cortex directly stimulating the STN, forcing the movement arrest through SNr and GPi (Nambu, 2004; Nambu et al., 1996, 2002). This pathway is particularly involved before the motor choice in inhibiting all movements, and during the execution in suppressing the competing motor schemes. Beyond the hyperdirect pathway, STN receives similar projections to those in striatum, including the thalamus, the PPN, the forementioned GPe and the SNc. It is mostly composed of glutamatergic neurons, which show a phasic discharge during movement (Rinvik & Ottersen, 1993; Takakusaki et al., 2004). Recently, studies on common basalo-cerebellar modulation network in non-human primates have equally demonstrated STN's projections to the cerebellum, probably through its outputs to the pontine nuclei (Figure 1-10; (Bostan et al., 2010; Brodal, 1979; Jwair et al., 2017).

This hypothesis was partly confirmed in rats by studying STN deep brain stimulation (DBS) effects on the cerebellar activity. When stimulation was applied, researchers observed a reduced STN activity, with, in consequence, a disinhibition of the cerebellar nuclei activity (Bostan & Strick, 2018; Moers-Hornikx et al., 2011; Sutton et al., 2015). Therefore, this suggests that STN has a direct and indirect influence on extra-basal modulatory structures (Figure 1-10). These modulatory tracts' activity is itself modulated through the dopaminergic input from the substantia nigra pars compacta (SNc) - to the striatum and to the STN.

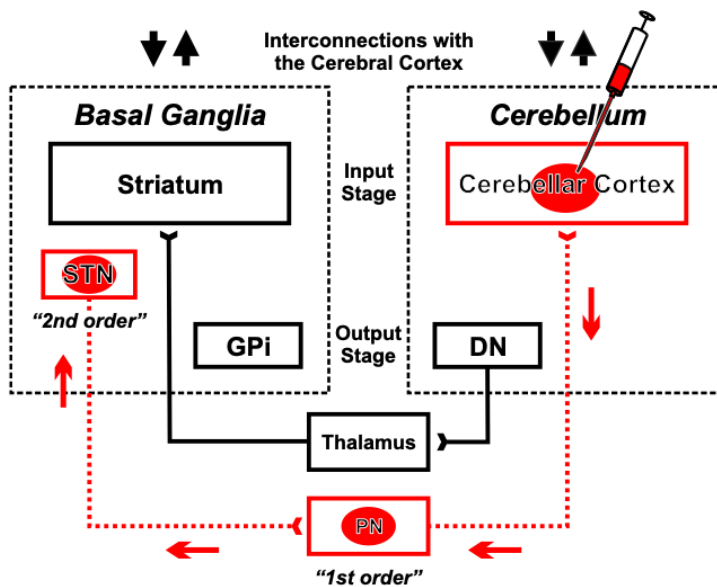


Figure 1-10: Disynaptic projections from the subthalamic nucleus (STN) to the cerebellar cortex in primates.

Rabies virus injected to the cerebellar cortex in monkeys showed labelled neurons in the STN and other basal ganglia structures in a paradigm of the retrograde trans-neuronal transport.

Bostan et al., 2010

- **Cerebellar modulators**

One of the non-dopaminergic modulatory centres implicated in the motor control and learning, and in the automatic processing is the cerebellum. It has long been considered a basic region for the motor coordination, balance, and voluntary and automated movement adjustments – an online correction centre for motor errors. Although, following studies of Masao Ito (1982, 1993, 2000), other authors have recently confirmed cerebellar role in feedforward control (Bastian, 2006), motor learning (Boyden et al., 2004; Diedrichsen et al., 2005; Doya, 2000; Ito, 2000), and motor memory retention (Herzfeld et al., 2014; Liebrand et al., 2020).

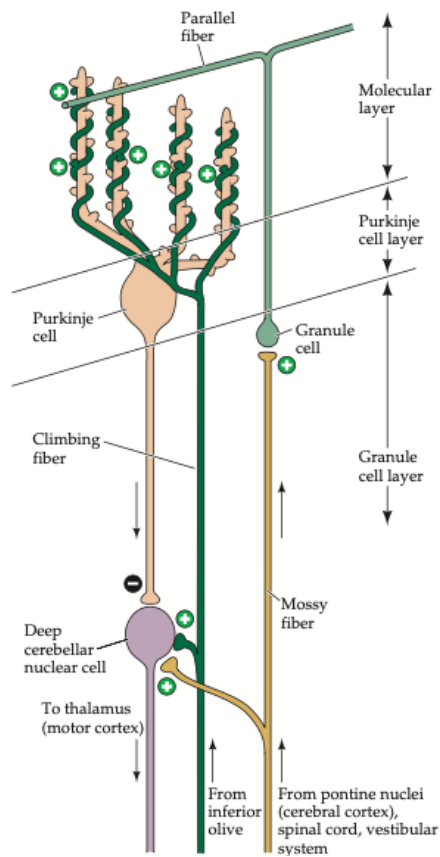


Figure 1-11: Anatomical organisation of cerebellar inputs and outputs.

Excitatory (+) and inhibitory (-) projections from pontine nuclei and inferior olive towards the cerebellar cortex and deep cerebellar nuclei, themselves projecting to the thalamus.

Purves et al., 2004; Stein, 1986

First of all, cerebellum has four main inputs: mossy fibers, climbing fibers, pontine and vestibular nuclei (Figure 1-11; Apps & Garwicz, 2005; Purves et al., 2004). These projections assure the input of proprioceptive, sensory, and vestibular signals, as well as those of motor planning and the feedback information for timing and accuracy of executed movements (Stein, 1986; Zhang et al., 2016). However, cerebellum has only one output structure – the GABAergic Purkinje cells, which further project to vestibular nuclei and through deep cerebellar nuclei (cerebellar white matter) to the thalamus nuclei, brainstem reticulate formation, inferior olive, and red nucleus (Purves et al., 2004; Stein, 1986). The latter are the basis of cerebellar communication with the basal ganglia, midbrain, and the cortical structures.

The vestibular nuclei are involved in motor coordination and control of balance (Ito, 1982; Takahashi & Shinoda, 2021). Indeed, as shown in decerebrate cat the stimulation of the vestibulospinal tract provokes excitatory signals to the extensor motoneurons, and inhibitory signals to flexor motoneurons of hindlimb muscles, thereby assuring the inter-muscular coordination (Grillner et al., 1970; Takahashi & Shinoda, 2021). Meanwhile, the lateral vestibular nucleus, seems to be involved in keeping the balance of head and body (Shinoda et al., 2006). Other vestibular nuclei (flocculus) are equally involved in modulating the oculovestibular reflex in cats and rabbits. Their projections to the midbrain serve to coordinate and predict the interaction between visual and vestibular systems (Ito, 1982). The mechanisms involved in this circuit also served to demonstrate the modulatory role of the cerebellum. In case of long-lasting changes in the visual input, long term depression and potentiation were observed in the cerebellar synapses, thereby making it possible to integrate and automatize new state-dependent behaviour of both systems (Takahashi & Shinoda, 2021). Furthermore, this kind of processing being characteristic of motor learning, cerebellar circuits

have thereby joined the vast circuitry implicated in motor automatization, beyond the online movement adjustment.

In fact, cerebellum has long been considered an online corrector of movement – its activity was perceived as reactive to the sensory feedback during and after the movement execution. The feedback is thought to be integrated through the vermal and paravermal cerebellum, before being transmitted to the cerebellar cortex for further processing (Jahn et al., 2008). If an error was identified, adjustment parameters were sent back to the motor cortex either through the cerebellar nuclei and the thalamus, or the pontine nuclei, in order to correct it (Bostan et al., 2010; Bostan & Strick, 2018). The correction can be applied instantly or learned through time – providing evidence that cerebellar neural processing ranges from milliseconds (through the cortico-pontine pathway) to days (Heck et al., 2013; Miall & Jenkinson, 2005). It is noteworthy that this type of learning is efferent-dependent: an adaptation learned for an upper limb will not activate the same regions in the cerebellum, as the ones learned for the visual system (Miall & Jenkinson, 2005).

It has also been proposed that cerebellum is not only creating adjustments following feedback information, but equally computing the feedforward predictions of the posture and the expected sensory input post-motion (Morton & Bastian, 2006). Studies in humans helped to discriminate the feedback-based predictions from those feedforward (Bastian, 2006; Diedrichsen et al., 2005; Morton & Bastian, 2006). They've argued the independence of these two processes, as well as different degrees of their dependency on the cerebellum. Feedforward control in patients with cerebellar lesion was clearly impaired compared to healthy subjects, meanwhile the reactive online control was maintained. In addition, trial-by-trial learning from error did not occur, as it relies on the successful proactive movement control. Recent studies continue to show that stimulation of the cerebellum may increase the capacity to learn from error, and quickly decrease the number of errors, therefore enhancing the process of motor automatization (Bastian, 2006; Diedrichsen et al., 2005). These motor learning mechanisms are equally supported by studies on basalo-cerebellar common circuitry demonstrating indirect projections of the cerebellum to the striatum and the GPe (Bostan et al., 2010, 2013; Bostan & Strick, 2018). In fact, through its outputs to the thalamus (through the cerebellar nuclei), cerebellum participates in inhibiting and reinforcing cortico-striatal associative learning. In the same manner, its GABAergic projections to the indirect pathway further modulate the basal ganglia inhibitory circuits (Figure 1-12 ; Bostan et al., 2013; Bostan & Strick, 2018).

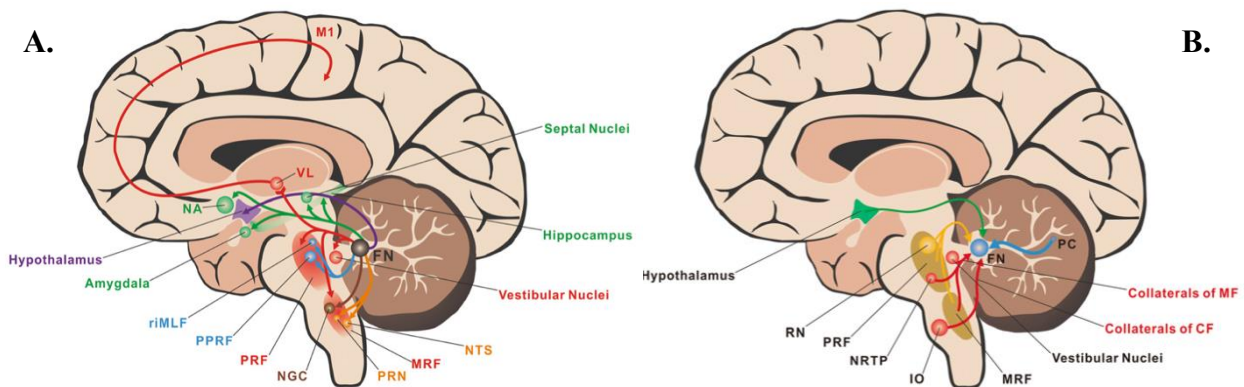


Figure 1-12: Location, efferent (A.) and afferent (B.) pathways of the fastigial nucleus (FN), corresponding to the cerebellar locomotor region (CLR).

A. FN situated in the midline cerebellar cortex was identified by Jahn and colleagues (2007) as the CLR because of its direct axial and proximal motor (red) and oculomotor (blue) efferent projections. Emotional (green), and visceral (purple, orange, brown) pathways have also been reported. FN projects indirectly to the primary motor cortex (M1), through the ventrolateral nucleus of the thalamus (VL), and directly to the pontine nuclei (PRN, PPRF, PRF), the amygdala and the nucleus accumbens (NA).

B. From inside the cerebellum, the Purkinje cells (PC) send inhibitory GABAergic inputs (blue) to the FN. From the other side, it receives excitatory glutamatergic (red) input from the vestibular nuclei, the inferior olive (IO), and the nucleus reticularis tegmenti pontis (NRTP); as well as serotonergic projections from the pontine and medullary reticular formations (PRF, MRF) and from the raphe nucleus (RN). It is noteworthy that the pontine nuclei may indirectly provide inputs from the basal ganglia, as proposed earlier (not presented).

Zhang et al., 2016

When it comes to the cerebellar direct relation to gait, the evidence of the cerebellar locomotor region (CLR) corresponds to the fastigial nucleus in midline cerebellum (Figure 1-12; Zhang et al., 2016). It was brought to light in cats, and further reported in humans too, as the origin of the rhythmical pattern of activity in MLR cells (Jahn et al., 2008). More precisely, after removal of the cerebellum, the fore-mentioned activity is no longer rhythmical (Armstrong, 1988). On the other hand, Mori and colleagues (1999) have demonstrated that stimulating the CLR in cats induces locomotion. In humans, cerebellar lesion or atrophy provokes gait and posture instability, while the cerebellar transcranial stimulation in healthy individuals shows the modulation of the spatial gait parameters in the adaptation paradigm (Jayaram et al., 2012). In addition, in neuroimaging studies using motor imagery CLR is active during imaginary walking and is further enhanced in condition of running (Bohnen & Jahn, 2013; Jahn et al., 2008). All these data suggest the importance of the CLR in controlling the pace and its rhythmical aspect of gait, as well as its direct role in trigger locomotion (Jahn et al., 2008).

Lastly, the cerebellar modulatory centre is interconnected with other modulators, thereby creating a vast circuitry for gait and balance control at the middle level of automaticity – automated, yet fully flexible. All these centres stay in constant communication with the higher order cortical centres, which can themselves play a role of a modulator.

E. Automatised motor control – the ultimate motor learning

The bases of motor learning

Motor learning corresponds to the internal processes related to the exercise repetition and leading to the lasting improvement of its performance, with no link with processes of maturation, fatigue, nor growth (Eversheim & Bock, 2001; R. A. Schmidt et al., 1989). It applies to the novel motor tasks, but also to those already learnt in the past and not automatised yet. Moreover, its specificity among other types of learning is the multiple encoding. In fact, when learning a new skill, the cognitive resources are needed to identify the goal of an action and create its internal representation in relation to the external constraints, to further choose and plan motor sequences correspondingly. Then the attention shift towards the planned action execution is necessary awaiting for the feedback. Thus, this process is highly dependent on the attention attribution, the external cues, and integrating them to better control the movement's accuracy (Diedrichsen & Kornysheva, 2015; Eversheim & Bock, 2001; Ferrazzoli et al., 2018; R. A. Schmidt et al., 1986). Motor learning is therefore a complex process, involving multiple brain structures involved in movement preparation and execution (Figure 1-13; Krakauer et al., 2019), including the M1, the SMA and its anterior part (pre-SMA), the premotor cortex, somatosensory and prefrontal cortex, but also the hippocampus, the cerebellum (according to Doyon et al., 2009; Willingham, 1998), and the basal ganglia (Doyon et al., 2009; Hikosaka et al., 2002; Miyachi et al., 1997, 2002).

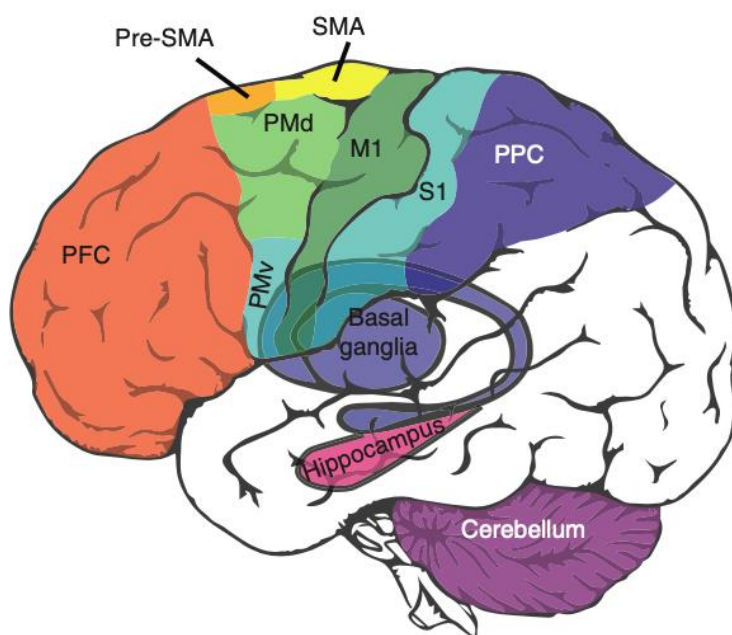


Figure 1-13: Regions involved in motor learning.

Cortical sensory, motor, premotor, cognitive, and associative regions support motor learning mechanisms through communication with the basal ganglia, the cerebellum, and the hippocampus.

Krakauer et al., 2019

At the cortical level, the motor cortex is mostly associated with learning fine motor skills, yet it also plays a role in simpler motor learning (Hikosaka et al., 2002). Kawai et al. (2015) demonstrated in their work that lesions in the primary motor cortex in rodents make learning new complex motor sequences impossible, while learning simple motor sequences is still possible. The SMA would be involved in the acquisition of new sequential movements, such as the sequence of "palm, fist, edge" (Kawai et al., 2015). Within SMA neurons, some are modulated by the transition between movements belonging to the same motor sequence (Nachev et al., 2008), and others are "specialized" for a defined motor stimulus (Escola et al., 2002). In its anterior part, the pre-SMA, some neurons code for the order of movements in a sequence and are involved in learning new motor sequences. Furthermore, the hippocampus is involved in the encoding and consolidation of all types of learning. However, motor learning (Hikosaka et al., 2002; Miyachi et al., 2002) can occur without the integrity of this structure. Patients with hippocampal damage and amnesia can still learn new motor sequences and easily access their procedural memory (Doyon & Benali, 2005; Willingham, 1998).

Regarding subcortical brain structures, the associative striatum was reported central to the new task acquisition and the regulation of goal-directed behaviours, while the sensorimotor striatum has been shown as essential to execution of the automatised tasks (Miyachi et al., 1997, 2002; Yin et al., 2005, 2006). Moreover, the basal ganglia and the cerebellum appear to be essential for motor learning and are associated with two networks: the cortico-striatal and the cortico-cerebellar loops (Figure 1-14; Bostan & Strick, 2018; Doyon & Benali, 2005; Ferrazzoli et al., 2018; Lehericy et al., 2005; Seidler et al., 2006). As formerly presented, these two loops are involved in reinforcement and supervised learning (Doyon et al., 2003, 2009; Hikosaka et al., 2002; Penhune & Steele, 2012).

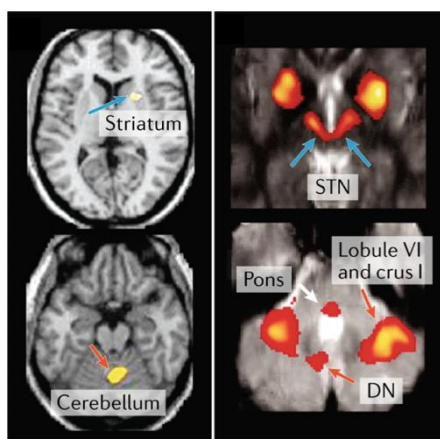


Figure 1-14: Cerebellar and striatal activation during motor learning.

The increased activations of the cerebellar and the striatal regions have been reported in the fMRI study on healthy individuals adapting to visuomotor rotations in a joystick aiming task (on the left; Seidler, Noll & Chintalapati, 2006). While the activation of the dentate nucleus (DN), lobule VI and crus I, along with the subthalamic nucleus (STN) has been reported in early motor sequence learning (on the right; Lehericy et al., 2005).

Bostan & Strick, 2018

The activation of dopaminergic neurons and the release of dopamine in successfully executed tasks are involved in behaviour reinforcement through the reward system and therefore, improving decision-making processes and goal-directed behaviours (Hollerman et al., 2000; Schultz, 2002; Schultz et al., 1997; Suri & Schultz, 1999). It is important to note that this type of reinforcement is the basis of associative learning. A link between a stimulus and an outcome is created (Ruff & Fehr, 2014; Schultz, 2013), thereby creating preferences among different motor programs according to the context (Ernst & Paulus, 2005). In fact, the cognitive control of action is dependent on a fronto-striatal loop, with the frontal cortex receiving projections from dopaminergic neurons that encode the value of the reward and allow the selection of the most suitable motor program for the goal of the action (Doyon et al., 2003; Dudman & Krakauer, 2016b; Rushworth et al., 2011). These mechanisms facilitate the selection and execution of actions, as well as the evaluation of the obtained results.

All these mechanisms would shorten the time required for appropriate action choices by creating and implementing automated responses (Escola et al., 2002; Pessiglione et al., 2003, 2004), making them less conscious and less tiring.

Motor skill transfer

The motor learning models were further developed by Schmidt (Eversheim, 2001; R. Schmidt, 1975) to introduce the theory of motor schemes. The motor scheme is "the organisation common to all motor acts with a certain identity of structure, a global resemblance, that can be transferred to a whole category of analogous actions" (R. Schmidt, 1975; R. A. Schmidt et al., 1986). The main idea of Schmidt's model is to identify the invariants (spatial and temporal) of motor gestures to then be able to generalize them and make the learning of new gestures faster and more efficient. What remains to be learned is only the parameterization of the movement, that is, the adaptation of the schema to the goal of the action and to the external and internal conditions of its execution. Thus, a motor skill is acquired through the repetition of an effective and precise sequence of movements to achieve a goal. It can be modified explicitly and implicitly through feedback. The encoding occurs in parallel in the form of the generalized motor schema and a very precise movement with defined parameters. This organization allows for the transfer of learning from one task to another (R. A. Schmidt et al., 1986).

From cognitive to automatized motor control

Often the motor learning has been separated into different phases, describing the level of proficiency in the acquired skill. The model from Fitts and colleagues (1964) distinguished three levels of motor control in healthy humans: 1) cognitive, 2) associative, and 3) autonomous. The first one corresponds to the first steps of motor skill acquisition, demanding constant cognitive supervision of the executed movement in order to be able to compare it to the expected outcome, and eventually correct it. At this stage, motor execution would demand high attentional resources for the motor task to be planned and executed. Indeed, the neuroimaging research have shown that during learning novel or relearning lost skills individuals show higher activation in the premotor cortex, the pre-SMA, the parietal cortex, and the cerebellum, along with the dorsolateral prefrontal cortex (DLPFC), and the anterior cingulate cortex (ACC), when compared to the automatised task execution (Poldrack et al., 2005; T. Wu et al., 2008; T. Wu, Hallett, et al., 2015; T. Wu & Hallett, 2005). High activity of these regions is related to the cognitive engagement in information processing, motor planning, and their updating. Moreover, the activation level of the DLPFC and the ACC during this phase seems to correspond to and predict the observed learning rate across individuals (Bassett et al., 2015).

The observed learning mechanisms during this phase correspond to rapid and slow learning, according to Doyon & Ungerleider (2002; Doyon et al., 2009; Doyon & Benali, 2005). In fact, rapid learning would describe the progress made on a task during a single training session. Other authors also consider this phase as adaptive learning (Hikosaka et al., 2002). On the other hand, slow learning would require multiple training sessions to achieve a significant improvement in performance. The proposed models of learning equally highlight the role of feedback to assure correction and adaptation of movement on the trial-to-trial basis (J. A. Adams, 1971; R. A. Schmidt et al., 1986, 1989). The integration of external and internal effects of the executed movement is compared to its internal representation and those of the goal to reach. Movement repetition would help adjusting the motor scheme for each objective and saving the one the most efficient over trials. Schmidt further dwelled on the cortico-striatal mechanisms observed in the motor learning. As fore-mentioned, this modulatory process is supported by the cortico-striatal and cortico-cerebellar learning mechanisms.

The associative control level is what can be considered as the precursor of the skill automatization and corresponds to the consolidation phase (Doyon et al., 2009; Doyon &

Ungerleider, 2002). This phase, beginning approximately 6 hours after training and persisting during sleep, would help maintain a stable level of skill in task performance. The fluidity and the speed of movement increase, along with decreases in its variability and uncertainty. Moreover, in this phase we also start to observe the anticipatory movements and quicker decision making as for the motor programs to execute. (Eversheim & Bock, 2001) equally suggests that in consequence, the cognitive resources used by the motor action would be diminished, making its execution infra-conscious. However, when introducing a competing task during the consolidation period, interference between tasks and a considerable decrease in the performance of the first learned task is observed (Doyon et al., 2009; Doyon & Benali, 2005). From the neural perspective, during motor automatization, researchers observed a progressive decrease in the activation of the anterior putamen (associative), and a progressive increase in the activation of its posterior (sensorimotor) part (T. Wu et al., 2008; T. Wu, Hallett, et al., 2015). It was equally mimicked in terms of their connectivity with the primary motor cortex (T. Wu, Liu, et al., 2015).

Finally, once consolidation is completed, learning would become resistant to interference with other tasks, corresponding to the automatization phase (Doyon et al., 2009; Ferrazzoli et al., 2018), where direct motor control (online control) is no longer necessary. Thus, the attentional cost would be minimized, task execution would become almost unconscious or automatic, and it would be possible to perform other tasks in parallel. Indeed, the automatised skill becomes less demanding and/or dependant on cognitive and associative resources and therefore can be executed in parallel to other actions (motor or non-motor). In fact, we observe a decrease in the activation of the DLPFC and the ACC, along with higher effective connectivity between motor regions of the cerebellum, the cingulate cortex, the SMA, and the putamen. Such an enhancement of the connectivity is interpreted in the field as the increased synaptic strength and higher efficiency of the motor network (Mazzoni, 2008; T. Wu et al., 2008), which goes in line with the observed changes in behaviour. In parallel, the observed changes in the striatal functional activity remain long after the skill automatization, even if the task is executed with focus imitating the learning phase. Indeed, once attending to the automatised task, we observe stable dynamics between the two parts of the putamen, with high importance of the sensorimotor striatum, while observing an increase in the pre-SMA, the ACC and the DLPFC activations relative to increased attention engagement (T. Wu, Liu, et al., 2015). Furthermore, the performance becomes optimal in speed and precision, and independent

from the context in which the skill was learnt – which corresponds to the autonomous level of motor control.

It is important to note that these automatisms are the basis of many activities in daily life, such as walking, eating, speaking, but also riding a bicycle, driving a car while being able to have a conversation, or playing a musical instrument.

1.2 “Integrated” gait and balance mechanisms: the interplay between automated and volitional motor control

Since our gait is affected by external and internal factors, and because we evolve in a dynamic environment, our gait is rarely as simple as in laboratory/clinical context, and often becomes a secondary task. In fact, gait and balance control is assured with small attentional load, for us to allocate our cognitive resources to other actions like prospective and retrospective thinking, conversation, or simply observation of the changes in our surroundings. It is only possible thanks to a successful motor learning process, leading to optimization of the fore-mentioned modulatory activity on lower and higher order processing - essential for everyday life activities. In the following part, I will relate to it as “integrated” gait and balance mechanisms.

1.2.1 Multisensory integration and motor planning in a dynamic world: motor learning mechanisms

As mentioned before, afferent sensory information, as well as modulators of gait and balance have an essential role in adapting the motor commands and the motor execution in new contexts. The presented earlier continuous sensory data integration is essential for interacting with our surroundings adequately. The reactivity of all underlying motor systems is dependent on it. Indeed, identification of possible obstacles, which can be stationary or mobile, on our trajectory is crucial in motion planning. Therefore, a particular accent is to be put on the visuomotor system regulated partly by the superior parietal cortex, Frontal Eye Fields (FEF), cerebellum and the PPN (Chu et al., 2021; Goodale, 1998). Having an efficient visuomotor control system is equivalent of a good multisensory integration, and by this to an efficient reaction to unexpected external factors jeopardising our balance and efficient locomotion. In fact, the more we can direct our vision in the functionally important directions, the better update of our surroundings we can make, hence the better is anticipated and executed the movement. If we imagine locomotion on a crowded street, it seems obvious that in order to avoid collision, one needs to thoroughly update its surroundings and sometimes change one’s trajectory and posture. Besides the stationary signs, postal boxes, or road delimitation, one has to be attentive to other mobile obstacles like children playing football on their way home or cyclists getting on the pavement from the cycle lane. It may even happen that we only see them at the last minute, yet the processing of these data, arrest/modulation of automatised activity, and finally,

elaboration of new motor scheme and new motor command are there in barely seconds. This may be very challenging for the visuomotor control and the parietal cortex to dynamically integrate and communicate all these stimuli to higher order processing centres, all while sending a signal to modulators to stop/change the current movement. That is why the executive functions, along with frontal-prefrontal cortices are engaged, just the way they are in dual tasking – tackled in the next part of this chapter. Even an automatised motor skill may require the intervention from the cognitive processes, although it is fully dependent on functional modulatory systems.

In fact, earlier in the manuscript we have exposed those modulatory systems, which are responsible for the activation and deactivation of the automatised processes, step in to make the volitional ones when needed. The executive functions support abilities such as attention shifting and motor program choice, related to the decision-making processes. Indeed, the choice of the reaction to have in front of an unexpected obstacle is fully dependent on the efficiency of the executive network. As presented in the previous chapter, automatised movements rely on efficient executive functions allowing for the attention allocation, or cognitive flexibility. These processes allow for the disruption of the automaticity and initiation of a movement adapted to the dynamic circumstances. Another structure involved in this kind of motor adaptations is the cerebellum, helping to adapt and predict the outcomes of the recently programmed motor plan. Therefore, cerebellum is among the main actors of sensorimotor anticipation and on-line motor adaptation. In the same manner, using a motor skill in the novel environment or in different conditions than when it was acquired corresponds to a higher level of motor control, related to motor automatization and learning transfer.

1.2.2 Dual tasking in real life

From the evolutionary point of view, humans went from quadrupedal to bipedal gait, and even on our life's spectrum we still do, if we look at the development of gait in infants. The arrival of the up-straight posture and the bipedal gait in humans seemed necessary when humans started to free their hands free for other activities – communicating, hunting, harvest, etc. Hence, the automatization of gait was the next step in this axis, that is - making the cognitive resources available for all the other aspects of life and goal directed behaviours. We have finally reached the highest level of motor learning when it comes to gait and balance. In fact, it is important to remind that the successfully automatised motor skill demands less input from higher order control structures such as DLPFC and the ACC, as well as from the cerebellum,

the pre-SMA, premotor and parietal cortices. On the other hand, the connectivity between different motor areas: motor cerebellum, cingulate motor area, SMA, and the putamen is increased (T. Wu, Hallett, et al., 2015). That is why, in real life we barely acknowledge that locomotion is not fully automated.

Nevertheless, in condition of dual tasking, which means performing two independent tasks aiming at different goals simultaneously, studies have shown a link between the difficulty of a secondary task and our performance in the primary activity (Chipunza & Mandeya, 2005; H.-T. Goh et al., 2021; Smith et al., 2017). When one thinks of it, even after automatization of gait, it may happen that during a captivating conversation we miss a step or stumble, because our attentional resources were attributed elsewhere. Moreover, studies demonstrated the effect of the interference when tasks depend on similar mechanisms (Chipunza & Mandeya, 2005; Cocchini et al., 2002; Shea & Morgan, 1979). Precisely, when one task is interrupted or slowed down by another, we can speak of interference and cost of dual tasking (Plummer et al., 2014; D. D. Wickens et al., 1981). In laboratory conditions usually cognitive-motor task combination is used to identify the prioritization effect in each task – which one is privileged respectively to the other, but also as means to evaluate executive functions and motor skill automatization (Plummer-D’Amato et al., 2012; Shea & Morgan, 1979). The more the task is demanding, the more one needs to activate frontal and prefrontal areas, therefore if the skill is not perfectly learned, it will result in concurrent demands on frontal regions of the brain. Indeed, even the information processing can represent a burden for the cognitive resources already involved in motor control, hence when individuals walk while executing simple working memory tasks, they show decreased motor speed (H.-T. Goh et al., 2021; Plummer et al., 2013; Smith et al., 2017). Moreover, once the uncertainty is introduced to the choice of motor program to execute, the movement trajectory can also be impacted showing higher variability and/or decreased velocity (Pessiglione et al., 2003, 2004, 2005, 2005).

As formerly presented, navigating in real world, with its dynamics and new contexts, puts us permanently in a situation demanding cognitive and executive control, as in dual tasking. This may represent a big challenge in case the automatisms are lost, for we don’t dispose of unlimited cognitive and attentional resources. Moreover, we depend on the integrity of a considerable number of structures implicated in motor control and automatization. As fore-mentioned, these functions rely on complex multi-level interactions between cortico-subcortical modulatory regions that are impacted in different pathologies. One of them

demonstrating clear relation between the functionality of these pathways and patients' autonomy is Parkinson's disease – characterised by the degeneration of dopamine in the striatum.

Chapter 2: Gait and balance disorders in Parkinson's disease: the mysterious freezing of gait phenomenon

2 Parkinson's disease: multi-faceted pathology

2.1 Physiopathology

Parkinson's disease (PD) is the second most important neurodegenerative disease in terms of frequency, and the second most important cause of motor handicap in adult population. In fact, there are over 6 million cases of PD worldwide and this number is expected to continue growing exponentially, given the growing life expectancy of our societies (Dorsey et al., 2018). It is usually diagnosed in patients between 60 and 70 years old but first symptoms can appear much earlier, with a preponderance in men (Van Den Eeden et al., 2003). The appearance of first motor symptoms typically coincides with up to **80% of loss of dopaminergic neurons in the striatum** (Marsden, 1990), and **60% in the SNc**. The principal symptoms necessary for the diagnosis include the so-called motor triad: **tremor at rest, muscular rigidity, and bradykinesia** (an abnormal slowness of movement and reduction of speed or amplitude of continuous movements; Defebvre, 2007; Parkinson, 2002 republished original initially from 1817). Yet, the symptomatic spectrum starts on the periphery of the autonomic neural system at the prodromal stage and further broadens to other motor, cognitive, and emotional symptoms.

Indeed, neuropathologically speaking, Parkinson's disease is classified as an intraneuronal synucleinopathy, because of the presence of the intracytoplasmic inclusions mainly composed of the α -synuclein, called Lewy bodies (Figure 2-1; (Lewy, 1912; Menšíková et al., 2022; Spillantini et al., 1997). These protein aggregates are considered at the origin of the alteration of neural cytoskeleton and mitochondrial homeostasis, later leading to neuronal apoptosis (Galvagnion et al., 2015; Galvagnion & Buell, 2015; Kaur et al., 2019). α -synuclein as a presynaptic protein was also reported as involved in the liberation of

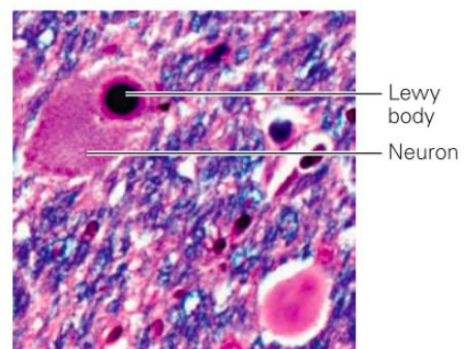


Figure 2-1: Lewy's body aggregation in a substantia nigra (SN) neuron in a patient diagnosed with Parkinson's disease (PD).

Lewy's bodies are composed of abnormal aggregations of the α - synuclein filaments.

Kandel et al., 2007

neurotransmitters in the inter-synaptic space and the synaptic plasticity mechanisms (Galvagnion & Buell, 2015). Targeted neurons are the ones with long, thin, and little/unmyelinated axons i.e., dopaminergic, glutamatergic, noradrenergic, serotonergic, and cholinergic neurons (Braak et al., 2003; Del Tredici & Braak, 2016). As hypothesised by Braak and colleagues (2003) their deposition starts in dorsal motor nucleus of the glossopharyngeal and vagal nerves, and anterior olfactory nucleus – that is in the autonomic nerve terminals. Lewy bodies later propagate in a caudo-rostral manner, through the medulla (stage I), pons (stage II), the SNc and the midbrain (stage III), before reaching the temporal trans-entorhinal/entorhinal cortex, amygdala, hippocampus (stage IV), and finally the associative and prefrontal cortices (stages V and VI) (Figure 2-2). This pathological progression of the α -synucleinopathy is known as Braak’s model and predicts the appearance of prodromal signs, such as hyposmia, constipation, depression, and/or rapid eye movement (REM) sleep behaviour disorder (stage II), before the appearance of motor signs (stage III), cognitive disorders, falls (stage V) and dementia (stage VI) (Braak et al., 2003; Del Tredici & Braak, 2016; Goedert et al., 2013).

The model’s accuracy has been recently tested in comparative studies opposing healthy

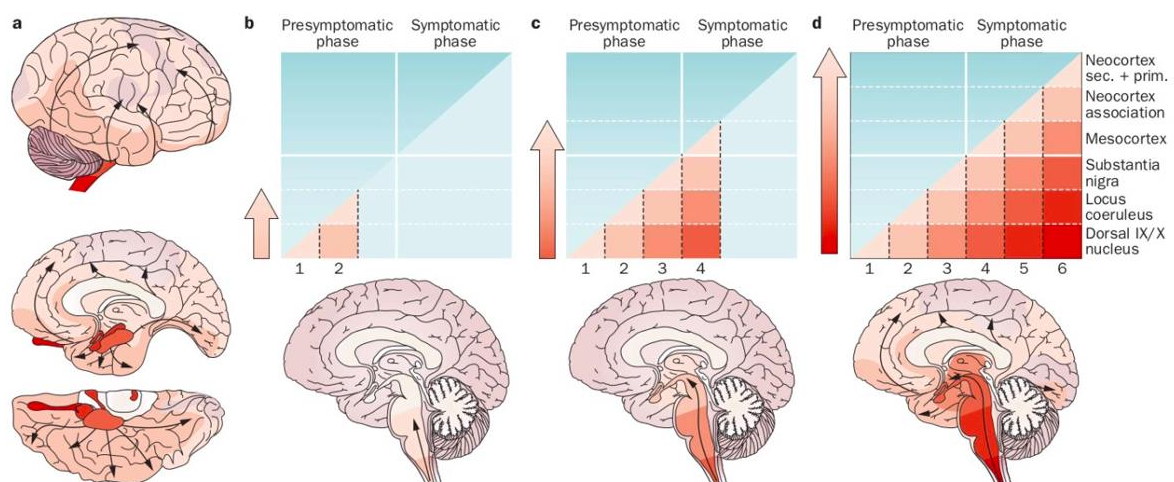


Figure 2-2: Neuropathological stages of the disease progression according to the Braak's model.

a. Caudo-rostral and centripetal cortical propagation of the pathology. Different shades of red correspond to the severity level (from light to dark). b. Prodromal Braak stages I-II. c. Appearance of first motor symptoms (Braak stages III-IV). d. Appearance of cognitive impairments (Braak stages V-VI).

Goedert et al., 2013

controls, PD patients and those presenting prodromal idiopathic REM sleep behaviour disorder (IRBD) (Knudsen et al., 2018; Stockholm et al., 2017). In fact, it is among the most common prodromal signs in individuals to develop parkinsonism (Högl et al., 2018). It corresponds to

recall of nightmares, dream-enactment, and excessive motor activity during REM in the absence of any related cause (motor, cognitive, or other disturbances). Moreover, biopsy samples of the nerves of colon, salivary glands, and skin of these patients present α -synuclein aggregates (Stefani et al., 2021; Vilas et al., 2016). Knudsen and colleagues (2018) measured the neural integrity of different structures corresponding to Braak stages I-III with use of scintigraphy, PET, computed tomography (CT) scans and MRI imaging in these patients in order to compare them with previous studies on healthy individuals and PD patients. They've shown that patients with IRBD present a damage to the cholinergic neurons in the small intestine and the colon, the noradrenergic neurons in the heart (Braak stage I) and to the neuromelanin and the noradrenergic neurons of locus coeruleus in the pons (Braak stage II) when compared to controls. A difference was also observed in striatal dopamine uptake (Braak stage III). When compared to PD patients there was no difference between groups when it comes to cholinergic colonic damage, noradrenergic damage in locus coeruleus and in neuromelanin. However, two groups differed in striatal dopaminergic neuronal degeneration. It would suggest that the difference between IRBD and PD patients is between Braak stages II and III – thereby validating the caudo-rostral gradient of α -synucleinopathy evolution and Braak's model up till stage III.

At the same time, the main characteristic of PD being the depletion of dopaminergic neurons in SNc (Damier et al., 1999; Defebvre, 2007; Devos et al., 2010; E. Hirsch et al., 1988; Kastner et al., 1992), it shows that it corresponds to the Braak stage III (Figure 2-2 c.). This degeneration provokes a dysfunction of basal ganglia circuitry and impairs a variety of processes ranging from movement initiation to decision-making, including gait and balance control (Nambu, 2004; Nambu et al., 2005). Patients diagnosed with PD present greater gait alteration than age-matched subjects even at an early stage of the disease (Pistacchi et al., 2017), and in 48-70% of cases they develop serious **gait and balance disorders** in first 6-10 years of disease progression. We then speak of **axial signs** of PD: **postural instability, diminished step length and gait velocity**, followed by transient symptoms like **freezing of gait (FOG), festination and falls** (Bloem, 1992; Nutt et al., 1993). Specifically preoccupying are the latter which normally occur in later stages of the disease (Giladi & Nieuwboer, 2008) along with dementia (Reid et al., 1996, 2011). Yet given the range of basal ganglia circuitry, one must acknowledge a vast heterogeneity in early-middle-stage PD manifestations, their severity, and their progression (De Pablo-Fernández et al., 2019; Greenland et al., 2019). In fact, some authors proposed separating PD in different phenotypes depending on predominant symptoms:

tremor, postural instability and gait difficulty (PIGD), dementia, depression, or psychosis (Fereshtehnejad et al., 2015; Greenland et al., 2019; Marras, 2015; Nyberg et al., 2015; Thenganatt & Jankovic, 2014). They argue that these subtypes don't share the same neural mechanisms, or follow the same evolution and hence, they should be studied separately or comparatively. This view is further highlighted by the pathophysiology. Although the clinical severity of the hallmark motor symptoms of PD seems correlated with the expansion of α -synuclein aggregates, in different phenotypes the link between both isn't as clear (Halliday et al., 2011). Generally, the evolution of the synucleinopathy differs among patients, and it is therefore different from a classical evolution proposed by Braak (De Pablo-Fernández et al., 2019; Halliday et al., 2011). In fact, in recent years works from Borghammer propose a hypothesis that two main evolution patterns are possible in all types of synucleinopathy: the brain-first and the body-first (Borghammer, 2023; Stokholm et al., 2017; Van Den Berge et al., 2019). It suggests that the pathology may start either through the inflammation of the gut and iRBD (body-first), or the olfactory loss (brain-first) corresponding to classical Braak model, thereby predicting the evolution of the disease (Borghammer, 2023). Usually, in the first case the disease is characterised by a late onset and increased risk of dementia when compared to patients with the brain-first type of evolution. The patients following the Braak model are usually characterised by an early disease onset, slower evolution and milder severity of motor symptoms, in relation with tremor-dominant phenotype (Jankovic et al., 1990; Thenganatt & Jankovic, 2014). On the other hand, those suffering from severe rigidity and bradykinesia in the early stage are more likely to develop gait and balance difficulties leading to a rapid degradation (Jankovic & Kapadia, 2001; Williams-Gray et al., 2007, 2013). Nevertheless, one shouldn't consider these phenotypes as rigid niches, but rather a gradient of impairment, given the possible overlays and interactions between them (Greenland et al., 2019). In fact, patients with PiGD phenotype are considered more at risk of developing cognitive disorders, both due to fronto-striatal dopaminergic depletion and more posterior cortical dysfunction, usually related to Lewy body pathology (Williams-Gray et al., 2007). Other authors suggested the phenotypes in relation to the age of the onset, which equally seems to play a significant role in the disease progression giving good or bad prognostics. Yet, the final milestones remain the same for all phenotypes (Figure 2-3; De Pablo-Fernández et al., 2019; Greenland et al., 2019; Halliday et al., 2011).

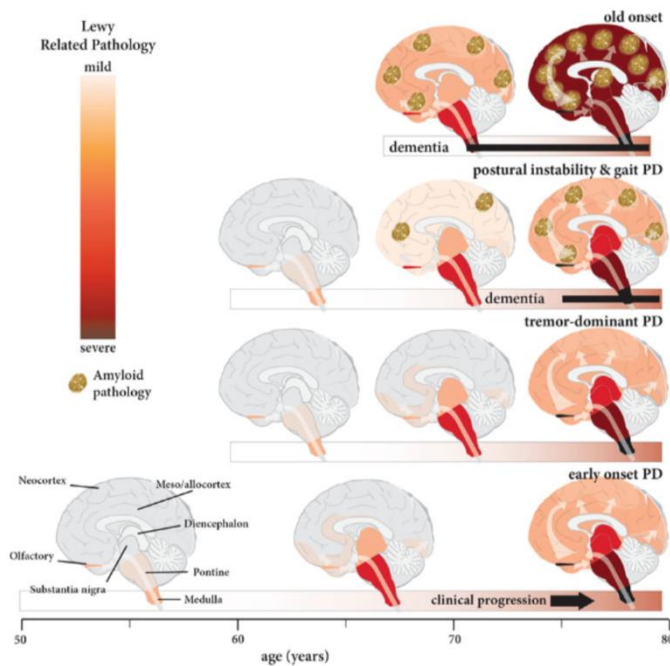


Figure 2-3: Disease evolution and severity relative to the time of onset and PD subtype.

Further studies by De Pablo-Fernandez et al., 2019 have shown that at the advanced stage all patients show diffuse malignant disease level (top right).

Halliday et al., 2011

In this work I will dwell on the gait and posture related impairments, yet without excluding studies not making the nuance between PD subtypes. Indeed, I chose to present the mechanisms underlying these disorders in relation to their identified dopaminergic and non-dopaminergic origins. In the present chapter I will try to expose main motor disorders, while pinpointing the possible neural mechanisms underlying them in PD evolution. In parallel, I decided to put them in the perspective of further deterioration, keeping in mind that in advanced disease stages the mechanisms remain the same for all phenotypes (De Pablo-Fernández et al., 2019; Kempster et al., 1989). As fore-mentioned, this deterioration is particularly aggravated with the appearance of FOG – a sign of advanced postural and gait dysfunction, situated at the heart of this thesis. I will focus on this phenomenon in the second part of this chapter, for still today it arouses a lot of questions.

2.2 Gait and balance disorders in PD: dopaminergic vs non-dopaminergic lesions

2.2.1 Inefficiency of basal ganglia dopaminergic circuitry

As explained in the first chapter (Chapter 1.1.2 D), dopamine is crucial for basal ganglia's correct functioning. Moreover, given basal ganglia's involvement as modulator in circuits of large functional variety, their abnormal activity implies multiscale disorders. The

overall depletion of dopamine in the cortico-basal circuits results in an unusual slowness (bradykinesia) and small amplitude (hypokinesia) in gait initiation, as well as execution in PD patients - shorter APAs and step length, higher gait and APAs variability, asymmetry, and sensibility to interference (Delval et al., 2014; Hausdorff, 2005; Mirelman et al., 2019; Okuma, 2014; Rochester et al., 2014). This can be explained by multiple parallel mechanisms showing a disequilibrium between inhibitory and facilitatory pathways. Even though originating in the subcortical structures, this dysregulation propagates to other interconnected circuits in the cortex, cerebellum, and the brainstem.

A. Subcortical effects of dopamine depletion

To start with, in early PD dopaminergic degeneration of SNc affects preferentially neural projections to dorsolateral putamen. Given that the latter is the motor territory of the striatum, the initial symptoms of PD first affect the motor loop. Indeed, striatum fails to activate the direct pathway, responsible for movement initiation and execution of voluntary movements (Figure 2-4; Peterson & Horak, 2016; Potvin-Desrochers, 2022). GPe is hence hypo-activated and fails to inhibit the STN, leading to the hyperactivity of the indirect pathway, and thereby, to the hyperactivity of basal ganglia inhibitory outputs – GPi and SNr. Moreover, a hyper synchronisation of GPi and STN has been observed, in relation to the increase of GABAergic tonus. Altogether, this imbalance between direct, and indirect pathway structures results in

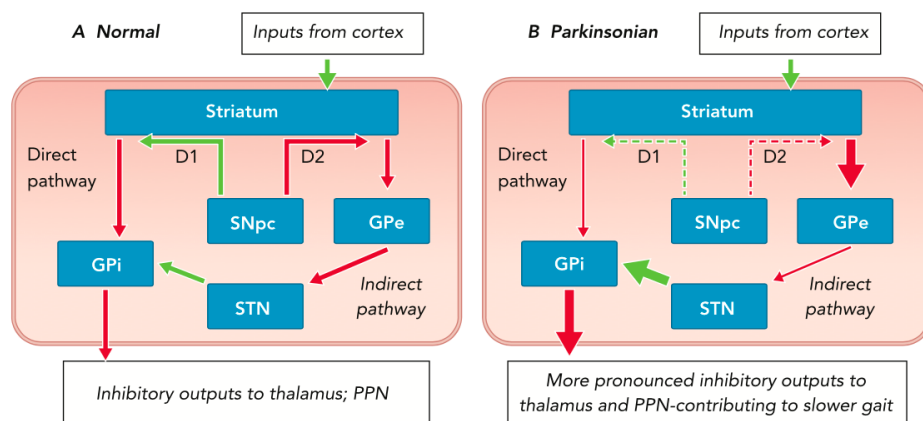


Figure 2-4: Parkinson’s disease dopaminergic degeneration effects on the basal ganglia function.

When compared to the healthy individuals (A), patients with Parkinson’s disease show decreased striatal inhibition (red arrows) of the internal pallidus (GPi), which further induces inhibition on the basal output structures (thalamus, PPN) thereby resulting in direct pathway/execution inhibition. On the contrary, striatal inhibition of the external pallidum (GPe) is increased, therefore we observe lesser inhibition of the indirect pathway and of the subthalamic nucleus (STN). The latter further stimulates GPi, thereby further inhibiting the direct pathway.

Peterson & Horak, 2015

excessive inhibition of the thalamus and the PPN, directly provoking a reduced activation of motor commands (Grillner & Robertson, 2016; Jahanshahi, 2013; Jahanshahi, Obeso, Baunez, et al., 2015; Peterson & Horak, 2016). Moreover, the degeneration progresses in a lateralised manner, thereby creating an asymmetry in observed hypokinesia and rigidity – the side contralateral to bigger lesions shows higher symptom severity (Fornaguera et al., 1994; Kempster et al., 1989; Kumar et al., 2003). Logically, this asymmetry induces an abnormal gait pattern distributed axially (impact on superior and inferior members) and usually alleviated by dopamine treatment (Galna et al., 2015).

B. Cortical effects of dopamine depletion

As previously presented, cortical communication with basal ganglia is bidirectional. Indeed, a choice of motor scheme and its execution is done with help of dopaminergic inputs to motor areas. Once the movement is chosen, cortical motor and premotor areas transmit the information through direct and hyperdirect pathways. The efferent projections to the thalamus initiate the movement, while the ones to the STN enable the inhibition of the remaining motor schemes. Therefore, the depletion of dopamine in the cortico-striatal circuits impacts the choice of the motor scheme, its activation, and the inhibition of conflicting motor schemes during movement initiation (Escola et al., 2002; Jahanshahi, 2013; Pessiglione et al., 2003, 2004). I will try to present how this dysfunction of basal circuits influences motor control at different stages, from motor planning, through movement automatization and initiation, to motor execution – all related to cortical dependence on dopaminergic projections.

- Dysfunctional motor planning

Studies in primates injected with 1-methyl-4-phenyl-1,2,3,6-tetrahydrophydrine (MPTP; Burns et al., 1983; D'Amato et al., 1987), a neurotoxin selectively provoking a progressive death of dopaminergic neurons, efficiently expose the mechanisms underlying motor disorders observed in PD. In line, it is the only mammal model of PD simulating all symptoms, including tremor, akinesia, rigidity, and the dyskinetic effect of dopaminergic treatments (Burns et al., 1983). In fact, this non-human primate PD model enables recording of neuronal activity in different regions and shows progressive changes after the toxin injection.

Firstly, at the level of motor planning, Escola and colleagues have shown a loss of specificity of SMA neurons in relation to the context and proprioceptive stimuli (Escola et al.,

2002). Indeed, in healthy monkeys stimulating through movement the different joints of upper members (wrist, elbow, shoulder) results in activation of SMA neurons – each axis of movement, as well as each joint results in a specific neuronal activation. In parkinsonian monkeys, the activation becomes more chaotic, thus all neurons respond to each type of movement (Figure 2-5; Escola et al., 2002).

However, according to authors this dysfunctional sensorimotor integration and proprioception in PD can be aggravated by other than dopaminergic degeneration (explained in chapter 2.2.1). Given that SMA is involved in motor learning mechanisms both through recognition of self-made actions and through integration of body schemes – it participates along the cerebellum to the internal/proprioceptive feedback (Escola et al., 2002; R. Schmidt, 1975). It is easy to imagine, that without a proper body scheme, nor feedback, the choice of movement to execute is compromised, and becomes uncertain. It is further accentuated by the loss of dopaminergic facilitatory feedback from formerly learned motor schemes (T. Wu & Hallett, 2005).

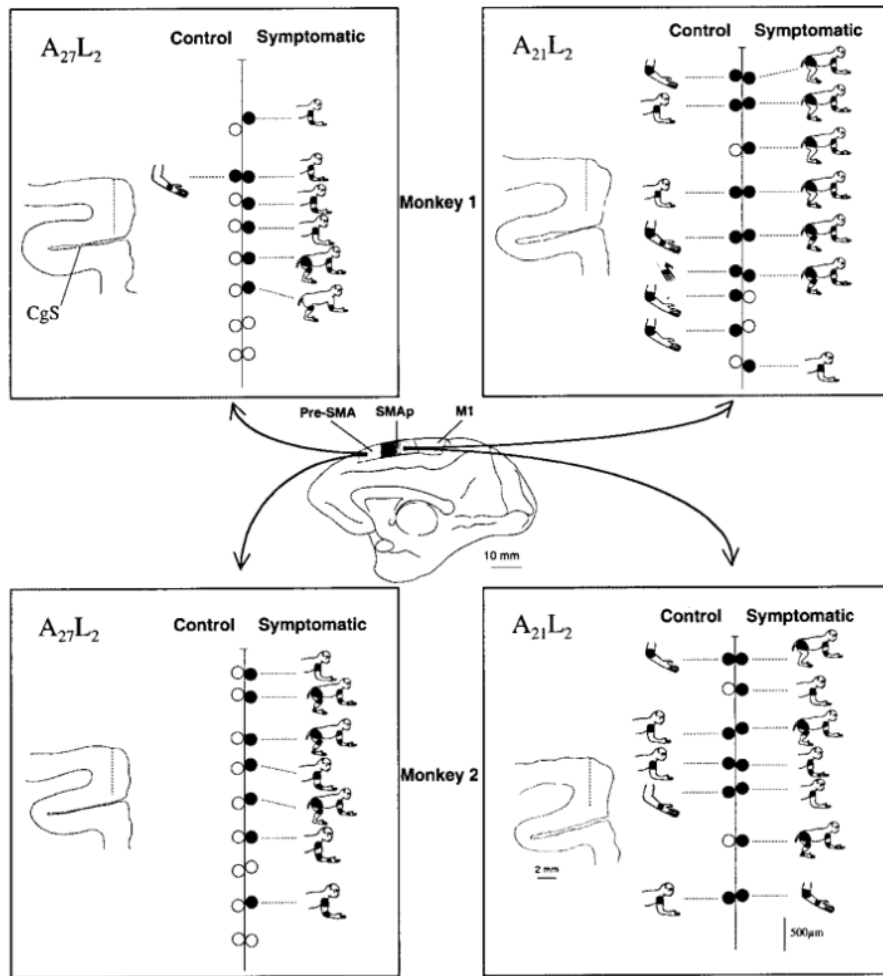


Figure 2-5: Somatosensory receptive fields of the Pre-Supplementary Motor Area (Pre-SMA) and SMA proper (SMAp) in control and PD symptomatic macaque monkey.

Preliminary delimitation of the pre-SMA and the SMAp by intracortical microstimulation is presented on the medial view at the centre (M1: primary motor area; CgS: cingulate sulcus). Different quadrants present data collected before and after the MPTP injection in pre-SMA (left), SMAp (right). The dotted line drawn on the frontal section on the left represents the electrode tract. The vertical line represents the recording track, juxtaposing circles indicate the position of the neurons encountered; empty circles correspond to neurons unresponsive to joint displacement; filled circles correspond to neurons activated by one or several joint displacements. This neuronal response is illustrated with pictures of monkeys, darkened areas show the joints whose passive displacement elicited a neuronal response.

Escola et al., 2002

- **Disturbed motor automatization & initiation**

In fact, it is important to highlight, that movement automatization is only possible thanks to recompensating dopamine neuronal activation when a movement leads to a successful goal (Hollerman et al., 2000; Schultz, 1997, 1998, 2010; Suri & Schultz, 1999). Striatal dopamine gives motor schemes a context-dependant value, which is communicated to the frontal cortices in order to accelerate the processing, every time when presented with an action choice (Doyon et al., 2003; Dudman & Krakauer, 2016b; H. F. Kim & Hikosaka, 2015; Rushworth et al., 2011). Therefore, once the dopamine is missing, the automatized context-movement associations start to disappear too, and in parallel their facilitatory role for the frontal cortex. In turn, it also puts an additional charge to the volitional motor control system, thus demanding more attentional resources for movement initiation and execution (H. F. Kim & Hikosaka, 2015; Wu, Hallett, et al., 2015; Wu, Liu, et al., 2015).

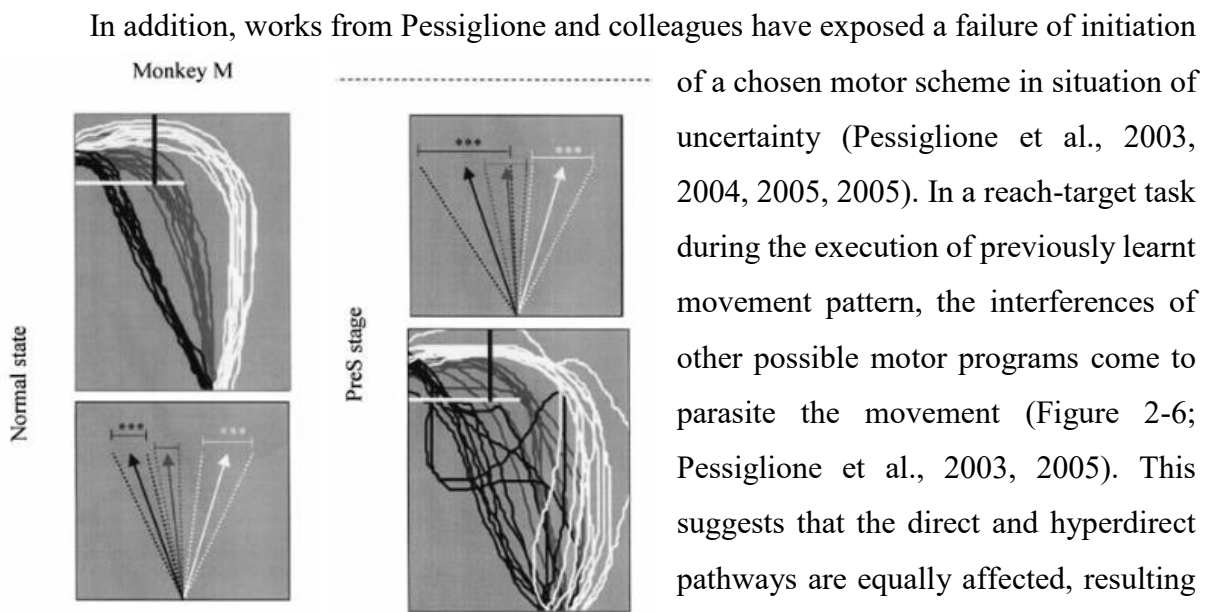


Figure 2-6: The example of the automatized movement trajectories in a reach-target task in macaque monkey.

Trajectories of learnt movement in no obstacle (grey), horizontal obstacle (white), and vertical obstacle (black) in the normal state and in the pre-symptomatic stage after MPTP injection. These results were further replicated in PD patients replacing the obstacles with varying uncertainty levels.

Adapted from Pessiglione et al., 2003

dopamine is essential for correct motor planning be it for new, or the automatised motor tasks.

In gait, this translates to increased APA and step to step variability in patients compared to healthy controls, as well as higher cortical activation in frontal and prefrontal areas (Ding et al., 2022; H. F. Kim & Hikosaka, 2015; Maidan et al., 2016; Wu, Liu, et al., 2015; Wu & Hallett, 2005). Indeed, according to the hypothesis of lost automated motor control, all automated mechanism would become fully volitional and thereby, cognitively demanding. This was further confirmed by studies using a dual-task paradigm measuring the level of automaticity of gait. Kelly and colleagues showed that patients experience higher interference effect than healthy age-matched individuals when performing a cognitive task while walking - both performances showed decreasing scores (Kelly et al., 2012).

- **Abnormal motor execution**

Finally, movement execution in patients is particularly reflective of global increase of muscle tonus (rigidity) and decreased activation of motor and premotor regions (hypo- and bradykinesia). In fact, patients show decreased and slower APAs, leading to smaller step length and gait velocity already in early stages of the disease (Figure 2-7; Peterson & Horak, 2016).

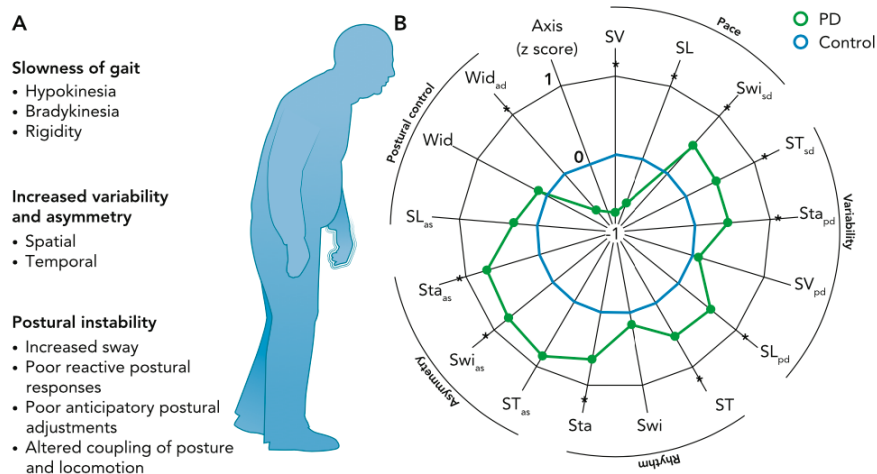


Figure 2-7: Contribution of symptoms to the continuous motor symptoms in Parkinson's disease (PD).

A: List of the continuous gait disturbances in PD patients. B: Satellite plot showing deviations of patients' biokinetic characteristics from control subjects (green line).

SV, step velocity; SL, step length; Swi, swing time; ST, Step time; Sta, Stance time; Wid, Step width; sd, standard deviation (gait variability); as, asymmetry. *Differences between the control and PD group.

Peterson & Horak, 2015 adapted from Galna, Lord, Burn & Rochester, 2015

Given the role of the SMA in volitional and automatised movement preparation and initiation, its reduced activity due to the thalamic inhibition could explain the hypokinetic aspects of movement in PD. Neuroimaging studies in patients have shown reduced activation of motor and premotor cortical regions (M1, SMA) during real and imaginary movement, as well as reduced functional connectivity at rest (de Lima-Pardini et al., 2020; Hanakawa, 2006; Hanakawa et al., 1999, 2003, 2008). Furthermore, the level of activation of the SMA during imaginary gait task was correlated with the performance during real gait task (Cremers et al., 2012; Maillet et al., 2015). This hypoactivity is accompanied with the reduction of dopamine availability in the nigrostriatal system during gait, when compared to healthy adults (Ouchi et al., 2001; Peterson & Horak, 2016).

At the beginning this abnormal activity, along with the gait hypokinesia, can be reversed with dopamine treatments, thereby demonstrating the dependence of gait initiation and execution on cortico-thalamo-basal dopamine circuits (Kuhman et al., 2020; Peterson & Horak, 2016). Indeed, these symptoms are among the most responsive to the dopamine replacement treatment.

C. Mesencephalic effects of dopamine depletion

Beyond hypo- and bradykinesia resulting from insufficient cortical activation, postural and motor symptoms observed in PD include the excessive segmental and axial rigidity. Indeed, leg and arm muscles present a hypertonicity, participating to the decrease of movement amplitude and velocity. This hypertonicity is particularly disturbing in hip and ankle flexor muscles, resulting in the displacement of the CoG further to the front in order to compensate for the lower limb and trunk rigidity. This antero-flexion results in a characteristic PD posture (Figure 2-8; Takakusaki et al., 2022).

As explained in the first chapter, the basal outputs (SNr & GPi) also project to the MLR - responsible for generating and modifying the muscle rhythm and tonus. Authors suggest that the excessive inhibition of MLR is probably at the origin of

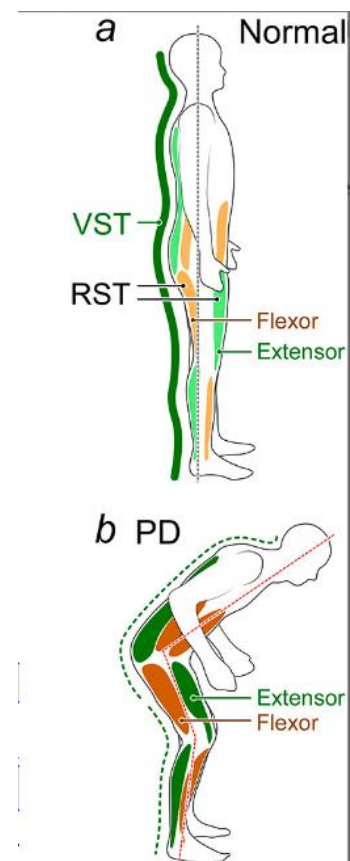


Figure 2-8: Parkinson's disease-induced postural modifications.

Increased rigidity of the hip and ankle flexor muscles provoking a flexed posture.

Takakusaki et al., 2022

hypertonicity, as well as more severe symptoms such as FOG and falls (Johnson et al., 2012). However, it would appear that axial and segmental rigidity don't share the same mechanisms – while rigidity of members is alleviated by dopaminergic treatment, the postural rigidity is less responsive (Franzén et al., 2009; Horak et al., 1996; Maillet et al., 2015; Wright et al., 2007). Authors argue that a lesion of cholinergic outputs from the PPN may be also participate to the axial hypertonicity. I will focus on this hypothesis later in this chapter (2.2.2).

D. Cerebellar effects of dopamine depletion

Due to disynaptic interconnection of the circuits between the basal ganglia and the cerebellum, abnormal STN's hyperactivity may drive the hyperactivity of the cerebellar cortex through its inputs to the pontine nuclei (Bostan et al., 2010; Bostan & Strick, 2018). This hypothesis is supported by studies showing that STN-DBS, alleviating the hyperactivity of the STN, is equally effective on abnormal activity of the cerebellum. In parallel, using positron emission tomography (PET) measures of the ^{18}F -fluorodeoxyglucose (FDG) metabolism showed that PD patients presented covarying increases in the putamen, GP and the cerebellar cortex, compared to age-matched controls (Asanuma et al., 2006). Moreover, cerebellum's hyperactivity has been equally suggested as responsible for resting tremor, given its projections to the ventral intermediate nucleus (VIM) of the thalamus. In fact, the surgical interventions on VIM and STN have met more success in suppressing tremor than those on basal inputs to the thalamus (Lenz et al., 1994; Narabayashi et al., 1987; Papavassiliou et al., 2004; T. Wu & Hallett, 2013), in relation with the normalisation of the cerebellar metabolism (Bostan & Strick, 2018; Mure et al., 2011). Moreover, some authors suggested that given the role of the cerebellum in maintaining tonus of inferior member flexor muscles, its hyperactivity may also participate to the observed rigidity of the limbs and trunk.

On the other hand, other authors hypothesise the compensatory role of this increased activity of the cerebellum (H. Yu et al., 2007). As explained in the first chapter, cerebellum is equally involved in the online motor correction and prediction of proprioceptive outcomes of the motor execution (1.1.2 D). Therefore, its increased activity may be in line with motor control become more volitional in PD, as well as reduced sensorimotor integration and proprioception from the cortical regions. Moreover, its hyperactivity isn't correlated with the severity of motor signs (H. Yu et al., 2007). It is further stressed by the fact that this hyperactivity tends to disappear in advanced stages of the disease (Sen et al., 2010).

2.2.2 Cholinergic, noradrenergic, and serotonergic abnormalities

A. Cholinergic depletion

Main centres of acetylcholine in the brain affected in PD are: 1) the PPN and 2) the Meynert basal nucleus (MBN). First one is situated in the MLR and projects to the reticulate formation, cerebellum, and the thalamus, while the second principally projects to the cortex, the thalamus, and the striatum (Figure 2-9; Morris et al., 2019; Rochester et al., 2012; Yarnall et al., 2011). Hence, these characteristics suggest different contributions to motor and non-motor symptoms in patients.

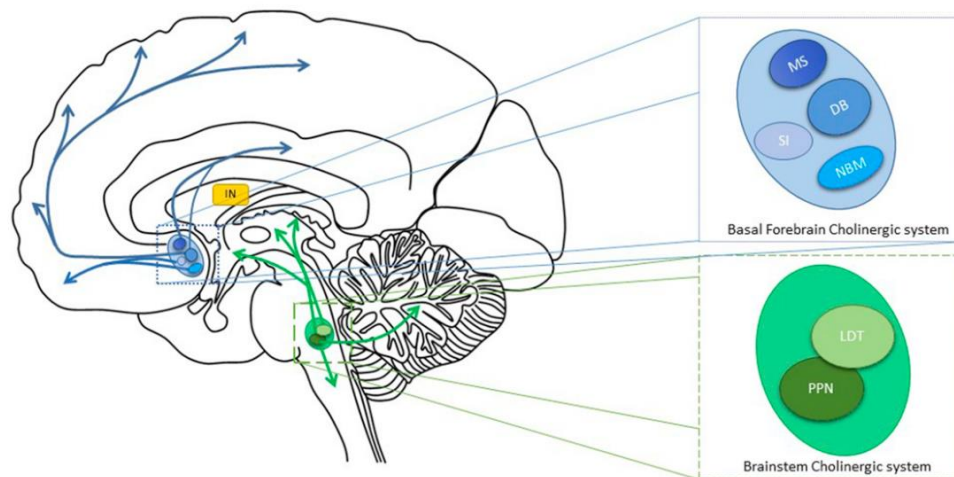


Figure 2-9: Cholinergic (Ach) projections in the central nervous system.

Two Ach hubs for basal forebrain projections (blue) from the nucleus basalis of Meynert (NBM) and the brainstem projections (green) from the pedunculopontine nucleus (PPN).

Morris et al., 2019

As a matter of fact, studies in MPTP monkeys have shown that injection of the neurotoxin in older individuals results in lesion of 20-30% of PPN cholinergic neurons, correlated with gait and balance disorders (Grabli et al., 2013; Karachi, Grabli, Bernard, Tande, et al., 2010; Sebille et al., 2017b). It is not the case in younger subjects; thus, older primate model reproduces the PIGD phenotype characteristics. Post-mortem histological analyses of PD patients show a 50% degeneration of cholinergic neurons in the PPN (Bohnen & Albin, 2011; E. C. Hirsch et al., 1987; Jellinger, 1988; Zweig et al., 1989). Patients presenting cholinergic degeneration equally show higher severity of PIGD, experience falls and freezing of gait (Figure 2-10; (Karachi, Grabli, Bernard, Tande, et al., 2010), as well as resistant akinesia (Bohnen et al., 2009; Karachi, Grabli, Bernard, Tande, et al., 2010; Rinne et al., 2008). These

data support the hypothesis that the loss of cholinergic neurons in the PPN results in decreased activation of the reticulate formation, thereby failing to modulate the muscular tonus (Takakusaki et al., 2016).

Yet, this depletion induces changes to the thalamic activity (intralaminar nuclei), resulting in hypokinetic compensatory stepping as reaction to the external balance disturbance. Indeed, reaction to balance disturbance relies on cortico-basal and pontine mechanisms (Jacobs

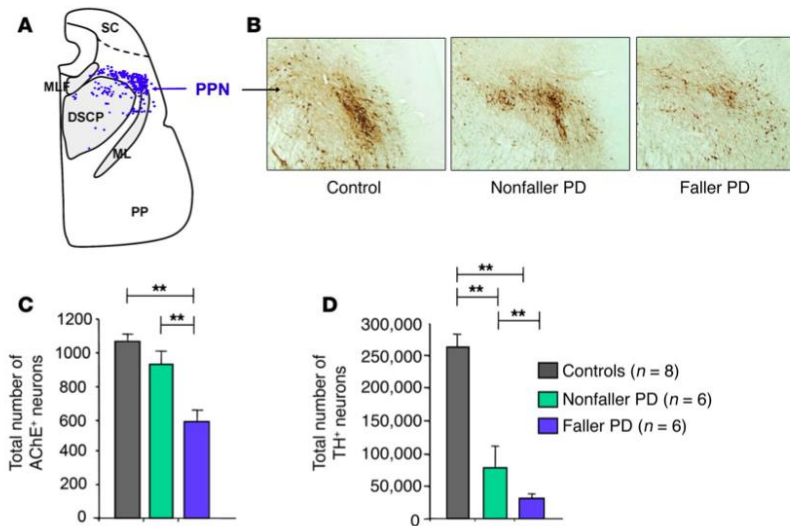


Figure 2-10: Cholinergic neuron degeneration in the pedunculopontine nucleus (PPN) in relation to postural impairments in Parkinson's disease (PD).

Cholinergic density in the PPN (A) in healthy controls, non-falling, and falling PD patients (B). Moreover, the size of the number of neurons was significantly different in each group (C & D).

Karachi et al., 2010

& Horak, 2007), and it is not alleviated by dopaminergic treatment (de Kam et al., 2014). In the same manner, the falls in PD are correlated with the level of pontine acetylcholine innervation in the thalamus, in contrary to the level of dopamine (Bohnen et al., 2009). These two dysfunctional mechanisms are closely related and thus contribute to postural instability. This role of the pontine cholinergic projections is further confirmed in some case-studies showing the efficiency of acetylcholine availability boosters (donepezil and rivostigmine) to reduce falls in PD patients, yet with a small clinical effect size (Chung et al., 2010; further developed inB below Chapter 2.3.4).

The depletion of acetylcholine in the MBN seems to have different consequences. PD patients with lower levels of cortical cholinergic innervation showed slower gait than those solely presenting dopaminergic depletion (Bohnen & Jahn, 2013; Müller et al., 2013; Rochester et al., 2012). Moreover, as reported in patients with Lewy body dementia, this degeneration has been mainly related to the cognitive and executive deficits, given reduced projections to the frontal cortex (Bohnen et al., 2009; Müller et al., 2013; Rochester et al., 2012).

B. Noradrenergic depletion

According to Braak staging of synucleinopathies and imaging studies in PD patients, noradrenergic neurons of caudal locus coeruleus are impacted early in the disease, with 70% loss of cells (Devos et al., 2010; Rommelfanger et al., 2007; Soldani & Fornai, 1999; Zarow et al., 2003). In post-mortem studies, this damage goes to 83% of mean neuronal loss in locus coeruleus (Zarow et al., 2003), resulting in 50% reduction of noradrenalin levels in frontal cortex, 72% in putamen and 60% in caudate (Goldstein, 2010; Ye, 2022). Locus coeruleus' role in gait and balance disorders has not been elucidated yet, but the coeruleo-cerebellar and coeruleo-spinal projections are shown as involved in postural reflexes and autonomous visceral motor system rhythms (Grabli et al., 2012; Purves et al., 2004; Timmann & Horak, 1997).

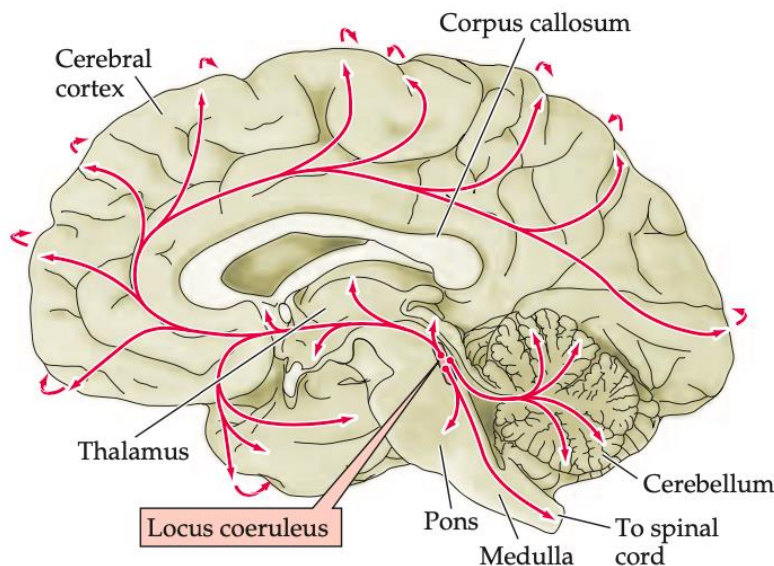


Figure 2-11: Noradrenergic projections in the central nervous system (CNS).

Noradrenaline projections from the locus coeruleus (LC) to the thalamus, the cerebellum, the spinal cord and cortical regions from frontal to occipital regions.

Purves et al., 2004

It is noteworthy, that the synthesis of noradrenalin in the brain is dependent on dopamine beta-hydroxylase. Indeed, dopamine in presynaptic vesicles of noradrenergic system is transformed in noradrenalin. In addition, in genetically impaired (knockout) mice lacking the beta-hydroxylase, emerged the motor disorders and dyskinesias, as those observed in advanced PD, but without dopaminergic striatal degeneration (Devos et al., 2010; Rommelfanger et al., 2007). In fact, noradrenalin is widespread in regions of motor control: cortex, basal ganglia, cerebellum, and spinal cord (Figure 2-11; (Grimbergen et al., 2007; Loughlin et al., 1986; Mason & Fibiger, 1979; Purves et al., 2004). In patients with severe gait and balance disturbances, reduced levels of noradrenalin in the CSF have been reported (Grabli et al., 2012; Grimbergen et al., 2007; Scatton et al., 1983; Tohgi et al., 1997). Although controversial, the link between locus coeruleus lesions and falls have been equally suggested in other pathologies

like the progressive supranuclear palsy (PSP), characterised by early postural disorders (Bloem, 1992; Grimbergen et al., 2007; Mann et al., 1983).

On the other hand, in advanced PD noradrenalin's depletion could have a supplementary deleterious effect on voluntary motor control, specifically in modulation of the indirect and hyperdirect pathway (Albares et al., 2015; Criaud et al., 2022; Tomassini et al., 2022). Recent imaging studies have demonstrated that fronto-striatal and fronto-subthalamic projections may be dependent on noradrenergic projections in task shifting and response inhibition (Albares et al., 2015; Tomassini et al., 2022; Xu et al., 2022). In fact, PD patients who executed an evaluation of executive functions through a stop signal task showed better results after an intake of a selective noradrenalin uptake inhibitor (atomoxetine), when compared to the placebo group (O'Callaghan et al., 2021; Rae et al., 2016; Ye, 2022; Ye et al., 2015). This was accompanied with higher right inferior frontal gyrus activity during inhibition, as well as increased functional connectivity between right inferior frontal cortex, subthalamic nucleus and striatum (Rae et al., 2016; Ye et al., 2015). The effect was even more pronounced in patients presenting more severe motor signs, thereby suggesting that noradrenergic depletion is probably more accentuated in these patients (Rae et al., 2016). In an attention-shifting task (Trail Making Test – TMT) de novo PD patients with and without cognitive deficits were compared to healthy subjects. Their performance was evaluated by the time of task completion, and they underwent a neuromelanin-sensitive imagery to evaluate the neuronal loss in locus coeruleus (Li et al., 2019). A correlation was found and further confirmed between these two parameters, showing that locus coeruleus plays a role in executive functions (Li et al., 2019). Therefore, lesions in this region may further contribute to gait and balance disorders, once the motor control has become dependent on cognitive control.

Given the chemical dependency between the dopaminergic and noradrenergic systems, as well as the demonstrated synucleinopathy progression, some authors hypothesise that dopa-treatment may have a double effect, impacting both neuromodulators (Devos et al., 2010, 2013; Purves et al., 2004).

C. Serotonergic depletion

In the same manner, lesions in raphe nucleus have been demonstrated in prodromal PD, resulting in a progressive depletion of the serotonergic neurons (Barber et al., 2018; Scatton et al., 1983). These neurons, found specifically in the upper brainstem and raphe region of the pons, project to a big variety of regions in the forebrain including frontal, motor, parietal and occipital cortices, along with cerebellum, basal ganglia, and spinal cord (Figure 2-12; Purves et al., 2004).

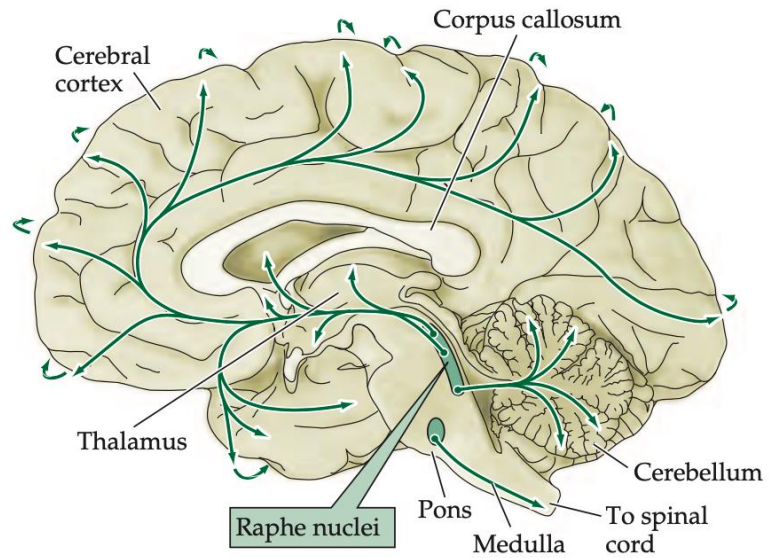


Figure 2-12: Serotonin projections in the central nervous system (CNS).

Serotonergic projections from the Raphe nuclei (RN) to the thalamus, the cerebellum, the cortical regions from frontal to occipital; along with projections from the pons to the spinal cord.

Purves et al., 2004

They are principally related to sleep, wakefulness, and mood regulation. While the serotonergic degeneration in PD has been linked to visual hallucinations (Politis & Niccolini, 2015), postural and rest tremor (Pasquini et al., 2018, 2020; Politis et al., 2010), fatigue, anxiety, and depression (Politis & Niccolini, 2015). Given that the latter are commonly observed in early stages of PD, some authors even proposed a phenotype characterised by a prominent neuronal loss in the raphe nucleus preceding the dopaminergic one (Beaudoin-Gobert et al., 2015; Prange et al., 2019; Sgambato-Faure & Tremblay, 2018). Some others even hypothesised a depression-related gait and balance disorders (Lord, Galna, et al., 2013). In fact, higher scores in depression were correlated to slower gait and increased variability. On the other hand, studies have equally shown that patients with severe gait and balance disorders presented lower serotonin levels in cerebrospinal fluid, when compared to other PD patients (Gao et al., 2020; Iacono et al., 1997). This would suggest an interdependence between these two neurotransmitter systems. Serotonergic implications in the emotion processing and anxiety may indeed contribute to the balance instability through the limbic loop, although to my knowledge no PET study investigated the direct link, only the intermediate ones between serotonin and anxiety, and

between the anxiety and risk of falling (Ehgoetz Martens, Silveira, et al., 2018; Pimenta et al., 2019).

Although it is little known on serotonergic effects on gait and posture, serotonergic innervations descend to the CPGs and permit to further modulate the spinal activations, as demonstrated in an isolated spinal cord in-vitro study (Dunbar et al., 2010). Therefore, serotonin seems also implicated in locomotion rhythm and pattern shifting (Dunbar et al., 2010; Grabli et al., 2012). However, more studies in that direction are needed to investigate the underlying mechanisms in healthy individuals, before understanding how these pathways could contribute to gait and balance disorders in PD.

2.3 The freezing of gait: an episodic gait disturbance

2.3.1 Clinical phenomenology:

As formerly introduced, among the most disturbing disorders of gait and balance is the FOG. It is “characterised by sudden, involuntary, and fairly brief episodes of inability to produce effective forward stepping” (Nutt et al., 2011). In fact, patients describe it as a sensation of having their feet glued to the ground, leading to loss of postural stability, and frequently preceding falls (Amboni et al., 2015). There exists a certain heterogeneity in FOG manifestations between sudden akinesia, trembling in place, or shuffling forward with small steps (Schaafsma et al., 2003). Although scarcely related to the main motor symptoms of PD (tremor, bradykinesia, and rigidity), FOG is closely related to severe axial akinesia. From distance it resembles to a sudden arrest of all ongoing motor commands, accompanied with an abnormal muscular activity (Breu et al., 2022; Cantú et al., 2019; Plotnik et al., 2005). It can be triggered during gait initiation, as well as during gait execution. FOG has been mainly reported during half-turn or termination of gait, in narrowing spaces, or dual-task situations – thus, its triggering can come from both external and internal factors (Nonnekes et al., 2015). Yet recently FOG triggers have been divided into three subtypes: motor, cognitive and limbic – in relation to basal ganglia functional loops (Ehgoetz Martens, Hall, et al., 2018; Ehgoetz Martens, Shine, et al., 2018). Indeed, the situations corresponding to the motor triggers are mainly complex locomotion scenarios including gait adaptation, obstacles clearance, narrowing or crowded spaces. Secondly, any condition adding up to the cognitive load of the gait, like unexpected visual/audio stimuli, new environments, along with dual tasks are of cognitive origin. Finally, limbic/affective triggers are related to internal states such as fatigue, stress, depression, anxiety and/or panic attacks (Giladi & Hausdorff, 2006; Lieberman, 2006). The variety of triggers makes it very disabling for everyday life, as well as difficult to target, given the inter-individual heterogeneity. It also decreases perceived quality of life and represents the main risk factor for falls, making it even more disabling by inducing multiple comorbidities (Bloem et al., 2004; Okuma et al., 2018).

Logically, episodes of FOG are preceded by multiple ineffective APAs when elicited during initiation, and by decreased step amplitude and increased step frequency when elicited during walking (Grabli et al., 2013). They are equally associated with increased variability in step time and amplitude from one step to another (Barbe et al., 2014; Hausdorff et al., 2003; A.

Weiss et al., 2015; D. Weiss et al., 2020). Furthermore, freezers present difficulties in weight-shifting during walking (Dijkstra et al., 2021), accompanied with impaired dynamic stability (Hasegawa et al., 2021) – thereby contributing to worse posture adaptation (Bekkers et al., 2018). Considered these characteristics and those of parkinsonian gait, PD patients seem naturally more prone to experience this phenomenon. Indeed, up to 27% of early-stage PD patients develop FOG (Perez-Lloret et al., 2014), with 79% of population in advanced stages (Tan et al., 2011). Moreover, patients with PIGD phenotype, as well as those with late disease onset are among those attained with FOG and falls the earliest. Therefore, with the global aging of world population, the prevalence of FOG across different disease stages is on the rise (Bardakan et al., 2022).

In addition, the more FOG progresses, the more executive and balance disorders come in line (Monaghan et al., 2022, 2023). In fact, patients experiencing FOG often present parallel cognitive and/or executive decay (Amboni et al., 2008). Hence, it seems to implicate a broader spectrum of circuits than those classically described in PD. Indeed, FOG can be observed in other pathologies than PD, including PSP, multiple system atrophy, hydrocephalus, cerebrovascular disease, primary progressive FOG and some genetical anomalies (Fasano, Baldari, et al., 2012; Fasano, Plotnik, et al., 2012). Moreover, freezing isn't exclusive to the locomotion, and can be observed in several everyday activities like speech (tachyphemia), writing, foot tapping or bimanual motor tasks (Giladi & Nieuwboer, 2008; Lewis & Barker, 2009; Nutt et al., 2011). This suggests that mechanisms underlying FOG go beyond the dopaminergic depletion observed in PD, or the locomotor control circuits.

2.3.2 Proposed models of FOG:

For a long time, FOG has remained a mysterious phenomenon due to the difficulties in obtaining objective measures explaining its complexity, as well as its resistance to proposed treatments (further developed at the end of this chapter 2.3.487). Therefore, multiple hypotheses of mechanisms underlying it have been suggested. In fact, the literature (Bardakan et al., 2022; Marquez et al., 2020; Nutt et al., 2011; Okuma, 2014) reports them in form of 5 pathophysiological non-exclusive models taking into account multilevel alterations in gait and balance (Figure 2-13; Marquez et al., 2020):

- M1: “Abnormal gait pattern generation model”: model suggesting an alteration of CPG output to the spinal cord resulting in asymmetrical and uncoordinated muscular activity preceding FOG (Hausdorff et al., 2003)
- M2: “Interference/Threshold model”: dynamic/rhythmical control of gait failure leading to more cognitive motor control, with disease progression become overwhelming on available basal ganglia resources (Lewis & Barker, 2009; Lewis & Shine, 2016)
- M3: “Decoupling model”: disrupted communication between motor planning and initiation neural networks (Shine, Matar, Ward, et al., 2013; Shine, Moustafa, et al., 2013; Snijders et al., 2011)
- M4: “Cognitive model”: conflict resolution deficit in line with executive functions failure (Nieuwboer & Giladi, 2013)
- M5: “Perceptual model”: multisensory integration deficits leading to difficulties in online locomotor adaptation (Almeida & Lebold, 2010)

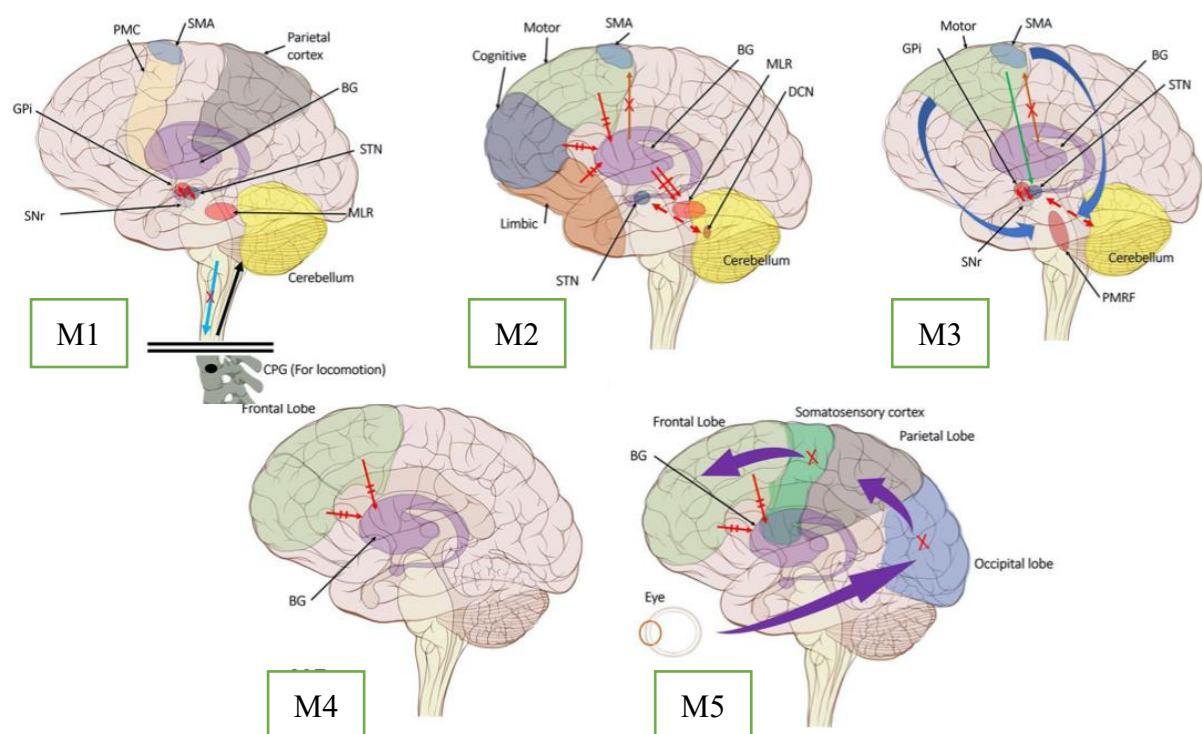


Figure 2-13: Hypotheses explaining freezing of gait (FOG) phenomenon.

M1: Abnormal activity of the Central Pattern Generators (CPG) induced by the disruption between spinal afferent (cues) and efferent (motor commands) projections. M2: Overwhelmed premotor, frontal, and basal communication, with enhanced inhibition of the mesencephalic locomotor region (MLR) coming from combined basal and cerebellar outputs. M3: Disruption between motor initiation and motor execution, combined with abnormal coupling between premotor (SMA) and subthalamic areas (STN), thereby increasing the inhibition of the ponto-medullary reticular formation (PMRF). M4: Frontal executive function failure. M5: Dysfunctional dorsal stream processing resulting in disruption of multisensory integration.

Adapted from Marquez et al., 2020; Medical Illustrations by Patrick Lynch, generated for multimedia teaching projects by the Yale University School of Medicine, 1987-2000. Patrick J. Lynch

These models were mainly deduced from neural changes observed at different stages of PD freezers – first three being a direct consequence of basal ganglia and PPN dysfunction. As explained earlier, with the progression of dopamine loss in PD, there is a significant loss of automaticity leading to increased uncertainty in motor activation. This transformation from automatised to volitional motor control puts multimodal (motor, cognitive, limbic) inputs to basal ganglia in competition for striatal resources, thereby rapidly reaching striatum overload when all inputs are activated. Therefore, along cortico-basal and basalo-cerebellar activity imbalance an over-inhibition of the thalamus results in easily provoked FOG episodes.

As proposed by Lewis & Barker in their theoretical interference model (Figure 2-14, 2009) and in animal FOG models, abnormal gait seems to be equally provoked by isolated PPN lesions. Moreover, the early unilateral disturbance of the striatal motor control pathways provoking parkinsonian gait add up to the lesions in PPN and further contribute to FOG. Indeed, both processes result in excessive inhibition of PPN, thalamus and cortical motor areas, and hence inhibition of their spinal output. In addition, third model suggests an abnormal

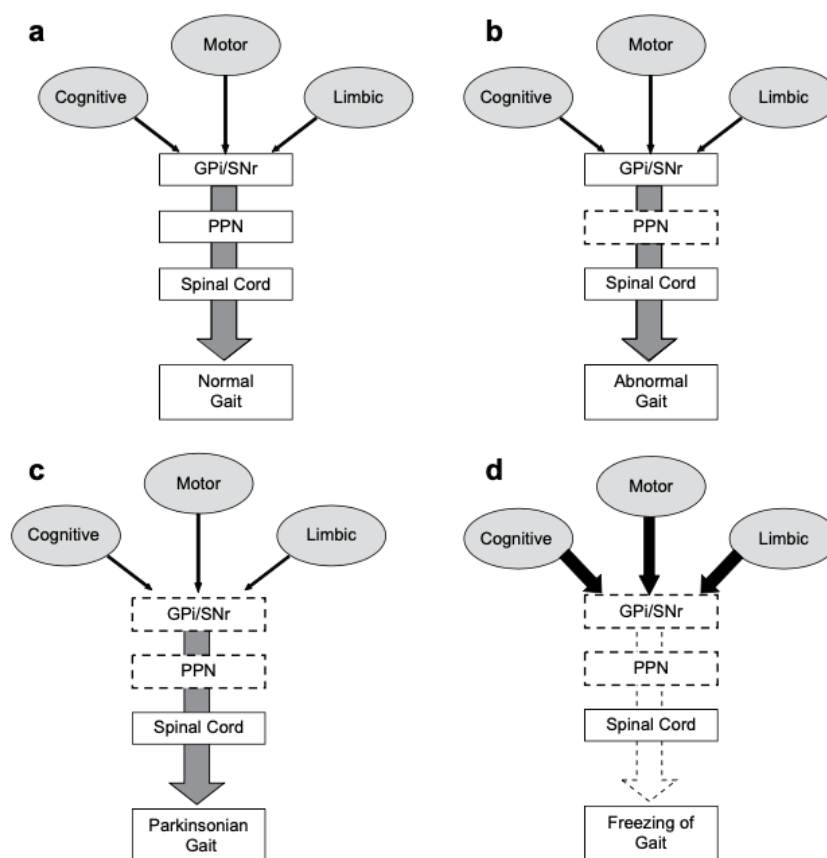


Figure 2-14: The interference model explaining the emergence of freezing of gait (FOG).

a. Normal gait supra-spinal control model with cognitive, motor and limbic inputs to the basal ganglia participating to motor planning and control. **b.** Model of the abnormal gait and posture resulting from the pedunculopontine nucleus (PPN) dysfunction. **c.** When PPN dysfunction is combined with basal ganglia abnormal activity it results in increased inhibition provoking a parkinsonian gait **d.** Once all functional loops (cognitive, motor, limbic) are activated and demand basal ganglia resources, the system is overwhelmed and the freezing of gait (FOG) emerges.

Lewis & Barker, 2009

communication between motor planning and initiation circuits – resulting in multiple ineffective APA leading to knee trembling during gait initiation FOG (Jacobs et al., 2009). Indeed, the observed tremor in place resembles the frequency of pathological cortical activity observed in PD. According to Lewis & Shine (Lewis & Shine, 2016), these effects would be in line with parasite SMA activity coming from the hyper-direct pathway (SMA-GPi), thereby leading to FOG.

In fact, these consequences of dopamine disruption, cumulated with cholinergic abnormalities are the most reported reason for gait and balance disorders. However, these models account mostly for motor FOG triggers and in first stages they are easily compensated by extensive frontal activity, and thereby involvement of cognitive resources. However, cognitive model suggests an early disruption of these circuits demanding more reliance on sensory inputs. Executive dysfunction observed in FOG patients concerns principally the decoupling between the frontal lobe and the basal ganglia circuitry (Amboni et al., 2008). In the most severe FOG cases, the last model comes to complete the pathophysiological image. Given the necessity for sensory cueing at this stage, Almeida and Lebold (2010) reported a dysfunction of visuomotor processing in situations when environment changes demand a locomotor adaptation. This model further explains the FOG induced by an excessive cueing, unexpected changes, as well as the doorway crossing FOG (Cowie et al., 2012).

To this day, the most essential model remains the interference/threshold model (M2), as it provides a homogenous theory of FOG generating mechanisms accounting for most of trigger types and interactions between them. The interference model considers the freezing as a phenomenon present in the real-life locomotion - it attempts to include all neural mechanisms involved: from the higher order processing to the modulation. The authors argue that FOG results from the overwhelming of the common downstream network by the concurrent upstream processing of cognitive, motor, and limbic information. As explained earlier, given the central place of basal ganglia, they are involved in a big variety of functions and hence receive inputs from all functional cortico-subcortical loops. Once their processing capacity is reduced because of the dopamine depletion and reduced metabolism, the information from different functional loops (cognitive, motor, limbic) would come to interfere with each other (Haynes & Haber, 2013). In line, this would provoke a rise of the response conflict, and therefore to the increased STN activity leading to the arrest of all actions. This would explain FOG episodes provoked by highly emotional or cognitively demanding situations, like walking through a scary or new

environment. This model is equally supported by multiple brain imaging studies showing structural and functional differences between freezers and non-freezers. Moreover, it covers the heterogeneity of freezing manifestations.

2.3.3 Physiopathology of FOG: from anatomy to physiology

A. Imagery

- Structural MRI

Anatomical alterations related with FOG in PD patients were reported in both GM volume and WM integrity, as well as connectivity.

In comparison with non-freezing PD patients, reduced GM volume was reported in higher order executive regions like precentral, prefrontal, and inferior parietal cortices, along with atrophy in associative occipital cortex (Bartels & Leenders, 2009; Herman et al., 2014; Kostić et al., 2012; Tessitore, Amboni, Cirillo, et al., 2012). Moreover, Kostic and colleagues (2012) have shown that GM volumes of these areas was related to FOG severity, meanwhile no such association was found with executive function evaluation (Frontal Assessment Battery - FAB) and general PD-induced handicap severity (Unified PD Rating Scale - UPDRS). Furthermore, a link between GM volume of the left cuneus was also correlated to the FOG severity, along with the atrophy observed in posterior cortical regions such as the cuneus, precuneus, lingual gyrus, and posterior cingulate cortex (Tessitore, Amboni, Cirillo, et al., 2012). These cortical alterations are in line with executive and visuomotor disorders observed in patients, as well as the proposed FOG models (M4, M5; Fasano et al., 2015; Stuart et al., 2016).

In subcortical regions, literature demonstrates a correlation between bilateral caudate GM volumes, and FOG severity (Fasano et al., 2015). Freezers have equally shown a decrease in thalamic (Sunwoo et al., 2013) and MLR GM volumes (Snijders et al., 2011). However, these alterations didn't correlate with FOG severity (Snijders et al., 2011). These studies partly support the interference model (M3) considering the extent of GM atrophy. Indeed, the bigger the variety of impacted regions, the higher load put on the striatal circuitry, and therefore the overload of the striatal processing capacity. Nevertheless, these findings, as well as methods of GM volume estimation remain debatable, so their relation to FOG episodes must be taken with caution (Fasano et al., 2015).

When it comes to structural changes in WM, alterations have been observed in fronto-parietal cortices, specifically between motor, limbic and cognitive regions (Canu et al., 2015;

Pietracupa et al., 2018). Other studies additionally reported reduced structural connectivity of the higher order motor control in relation to the STN, the cerebellum (Bharti, Suppa, Pietracupa, et al., 2019; Bharti, Suppa, Tommasin, et al., 2019) and the PPN (Fling et al., 2013; Schweder et al., 2010; M. Wang et al., 2016). Reduced structural connectivity between the PPN and the cerebellum has been equally highlighted (Nutt et al., 2011; Schweder et al., 2010). Most authors equally reported right lateralisation of the lesions, but this didn't seem to be correlated with the severity of the symptoms. Moreover, it is noteworthy that studied PD population presented executive impairment – in line with cognitive model of FOG (Bardakan et al., 2022; Canu et al., 2015). Freezing PD patients showed more pronounced cognitive impairment (MCI) than those without FOG and healthy controls, especially those with parietal visuomotor WM damage (Canu et al., 2015).

- **Functional MRI**

At rest a reorganisation of functional connectivity (FC) has been reported between locomotor/motor areas and the cognitive cortical and cerebellar regions. In fact, Fling and collaborators associated the increased functional connectivity of the SMA with MLR and CLR with FOG severity, suggesting an increased need for higher-order (cortical) motor control (Fling et al., 2014). An abnormal connectivity at rest has been equally reported between locomotor regions – hyperconnectivity between MLR and putamen (Mi et al., 2020). Furthermore, cortical sensorimotor areas have shown an increased connectivity with MLR (Fling et al., 2013, 2014; Lench et al., 2020) and with pallidum (Miranda-Domínguez et al., 2020), putamen with precuneus (Vervoort et al., 2016), thalamus with right inferior parietal lobule (S. Wang et al., 2021; Q. Yu et al., 2021), and CLR with other cerebellar regions (Bharti, Suppa, Tommasin, et al., 2019). Furthermore, these observations have been positively correlated with subjective or behavioural measures of FOG severity. All these data support the loss of automaticity and higher cortical/cognitive demands on effective gait, described in the decoupling model (M3). Higher involvement of cognitive resources has equally been demonstrated, although more specifically in limbic regions. In fact, higher frontoparietal cortices FC with the putamen and the insula were described by Gilat and colleagues (Gilat et al., 2018; Mi et al., 2020). In addition to further accentuating the involvement of cognitive cortical areas in balance and locomotion in freezers, this finding also demonstrates the disorganisation of the limbic circuitry among the amygdala, the putamen, and the insula (Gilat et al., 2018).

In addition, a decrease of connectivity has been reported in sensorimotor (Canu et al., 2015), attentional (Maidan et al., 2019; Tessitore, Amboni, Esposito, et al., 2012), default mode (Canu et al., 2015; Li et al., 2020) and visual (Canu et al., 2015; Lenka et al., 2016; Tessitore, Amboni, Esposito, et al., 2012; Q. Yu et al., 2021) networks. A decrease of FC was observed between visual and sensorimotor networks in freezers, when compared to non-freezers (Q. Yu et al., 2021), as well as between a few regions along the dorsal visuomotor processing stream (Canu et al., 2015; Lenka et al., 2016; Q. Yu et al., 2021). Moreover, FC alterations within occipitotemporal networks seem lateralised to the right, further stressing the hypothesis of visuospatial dysfunction contributing to FOG. Indeed, right hemisphere is classically associated with spatial processing, especially considering that this lateralised impairment was not related to the PD symptoms lateralisation (Bardakan et al., 2022).

Altogether, these findings indicate that the supposed compensation through cortical processing (sensorimotor, somatosensory) is not functional either as a consequence of the FOG development, or prior to it. Thereby the hyperconnectivity with higher order control could represent a biomarker for patients susceptible to experience this phenomenon (Bardakan et al., 2022). However, in a longitudinal study conducted by Jung and colleagues (2020), the increased FC between SMA and cerebellum was reported in patients who developed FOG and those who didn't, suggesting that it is not specific to freezers, but rather represent a concurrent deficit developing during PD (Bardakan et al., 2022). Moreover, the authors observed a decrease of FC between cerebellum and parieto-occipital regions in patients who later developed FOG. On the other hand, Bharti and colleagues have demonstrated a FC increase between these regions in PD freezers. At first sight contradicting, these effects may present evidence of FOG progression – hypoconnected visual regions being a signature for patients sensitive to FOG, while their hyperactivity being a result of struggle against it. In fact, in freezing patients an increase in FC robustness between putamen and retrosplenial cortex, involved in spatial cognition, has been noted (Bardakan et al., 2022; Potvin-Desrochers et al., 2019). Thus, these findings suggest higher reliance on external cues as compensation, as observed clinically in this patient population. All in all, the reported data at rest presents multisystemic and progressive changes – going from one compensatory system (frontal and premotor) to another (sensory, parieto-occipital) provoking FOG each time a compensation network fails. The final evidence, once the FOG is at its advanced form, indicates that the functional reorganisation put in place earlier is equally contributing to the disruption of striatal output, as proposed in the Interference model (Lewis & Barker, 2009).

In line with this, during gait simulation in virtual reality with stepping paradigm the alterations in functional connectivity have also been found between premotor and spinal regions, as well as between premotor and cerebellar regions (Fling et al., 2014). During the episodes of FOG, an increased BOLD signal was observed in the MLR and a decrease in the STN in correlation with the FOG severity (Shine, Matar, Bolitho, et al., 2013; Shine, Matar, Ward, et al., 2013). During motor arrests the activity was also reduced in basal ganglia, thalamus, and pre-SMA (Shine, Matar, Ward, et al., 2013), meanwhile its increase in frontoparietal networks was rather anti-correlated with FOG severity.

B. Physiology

Neurophysiology studies using electro encephalography (EEG), electromyography (EMG), and local field potential (LFP) recordings make it possible to take a closer step to separating neural mechanisms of motor preparation and motor initiation in FOG thanks to their temporal resolution. However, given the number and variety of circuits implicated in gait and balance control, as well as their extent, it is difficult to examine concerned network in its totality. Therefore, most studies focus on either cortical involvement in gait preparation and initiation, or subcortical activity. Data from these investigations provide further information on FOG mechanisms and support the proposed pathophysiological models.

In fact, EEG studies on self-paced upper limb motion of healthy individuals show a sequence of negative-positive potentials recorded in the central cortical area prior to the movement (Georgiev et al., 2016; Marquez et al., 2020). This activity sequence is called the readiness potential, negative one (early) corresponding to the motor preparation, and positive one (late) to the motor initiation. Negative potential is often linked to the pre-SMA, SMA, and Brodmann area 6 activation (Georgiev et al., 2016; Marquez et al., 2020), meanwhile the positive one to those of primary motor cortex (Brunia et al., 2011; Marquez et al., 2020). In PD patients, this early readiness potential shows reduced amplitude, and the contrary is found in the late readiness potential. Authors argue that these mechanisms are related to the loss of automaticity and the decoupled communication between basal ganglia and SMA (Dick et al., 1989; Marquez et al., 2020). According to the decoupling model this abnormal crosstalk may constitute a basis for FOG development. In fact, the more the conflictual commands arise between SMA, primary motor cortex, and subcortical circuits, the more cognitive and premotor areas need to compensate for the loss of automaticity. Moreover, time-frequency analyses

showed that during gait simulation with lower-limb pedalling paradigm patients with FOG exhibited lower mid-frontal theta (4-8 Hz) power when compared to PD patients without FOG (Marquez et al., 2020; Singh et al., 2020). Theta power in frontal cortex is usually related to cognitive control efficiency, hence its reduction in freezers would be related the reduction of executive functions during motor execution (Hall et al., 2014; Marquez et al., 2020). Nevertheless, theta activity during actual FOG episodes marks an increase in central and frontal areas (Marquez et al., 2020; Shine et al., 2014). The latter goes in line with increased need for cognitive conflict resolution during FOG (Bartels & Leenders, 2008; Handojoseno et al., 2012, 2013, 2018; Marquez et al., 2020). Although higher reliance and involvement of the impaired executive functions may be compensatory, it may also further contribute to the abnormal crosstalk and competition for neural resources between motor, cognitive, and limbic systems in basal ganglia. According to the interference/threshold model, such an overstimulation of this circuit could also be a factor of FOG event (Chen et al., 2019; Lewis & Barker, 2009; Lewis & Shine, 2016).

Another frequency alteration characteristic to this phenomenon occurs in the beta band (13-30 Hz). In comparison with non-freezers, FOG patients showed an increase of beta power in mid-frontal areas during motor execution (Marquez et al., 2020; Singh et al., 2020) and in parietal regions during the transition from normal gait execution to freezing events (Marquez et al., 2020; Shine et al., 2014). This excessive beta frequency synchronisation in frontoparietal regions supposedly reflects the failure of communication frontally generated plans to the motor regions (Handojoseno et al., 2018; Marquez et al., 2020). Beta frequency has already been typically associated with dopa-responsive FOG. Patients presenting freezing off medication show significant increase of beta band power while seated, which can be alleviated by dopaminergic treatments along with FOG frequency (further discussed in the next section; Marquez et al., 2020; Toledo et al., 2014). Furthermore, in an oddball task paradigm, freezers presented an impairment of event-related desynchronisation of beta frequency following the target stimulus, compared to healthy age-matched controls and PD patients without FOG. Thereby, freezers had worse performances despite correct recognition of the target stimulus, as demonstrated through similar event-related potentials between groups. These results indicate a dysfunctional communication between frontal cortex and the basal ganglia in integrative processing post-perception (Marquez et al., 2020; Toledo et al., 2014). In consequence, this further targets the impaired STN activity, specifically within the motor and associative loops.

At the subcortical level, LFP recordings from STN during single or dual-task walking showed an increased low-beta (13-20 Hz) and theta (4-8 Hz) power independently from the condition (Chen et al., 2019; Marquez et al., 2020). The level of the increase seemed to be related to FOG vulnerability, thereby contributing to the synchronous firing from the basal ganglia and supporting the interference FOG model (Lewis & Barker, 2009; Thenaisie et al., 2022). It is noteworthy that STN and GPi in PD show abnormally low and synchronised oscillations, usually related to the increase of beta band frequency in the cortex (P. Brown, 2003). Accordingly, these PD-related changes in neurophysiology provoke akinesia, hence their significant input to freezing episodes.

After clearing out the mechanisms behind FOG, the principal question remaining is how to use them in treatments. In the next section I will dwell on the proposed solutions and their limits to remediate the deterioration or offer the alleviation of the symptoms.

2.3.4 Inefficiency of pharmacological and neuromodulation treatments

A. Dopaminergic targets

Given the prevalence of FOG in advanced PD, it was firstly associated with the increasing dopamine depletion, resulting in the aggravation of axial motor symptoms. Indeed, PD patients following a dopamine replacement therapy (levodopa, L-DOPA) showed significantly less severe and less frequent FOG episodes ON medication, when compared to OFF medication (Schaafsma et al., 2003). However, 30% of patients present resistant FOG ON dopaminergic medication (Amboni et al., 2015), while others develop treatment-induced pathological dyskinesias in later disease stages (Espay et al., 2018; Fabbrini et al., 2007; Thobois et al., 2005). This data makes it clear that L-DOPA is not adapted for FOG treatment in all patients, sometimes even worsening their condition (Espay et al., 2018; Thobois et al., 2005). One of the hypotheses states that it would be related to the non-specificity of dopaminergic replacement treatment to the striatum. Authors suggest that at the advanced stage of dopaminergic depletion, levodopa can be intercepted by preserved serotonergic receptors and further distributed to the cortex (Carta & Tronci, 2014; Pagano et al., 2018). However, without the regulation loop specific to striatal circuitry, too much dopamine is released thereby overflowing the prefrontal cortex and disturbing its functioning in complex locomotor scenarios.

Following the same logic, to address the dopa-resistant freezing and avoid its future deleterious effects on the cortex, deep brain stimulation (DBS) is applied in the STN. The alleviated symptoms are principally those typical of parkinsonian hypokinesia - the stride length and amplitude (Pötter-Nerger & Volkmann, 2013; Scholten et al., 2017). The direct effects on FOG were reported only off dopaminergic treatment, yet they are not very consistent (Bourilhon et al., 2022). Some studies showed its effective reduction in the early period of 3-5 years after STN-DBS (Barbe et al., 2018; Fasano, Baldari, et al., 2012; Schlenstedt et al., 2017; Schüpbach et al., 2005), with a considerable reduction of efficiency in ~50% of patients after 1 year. Indeed, firstly observed positive effects did not last on the long-term – most of implanted patients reported loss of efficiency on FOG after two-year period (Karachi et al., 2019; B. Lau et al., 2019). Moreover, recent study suggests that only around one third of freezers are really improved with STN-DBS (Karachi et al., 2019). Others, show no effect, or even experience FOG aggravation with the DBS, thereby making this method debatable (Moreau et al., 2008; Thobois et al., 2005). In fact, in some cases STN-DBS used in non-freezing PD patients was reported to induce FOG. Multiple explanations were given for this deleterious effect of the DBS: the principal one being the misplacement of electrodes in the medio-antero-cranial direction (D. Weiss et al., 2020). Considering the size of STN (approximately 8x6x6 mm), as well as the fore-mentioned overlap between its different functional territories, the exact placement of the stimulation is a very important factor. In addition, an excessive energy delivery could induce the over-activation of the pallidum, resulting in the observed akinesia (Fleury et al., 2016; Moreau et al., 2008). Thus, some authors searched to change the stimulation parameters by making it asymmetrical (Fasano et al., 2011), or by lowering the DBS frequency from 130Hz to the range 60-80Hz, and maintaining the global electric energy (Moreau et al., 2008; Varriale et al., 2018; Xie et al., 2017). Nevertheless, these strategies suffer from the same long-term effect attenuation and response variability in patients (Ricchi et al., 2012; Sidiropoulos et al., 2013; Zibetti et al., 2016).

B. Non-dopaminergic targets

As fore-mentioned, ever since authors suggested a multisystemic damage at the origin of FOG and searched for non-dopaminergic treatment targets – be it for medication and DBS (Castrियोto et al., 2011; Collomb-Clerc & Welter, 2015; Ferraye et al., 2008; Schlenstedt et al., 2017). As formerly presented: noradrenergic, serotonergic, and cholinergic systems may contribute to postural instability and show alterations in PD. However, pharmacological studies

trying to use these alternative pathways failed to prove better results than those observed with previous treatments. Indeed, using methylphenidate (1mg/kg/d) to inhibit both dopamine and noradrenalin re-uptake showed improved FOG, but only as a replacement of DOPA treatment. FOG resistant to DOPA showed no changes (Moreau et al., 2012). In FOG patients with mild to severe depression the antidepressant treatments acting on noradrenalin and serotonin altogether (duloxetine), or on serotonin only (paroxetine or escitalopram) showed an improvement in FOG Questionnaire score (Gao et al., 2020). The depression was also improved, thereby pointing to the limbic FOG triggering mechanism. However, considering the lack of placebo control group, small sample size, and short treatment duration (10 weeks), these results need to be reproduced and confirmed in further long-term studies, and applied to a larger FOG population. When it comes to cholinesterase inhibitors (donepezil, 10 mg/d), one study found a significant reduction of fall rate in comparison with placebo (Chung et al., 2010). Yet the reported effect was of small order – the fall rate decreased by 0.12 per day ($p = 0.049$). Although statistically significant, the improvement was barely perceivable by patients. Moreover, the effect of these treatments on other autonomous systems should be evaluated. Donepezil and methylphenidate show cardiac side effects, thereby reducing save responder group in PD.

As formerly presented cholinergic centres in midbrain have shown strong implication in locomotor function, as well as lesions in different FOG populations (PD, PSP). Furthermore, animal studies have given proof of effective akinesia treatment through PPN stimulation. Therefore, PPN has been tested as possible low frequency DBS target in patients. In a group of patients with STN and PPN DBS an improvement of gait and balance was reported. However, these results were not reproduced in double-blind studies (Bourilhon et al., 2022; Stefani et al., 2007; Welter et al., 2014). On the other hand, a subjective alleviation of number of falls or FOG has been repeatedly reported (Ferraye et al., 2010; Moro et al., 2010). Nevertheless, the main challenge in PPN DBS is the precise anatomical limits of its cholinergic part, and more specifically the part receiving pallidal projections, supposed relevant for gait activation (Garcia-Rill et al., 2019). Stimulation parameters for PPN represent another challenge, and the consensus has not been met yet – therefore, this technique is as inconsistent and debatable as the STN-DBS. Further evaluation of network alterations it induces, as well as identification of eventual predictors for patients' responsiveness to treatment are necessary (Thevathasan et al., 2018; Thevathasan & Moro, 2019; D. Weiss et al., 2020).

On the cortical level, stimulation is equally possible and has been experimented with non-invasive techniques like repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) on cortical areas involved in gait modulation. For instance, applying rTMS (1 session, 10 Hz) over the lower leg area in the primary motor cortex in PD FOG patients showed improvements in comparison to sham stimulation. Changes concerned the timed up-and-go test, turn steps and turn times (Lee et al., 2014). When the stimulation sessions were multiplied, patients reported less trouble turning, and a small effect on the FOG questionnaire (M. S. Kim et al., 2015). The effect on FOG frequency and duration in the Stand-Walk-Sit test (SWST) was further pronounced in a study using anodal tDCS over primary motor cortex (Valentino et al., 2014). The latter was contradicted in another study, thereby putting a shadow of a doubt on its viability. Meanwhile a simultaneous tDCS of primary motor cortex and the dorsolateral prefrontal cortex (dlPFC) showed clinical FOG improvement (Dagan et al., 2018). Later, other studies tried to reproduce the effect using high frequency rTMS over primary motor cortex and anodal tDCS over dlPFC, yet the improvement didn't reach statistical significance (Chang et al., 2017). Along FOG, authors reported an increase in executive function measures, thereby confirming the efficiency of dlPFC stimulation in restoring cognitive functions. It further indicates that observed FOG improvement was mainly related to better executive control, and therefore cognitive triggers.

The main issues with these promising results are the sample and effect sizes, as well as the problematic of durability of the observed effects. Taken altogether, FOG mechanisms remain poorly understood and hence poorly taken care of. Its paroxysmal and heterogenous nature seems to make it impossible to address by targeting isolated regions or neurotransmitters. As presented in this chapter, FOG is a multilevel, multimodal and multisystemic disorder, therefore its treatment should be too.

Chapter 3: Multimodal rehabilitation as an effective tool in PD with FOG and emerging exergaming as therapeutics

3 Rehabilitation: rationale and techniques for PD with FOG and falls

- Goals and methods according to FOG severity

As formerly presented (Chapter 2.3.4) pharmacological treatments are not sufficient for PD patients experiencing progressive gait and balance disturbances at different stages of the disease. For the last three decades researchers focused on different means to slow down the degenerative process of PD and to help partly recover lost automaticity through combination of pharmacological and non-pharmacological treatments. The main adjunct to the fore-mentioned methods used in this perspective has been the motor rehabilitation. First introduced in the middle of the 20th century (Abbruzzese et al., 2016; Clark et al., 1956) and applied from the early stages of PD, it was considered as a complementary strategy to prevent secondary complications and maximise functional ability. It was also found that it contributes to improving the parkinsonian motor disability and activities of daily living scores (Abbruzzese et al., 2016; C. L. Tomlinson et al., 2012). It is noteworthy that rehabilitation techniques and goals evolve in parallel to the disease symptoms and severity – making this therapeutic particularly flexible and patient-oriented.

At the beginning motor rehabilitation sessions are sporadic, adapted to each patient's needs, aiming mainly at anticipating future disorders (French National Authority for Health - HAS, 2016). As the disease progresses to “mild to moderate” stage, an increase of the frequency (2-4/ week) and the regularity of the rehabilitation sessions should be put in place, while in younger individuals higher training intensity is advised. The rehabilitation itself is further adapted to the developed symptoms and focusing on actions of everyday life like movement initiation, turning, balance, and postural reactivity. The expected effect concerns developing maximal respiratory and musculoskeletal abilities, as well as increasing neuromuscular proprioception (Morand, 2022). Finally, in the advanced stages, rehabilitation targets preferentially posture verticalization, correcting postural defects, helping to identify and avoid deleterious postural behaviour. It remains systematic, often home-based, and attempts to maintain and reinforce patient's autonomy, as long as it is possible (HAS, 2016).

In perspective of the PD and its multi-layered disorders, that is beyond the motor symptoms, it was equally pointed out that the rehabilitation should include non-motor components. The latter are often related to as cognitive-motivational, and further expand to sensory and spatial components. One may consider them a guide to compensation techniques proposed to or spontaneously applied by patients.

In fact, typical rehabilitation evolved from purely motor one, to its multimodal version – often through using new technologies and robotic-mechanic devices (video games, smart glasses, treadmill, laser-shoes). Very common in neurological rehabilitation for stroke, these methods have shown that engaging attention may benefit to motor learning and therefore to the neuroplasticity (Ferrazzoli et al., 2020). It goes in line with the observed cognitive compensation used by PD patients in “mild to moderate” FOG (Bardakan et al., 2022). Thus, although classical rehabilitation at first targets the articular mobility, muscular force and/or endurance, in PD physiotherapists often add cognitive tasks to work on motor execution in double-task conditions (C. L. Tomlinson et al., 2012). Decomposing complex motor sequences into simplified ones is equally proposed, in order to help avoiding the overload of cognitive resources (Abbruzzese et al., 2016; Ferrazzoli et al., 2020; Keus et al., 2009).

Moreover, as it was presented earlier (Chapter 2.3.2), in advanced PD with FOG the impairment of visuomotor processing capacity results in higher reliance on the sensory cues (visual or auditory). Therefore, the sensory and spatial components used in rehabilitation may play a role of feedback to further enhance the learning process and help put in place compensatory mechanisms (Ferrazzoli et al., 2020). In fact, recently Gilat and colleagues (Gilat et al., 2021) proposed to separate the rehabilitation techniques in PD according to three axes: 1) learning mechanical compensation strategies to avoid or overcome FOG, 2) learning FOG triggers and dealing with them, 3) targeting neural correlates of FOG to stimulate the neuroplasticity. These strategies are all part of a multi-dimensional rehabilitative approach - necessary to the transformation of classical therapeutics (dopaminergic replacement therapy, DBS).

To date, the fore-mentioned techniques are applied through a large choice of therapies using balance training, treadmill walking, fitness, dance, and combat sports, alongside action-observation therapies (AOT) and motor imagery training, however scientific evidence for choosing the optimal method is still lacking (C. L. Tomlinson et al., 2012). Most studies in this domain focused on short-term (less than 12 weeks post training) improvements in FOG severity

following the cue-enhanced balance training (Allen et al., 2010; Plotnik et al., 2014), the AOT (Mezzarobba et al., 2018; Pelosin et al., 2018), the classical physiotherapy (Cosentino et al., 2020), and the general exercise training (Silva-Batista et al., 2020; Wroblewska et al., 2019); while the combination of balance training and physical therapy showed promising 12-month retention of the effects. Thus, there is a high probability that once the optimal rehabilitation protocol is found, the beneficence retention would last even further. On average, when compared to no intervention, nearly all rehabilitation programs showed beneficial effects on gait, balance, functional reach test, and FOG in PD. Data suggests that the observed behavioural and clinical changes are intensity- and task-specific, suggesting that depending on what has been trained, different motor skills will be impacted (Ferrazzoli et al., 2020; C. L. Tomlinson et al., 2012; van der Kolk & King, 2013). In fact, effects of the balance training will be foremost visible in postural stability, meanwhile bimanual trainings will foremost benefit to the upper limb motricity (Ferrazzoli et al., 2020). Nevertheless, some degree of transfer is possible. Notably, some authors argue that improving gait through cognitive training may be the effect of better executive functions, implying more efficient compensation to FOG (Bardakan et al., 2022; Ferrazzoli et al., 2020). Furthermore, the more the training is intense, the bigger its effects and the longer they last (M. K. Mak et al., 2017; Sehm et al., 2014). Yet, the intensity of the training is directly dependent on patient's motivation and perceived fatigue.

The idea of further targeting the motivational and cognitive aspects of rehabilitation, accompanied with improving the resemblance between the rehabilitation and real-life walking conditions resulted in creation of training devices and/or use of existing technologies to this means. This aspect was addressed specifically by Mirelman and colleagues (Mirelman et al., 2011) who suggested adding a low-level immersive virtual reality (VR) to the training. In consequence they observed an effective increase of the training intensity, as well as the level of cognitive involvement, and motivation. In fact, research on VR and video games showed the evidence for enhanced attentional, visuospatial and executive functions in healthy individuals and in patients (Kühn et al., 2019). The mechanisms underlying performance in VR and/or gaming are based on multisensory feedback and goal-oriented behaviours, while using exercise-based immersive video games (exergames), adds a motor component to it. Stimulating multiple systems simultaneously, all while maintaining high level of alert, further promotes facilitated execution of repetitive movements, and in turn boosts motor learning and problem solving. Given that the motor rehabilitation is based on the movement repetition too, using VR and/or video games presents a solution to counter fallouts from the therapy. Indeed, most of patients

who abandon the rehabilitation programs do it due to the loss of motivation or decreased belief in exercise effects (Afshari et al., 2017). Therefore, researchers turned to the growing field of serious games and exergaming as tools in neurological rehabilitation. Pilot studies have shown positive effects on gait parameters, dual-task walking, along with the increase of executive functions (Barry et al., 2014). Nevertheless, as in case of rehabilitation alone, no consensus was met in terms of the methods and parameters assuring the most significant and long-lasting effects.

In the present chapter I will first attempt to review the effects of the existing rehabilitation strategies presented in this introduction - going from the classical physical training, through the motor-cognitive approaches, to the multimodal rehabilitation with VR/video games. The goal of this work is to further understand which compensatory strategies seem the most adapted to PD with FOG. Finally, I will examine the potential neuroplasticity mechanisms induced by the multimodal rehabilitation using video games. I will base this work on already mentioned compensatory circuits present in PD, as well as on the separate and combined effects of different rehabilitation components (motor, cognitive, motivational, sensory) on brain circuitry.

3.1 Effects of different rehabilitation strategies

3.1.1 The role of motor exercise

A. Basic practices

Clinically speaking, motor exercise through physical therapy is a common strategy in elderly and patients with motor disabilities (PD, post-stroke, etc.), that aimed at increasing functional mobility. According to the “European Physiotherapy Guidelines for Parkinson's Disease” the major goal of motor rehabilitation is to improve patients’ physical abilities, manual activities, transfers, gait, and balance (Abbruzzese et al., 2016; Keus et al., 2009). The main techniques include aerobic and muscle reinforcement trainings characterised by alternating sequences of active movement repetition and rest, thereby working on muscular force and endurance. The duration of the active sequence and number of repetitions defines how much physical effort one can endure before reaching fatigability. Usually, the fatigability threshold tends to increase with training (Briennesse & Emerson, 2013; Saltychev et al., 2016), therefore training intensity and difficulty increase too according to patient’s capacities. It is also a

common practice to target multiple articulations at once, or big muscular groups like knee flexors and extensors (Schilling et al., 2009).

The principal building blocks of muscular reinforcement training are concentric, eccentric, and isometric muscular contractions of trunk, upper, and lower limb muscles in progressive resistance training, cycling, walking and balance exercises. This kind of intervention has a variable duration going from few weeks to 2 years, depending on symptoms severity. Aerobic training already implies a goal-based approach, thereby adding a motivational and cognitive aspects to the rehabilitation. Indeed, in an aerobic training there is more complexity and hence more attention needed to focus on the goal to reach. Nevertheless, it is still considered as motor rehabilitation, therefore I will present it as such.

B. Prevention and neuroprotection: sedentary lifestyle as a risk factor

This type of intervention specifically applies to PD patients, because when compared to their peers they present higher motor handicap, reduced muscle strength (force) and power (force x velocity), as well as excessive sedentarism (M. K. Y. Mak & Wong-Yu, 2019; van der Kolk & King, 2013). Indeed, at the beginning PD patients show 20% decrease of daily step count, when compared to healthy people, but at the moderate stage of the disease (Hoehn & Yahr score 3) this reduction reaches 40% (Lord, Godfrey, et al., 2013). The link between muscular characteristics and sedentarism has long been defended. Researchers suggested the existence of a vicious circle going from motor symptoms aggravating the observed sedentarism, which would further lead to the increase in severity in motor impairments and non-motor symptoms (Figure 3-1, van der Kolk & King, 2013).

In fact, it seems logical that unused muscles lose their functionality, yet as it enhances gait and posture impairments, it further leads to falls and comorbidities induced by them (i.e., fractures, hospitalisation), finally resulting in loss of autonomy and further immobilisation.

Sedentary lifestyle is equally supported by the non-motor symptoms like depression, apathy, anxiety, fatigue, sleep disorders, and constipation. Of course, main limits of physical activity are the lack of motivation and low fatigue threshold. PD patients who decide to stop the physical exercise training often report high fatigue, and lack of a person to motivate them (Afshari et al., 2017). Moreover, depressive and anxious signs of PD may also be at the origin of lower belief in exercise efficiency, as well as less confidence when it comes to one's capacities. These patients are among the less prone to engage in motor rehabilitation program (Cavanaugh et al., 2015; T. Ellis, 2019). It is also important to highlight that the amount of non-motor symptoms has been associated with parkinsonian motor disability (Colcombe et al., 2004; van der Kolk & King, 2013), yet it may also be the simple effect of PD severity.

Secondary comorbidities related to prolonged sedentarism include osteoporosis and

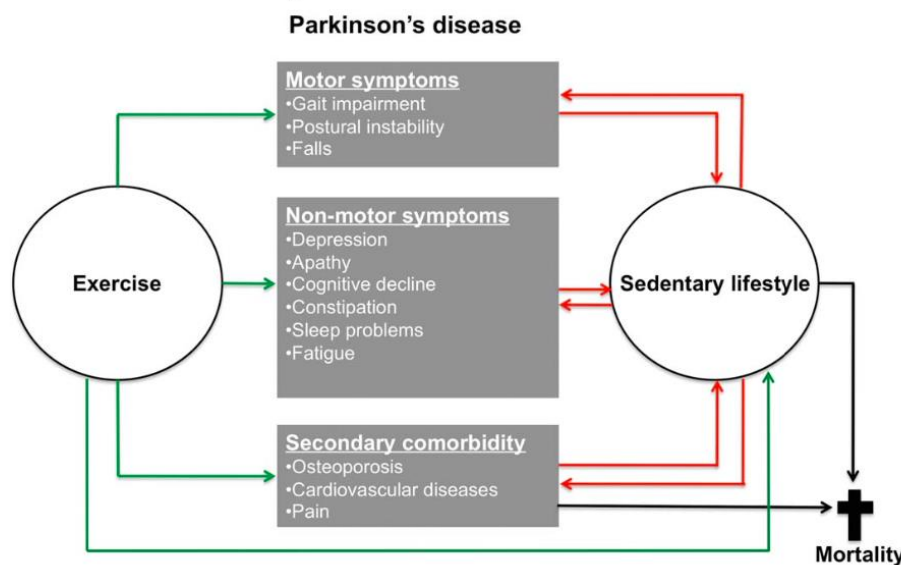


Figure 3-1:
Effects of
sedentarism in
the Parkinson's
disease (PD)
and the related
vicious circle.

The model shows observed symptoms in PD in relation to the sedentary lifestyle and exercise

Van der Kolk & King, 2013

cardiovascular diseases, which can further increase the risk of mortality, as well as further maintain the sedentary lifestyle (van der Kolk & King, 2013). Osteoporosis is an added risk factor for comorbidities from falling. Moreover, studies have shown that patients with lower bone mineral density experienced higher gait and posture disturbances – slower walking speed, lower walking capacity (in terms of distance walked in 6 minutes time), as well as reduced muscle strength (Pang & Mak, 2009).

As observed in clinical trials, motor exercise can improve motor handicap scores by up to 50% (Alberts & Rosenfeldt, 2020; Miller Koop et al., 2019). Globally it represents an argument for better physical function induced by training (Prodoehl et al., 2015; M. Schenkman et al., 2018). Moreover, enhanced gait initiation (Hass et al., 2012) and speed (Goodwin et al.,

2008; Miyai et al., 2002; Palmer et al., 1986; Shulman et al., 2013), stride and step length (Rafferty et al., 2017), as well as muscle strength (Shulman et al., 2013) and balance performance (Krumpolec et al., 2017; Shen & Mak, 2015) have also been observed across studies. Some researchers even argued a decrease in number of falls and increase of quality of life (Allen et al., 2011; Ashburn et al., 2007; Shen & Mak, 2015). Although well established in the elderly, it remains debatable in PD population (C. L. Tomlinson et al., 2012).

Despite that the vicious circle is in fact evident, the changes in muscular activity don't seem solely dependent on the sedentary lifestyle. As formerly presented, rigidity, weakness and muscular hypotrophy are found especially in ankles, hips, and knees, thereby reducing their effective functional role. These alterations in muscular physiology were also associated to reduced gait speed and increased postural instability (Allen et al., 2011; Chapitre 2). Moreover, just as the hypokinesia, these muscular alterations could be improved with dopamine replacement treatment (van der Kolk & King, 2013). It would imply that the observed hypotrophy, along strength and power decrease is also the effect of the neurodegenerative processes (van der Kolk & King, 2013). Therefore, the increase in muscle strength induced by physical therapy implies better mobility, and therefore preservation of the musculoskeletal system against degeneration (M. K. Y. Mak & Wong-Yu, 2019). The increase of stride length and gait velocity are the secondary effects of these mechanisms. However, considering that motor rehabilitation and dopamine replacement treatment have similar effects, some authors argue that there might induce similar changes on the neuronal level (Fisher et al., 2013; Petzinger et al., 2013; Speelman et al., 2011). Furthermore, the initial severity of the motor symptoms is also an important factor predicting whether motor exercise would be beneficial. Ellis and colleagues (T. D. Ellis et al., 2021) demonstrated that patients with lower UPDRS scores benefited more from the motor exercise training.

This encourages to propose the rehabilitation at early stages of the disease in the objective of inducing a neuroprotective effect of exercising. It would imply, that exercising works not only through the biomechanical mechanisms, but also at the molecular level. The retention effects of reported benefits of aerobic and reinforcement therapies have been demonstrated on short and long term. According to the recent review by Mak & Wong-Yu (2017) balance training effects can last up to one year after therapy completion (M. K. Mak et al., 2017; Shen & Mak, 2015; Wong-Yu & Mak, 2015), while gait training only 6 months (Carda et al., 2012; M. K. Mak et al., 2017; Miyai et al., 2002; Picelli et al., 2013). Of course,

the retention effect remains dependant on duration and intensity of the training. In addition, Sasco and colleagues (1992) proposed that those leading a physically active life were at a significantly lower risk of developing PD, which was recently confirmed in a few epidemiological studies (Shih et al., 2016).

In consequence, motor rehabilitation represents a solution to transform the vicious circle into a virtuous circle. Encouraging PD patients to move more may play a beneficial role on the motor and non-motor symptoms, as well as help avoiding secondary comorbidities (van der Kolk & King, 2013). Meanwhile in healthy adults it may contribute to a delay of the development of motor symptoms through the underlying metabolic, structural and functional mechanisms (developed in the next part, 3.1.2). Nevertheless, considering that the effects of motor training are dependent on training regularity, intensity, and specificity, it is logical that preventing FOG and falls must go beyond muscle reinforcement.

C. Restoring motor functionality through goal-based training & aerobic

As formerly introduced, gait and balance disorders are among the least responsive to the classical treatments, hence their rehabilitation represents a big issue in the field. Muscle reinforcement indeed helps improving stability and mobility, but it isn't enough to correct postural anomalies leading to muscular degeneration. From the therapeutical perspective, due to an abnormally flexed posture, PD patients have also a reduced neck and trunk range of motion (M. L. Schenkman et al., 2001; van der Kolk & King, 2013). It results in a decreased functional reach, further contributing to the postural instability (M. Schenkman et al., 1998; van der Kolk & King, 2013). Although this impairment can be effectively addressed through muscle reinforcement training, it is primordial that patients abandon bad postural habits for the effects of the rehabilitation to last. In fact, there is evidence that following muscular changes due to the disease patients lose the compensatory mechanisms such as hip-to-ankle strategy and/or compensatory stepping in case of external balance disturbance (Mak & Wong-Yu, 2019). Instead, they try to compensate through hip and ankle muscles at the same time, thereby failing to do it. Physical therapy focusing on correcting these behaviours is necessary to improve patients' mobility.

Moreover, such a targeted training may further recreate lost automatisms of dynamic postural control. Motor training rehabilitation programs targeting gait and balance are based on the principle of movement repetition followed by feedback – two components of effective

motor learning. A challenging balance training usually involves a displacement of body CoM, and reduction of the size of the base of support and upper limb support (Allen et al., 2011). To address PD population usually 3 principal domains are targeted in the balance training: biomechanical constraint, APA, and dynamic gait stability. Rehabilitation programs aiming at improving balance include movement strategy training (M. E. Morris et al., 2015), anticipatory and reactive balance exercises (Ashburn et al., 2007; Schlenstedt et al., 2017) and aquatic therapy (Zhu et al., 2018). Therefore, there exists different means to implement a training based on correcting bad postural habits, replacing them with compensatory postural strategies leading to increased stability during gait initiation and execution (Mak & Wong-Yu, 2019).

The targeted training is widely used in clinical practice including the fore-mentioned techniques and other goal-based trainings. It generally shows an increase in gait velocity and a decrease of postural instability (C. L. Tomlinson et al., 2012). Other goal-based rehabilitation techniques are treadmill and amplitude training, forced cycling, yoga, dance, martial arts, and combat activities (Abbruzzese et al., 2016; Petzinger et al., 2013). In addition, the evidence shows that gait and balance training coupled with muscle reinforcement can show positive effects on gait variability with a lasting effect of 12 months, after a 2-year rehabilitation with 3 trainings per week (Mak & Wong-Yu, 2019).

Treadmill walking training is among the most frequently used technique in goal-based rehabilitation. Patients are demanded to walk with long stride, and they are provided with a harness supporting their trunk, and preventing them from falling (Toole et al., 2005). The training may be executed with or without partial body weight support (Miyai et al., 2002), and the belt speed can be progressively increased from one session to another (Herman, Giladi, Gruendlinger, & Hausdorff, 2007). The results observed on walking speed, stride length, and walking endurance are consistent across studies and demonstrated a maintained effect after 3-6 months after the end of the training period (Miyai et al., 2002; Picelli et al., 2013; Toole et al., 2005).

An intensive (3 sessions per week) 8-week stationary cycling training with voluntary pace showed an improved performance of Timed Up and Go (TUG) test in PD patients OFF medication (Miller Koop et al., 2019). TUG is primarily used to measure global functional mobility, and it is decomposed in several functional tasks like sit-stand, stand-sit, ambulate in straight line, turn (E. L. McGough et al., 2016; Nadeau et al., 2017; Uygur et al., 2017). In this study, aerobic training improved turning velocity, time of gait phase and stand-sit duration in

voluntary and forced pace (Koop et al., 2019). Thus, we can speak of beneficial effects of intensive cycling on different aspects of mobility going from transfers, through gait to turning. Nevertheless, the study was done in early PD population (mild impairment stage), hence more data is needed to see how aerobic-endurance training impacts patients in more advanced disease stages.

Some other studies also reported an improvement in domains related to non-motor symptoms of PD, like attention and working memory (Crowley et al., 2019; David et al., 2015), as well as fore-mentioned executive function (Altmann et al., 2016; Crowley et al., 2019).

In summary, aerobic and goal-based exercise altogether promote cardio-pulmonary functionality, along with improving targeted skills (balance, posture, manual dexterity). Furthermore, they address cognitive and automatised mechanisms of motor control thereby stimulating motor learning (Petzinger et al., 2013). However, motor learning implies increased cognitive compensation used to put in place new automatisms, at least at the beginning – therefore, coupling motor-training with cognitive control represents one of the efficient strategies to restore motor functionality.

3.1.2 The effects of multimodal (motor-cognitive & sensorimotor) trainings

A. Cognition and executive functions for FOG compensation

Cognitive approaches also correspond to the second type of rehabilitation techniques proposed by Giladi and colleagues (2021). Learning compensatory mechanisms to avoid FOG triggers or dealing with them, for example through defragmenting complex movements into simpler ones. Action observation therapy (AOT) is one of perfect examples of this approach. It uses instructive videos of compensatory movements and strategies to cope with FOG, often accompanied with auditory cues, which execution is then trained in presence of the physiotherapist. This method is based on mirror neuron systems, supported by the observed activation of frontal and parietal regions during action execution and observation of the same action (Rizzolatti et al., 1999; Rizzolatti & Craighero, 2004). Repeated series of action observation, and its imitation may help creating a motor scheme and stimulating motor memory (Agosta et al., 2017; Gatti et al., 2013). These methods have proven their efficiency in stroke rehabilitation, but some studies equally show beneficial effects in PD. Indeed, Pelosin and colleagues have shown a decrease in FOG rate in PD patients following this type of training

(Pelosin et al., 2010). In a later study this team also argued its effect on improving autonomy in daily activities (Pelosin et al., 2018). Some authors suggest that action observation may be particularly beneficial to MP because it would facilitate spontaneous movement initiation (Caligiore et al., 2017). Similar top-down technique is motor imagery, which can be used to consolidate and increase the effects of motor training through reactivation of the regions overlapping with those used during motor execution. More specifically the regions recruited in motor imagery correspond to those of motor planning, combined with mirror-neuron systems (Gerardin et al., 2000; Lehericy et al., 2004). However, considering the hypoactivity of the motor and premotor regions this type of training may be more difficult to implement in patients OFF medication (Caligiore et al., 2017). Both strategies go in line with cognitive compensation of FOG through understanding the mechanisms and actions to execute, also relative to the notion of the internal cueing or self-instruction. Indeed, strategies shown and explained become integrated as cues ready to apply in front of a FOG trigger or during a FOG episode.

Moreover, following a cognitive training in parallel, just as adding a cognitive task to gait training, may help patients improve their executive functions, and thereby increase their resources and problem-solving skills. In fact, multiple studies have shown a transfer of cognitive training benefits to the motor domain in PD patients. Milman and colleagues have shown that targeting attention and executive functions through 12 weeks of 30-minute computer training (3 sessions per week), results in an improved TUG performance (Milman et al., 2014). The patients decreased their time of task execution, including the time of turning. Furthermore, in another study on the population with resistant FOG, 14 sessions of cognitive training over 7 weeks were sufficient to diminish duration of FOG during TUG test (Walton et al., 2018). In addition, researchers equally reported an increase in speed of information processing in these patients.

Results from a few studies have also shown that following a cognitive and motor training in separate modules of the same rehabilitation or combining them through cueing, feedback, or dual task conditions shows similar effects on gait in PD patients (Strouwen et al., 2017). They present an increased stride length and duration, as well as the swing phase duration, accompanied with a decrease in double-stance duration. In an intensive cognitive-motor bootcamp training trial, patients with FOG have also shown a decrease in FOG severity (King et al., 2020). When compared to patients following a simple motor training, the combined strategy showed better retention time, suggesting that multimodal approach may be more

intense, hence more sustainable in freezers. The most common version of combining cognitive and motor aspects of the rehabilitation, beside the goal-based training, is motor training in dual task condition. In fact, after the loss of automatisms dual tasking represents a difficulty for patients, and therefore needs to be addressed specifically to improve patients' executive functions. In a controlled randomised study, 100 PD patients followed 10 weeks of motor training coupled with a cognitive task (Conradsson et al., 2015). The researchers observed an improvement in balance, stride length and velocity, and in dual task performance. Yogev-Seligmann and colleagues equally suggest that it would have an effect on the temporal variability of steps (Yogev-Seligmann et al., 2012). Furthermore, it has been proposed that increasing the complexity of the motor training and using dual task training, makes it closer to the conditions of gait in real life. In consequence, it would facilitate the transfer of learnt skills from training to everyday mobility.

All in all, cognitive aspects of the training, such as action mentalising, task-shifting and dual-task increase the observed clinical efficiency of the training. Firstly, because it is more cognitively engaging for patients than a simple motor rehabilitation, and thereby it assures higher adherence to the rehabilitation. Secondly, because modulating the difficulty of the second task is a good method for skill automatization and improving patients' executive functions. Through this strategy, cognitive resources become optimally distributed, and thereby may help avoiding FOG episodes. At last, these techniques stimulate the attention and cognition networks, thereby increasing their efficiency and enhancing the compensatory mechanisms, which become dysfunctional as the disease progresses.

B. Sensory implicit cueing for FOG compensation

As fore-mentioned, goal-based trainings use cognitive resources to implement strategies to correct posture, and for example maintain the verticality during balance or treadmill training. It is partly equivalent to internal cueing strategy, that is self-instruction, used to guide attention. Therefore, the use of cueing is yet another way to increase cognitive involvement in the training. It helps directing and maintaining the attention all along the rehabilitation session, making it more efficient. Internal and external cues differ substantially in function and modalities. External cueing is defined as “discrete targets or references for the execution of a movement, thereby invigorating and facilitating movement” (Ginis et al., 2018a; Rochester et al., 2007). These methods aim at movement amplitude scaling and rhythmicity issues experienced by

freezers. Scaling is principally addressed by spatial cues (visual), while temporal cues (auditory, haptic) help stabilizing gait timing (Crasta et al., 2018; Nieuwboer et al., 2007; Thaut et al., 1996). Its goal is to maintain optimal gait through adapting amplitude of motor actions and improving interlimb coordination. In case of FOG episode, these techniques may equally serve to implement rescue strategies (Figure 3-2, Ginis et al., 2018).

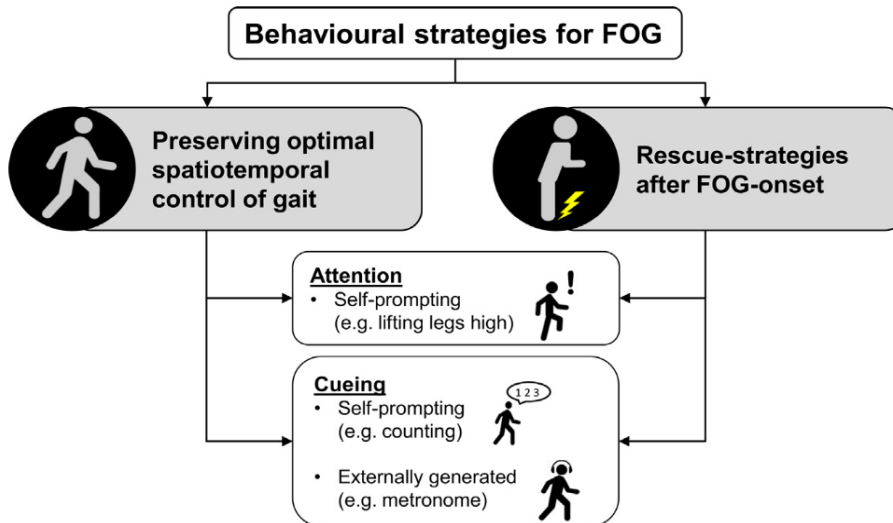


Figure 3-2: Strategies to alleviate freezing of gait (FOG).

Ginis et al., 2017

We distinguish explicit and implicit cueing. The explicit cueing is the conscious estimation of a duration and is principally based on conscious perception of timing delivered by the motor network structures (premotor cortex, SMA, basal ganglia and cerebellum; (Zatorre et al., 2007). Due to dopamine depletion and resulting dysfunction of these circuits, PD patients present difficulties in using this technique to adapt their movement timing. On the other hand, the implicit cueing is managed by automatised information processing of the cerebellum (Ashoori et al., 2015). Thus, this implicit cueing would contribute to improving internal temporal rhythm perception and accessing motor schemes through the cerebellum (Ashoori et al., 2015). In consequence, the cognitive charge put on controlling movement rhythmicity through dysfunctional neural circuits would be taken over by the automatised compensatory pathway.

Sensory cueing can be either delivered independently from the behaviour (open loop), or action-dependant (closed loop; Muthukrishnan et al., 2019). Using sensory cues in an open loop paradigm acts principally on initiating and maintaining gait rhythmicity. The efficiency of the treatment is measured through improvement of spatio-temporal gait parameters and FOG severity. When compared to training without cueing, researchers demonstrated improvements in gait cadence, step and/or stride length, and velocity (Lohnes & Earhart, 2011).

It can also efficiently act on FOG episodes through redirection of attention from the trigger(s) back to the gait (Ginis et al., 2018a), gait being then prioritized over other actions, thereby increasing the certitude to which action attribute the resources (Ginis et al., 2018). In fact, among the observed effects of combined auditory and visual cueing, one may find improvement in FOG severity (Ginis et al., 2017, 2018b; Mancini et al., 2018; Nieuwboer et al., 2007; Sweeney et al., 2020; Van Den Berg-Emons et al., 2010) and dual task performance (Ginis et al., 2018). Moreover, when compared to training without cueing, cue-enhanced interventions show generally better retention time, from 1 to 3 months (Ginis et al., 2018b; Murgia et al., 2018; Schlick et al., 2016; Sidaway et al., 2006; Straus et al., 2009). The effects concerned by the retention effect include improvement in spatio-temporal gait parameters, postural stability, and severity of parkinsonian handicap (Schlick et al., 2016).

Furthermore, some studies suggest that auditory cueing is more effective than visual one in improving temporal aspects of gait in PD patients (Mak & Wong-Yu, 2019). Auditory system is more adapted to processing temporal information and shows faster reaction time than the visual system (Crasta et al., 2018; Thaut et al., 2015). Moreover, it is noteworthy, that when the disease progresses, especially in FOG population, dorsal visual system may become dysfunctional. The choice of frequency of cueing is also important – in PD without FOG the best results are found in frequency superior to spontaneous pace, while freezing patients respond better to their natural pace frequency (M. K. Y. Mak & Wong-Yu, 2019; Willems et al., 2006). Higher frequency of cueing may even happen to trigger FOG episode. Indeed, cueing protocols must be well tailored to avoid over-stimulating the freezers.

The closed-loop paradigm seems to respond to this limit of the open loop cueing through user-oriented stimulation. They are conceived to improve global motor coordination through delivery of haptic, auditory, or visual stimuli at important points during the gait cycle. For example, patients would wear inertia captors to collect the information about kinetics of their gait and every time their foot would hit the ground a vibration or a sound would be emitted. This technique used by patients at home has shown benefits on gait velocity, balance, and quality of life (Ginis et al., 2016). Others proposed using a vibration bracelet and demonstrated an improvement in step length and cadence, as well as an increase in arm swing accompanying the gait, marker of coordination. Nevertheless, no effect was observed on gait speed (Thompson et al., 2017). FOG duration and turning fluidity were equally improved (Mancini et al., 2018). Some other studies which suggested using wearable visual cueing device (laser shoe) showed

a reduction in FOG rate and duration (Barthel et al., 2018). Such interventions and devices find more and more their place in everyday lives of patients and may help managing FOG compensation on a day-to-day basis.

3.1.3 Multimodal rehabilitation with virtual reality (VR) – an efficient mediator to the downfalls of the classical rehabilitation

A. New-technology-based rehabilitation assisted by a therapist

- VR: potential added value

To answer these issues, the field turned to the emerging new technologies, such as Virtual Reality (VR) environments. VR is generally associated to its flexible, interactive, and immersive character. It has been used for a long time in video games with different levels of immersivity. It means that the user integrates into the virtual environment to a certain limit as an observer, or an actor (Canning et al., 2020; Riva, 2004; Rose et al., 2018). The level of immersivity of VR used in the medical field doesn't need to be high, thus only small percentage of applications (<10%) uses its immersive component (Riva, 2004).

More general definition, proposed by Canning and colleagues (2020), presents VR as “the application of visual simulations (...) that mimic real world or conceivable environments, objects and events in real time, and demand interactivity via ongoing behavioural responses of the user”. In case of FOG research and rehabilitation, this technology represents an opportunity in terms of exploration of different hypotheses and parameter configurations in safe laboratory conditions (Canning et al., 2020). Moreover, it can effectively simulate real life conditions of gait and balance control, with dual task and goal-based training environment, implicating sensory integration, attentional shifting, information processing, and motor planning, while sending back adapted feedback (Freitag et al., 2019; Mirelman et al., 2013; Van Diest et al., 2013). According to formerly presented rehabilitation data, all these components play an important role in boosting motor learning (Jaffe et al., 2004; Mirelman et al., 2009, 2011).

- Commercial exergaming for PD

As mentioned earlier, one of the first and principal domains of VR is the industry of video games. Thus, the emerging physical exercise-based video games (exergames) environment became an accessible playground for motor rehabilitation research protocols (Herz

et al., 2013; Mirelman et al., 2011). Moreover, among the observed effects of video games in healthy adults and elderly, there was an increase of motivation, speed of information processing, and cognitive functions (Kühn et al., 2019). Video games use similar techniques as the fore-mentioned multimodal rehabilitation: cueing, feedback, high intensity movement repetition, sustained attention, reward-based learning and high level of motivation. These elements serve to rapidly teach new motor strategies or remind ones previously lost (Dockx et al., 2016). In addition, commercial VR systems of motion capture like Nintendo Wii or Microsoft Kinect have been reported as viable and efficient in motor rehabilitation of PD patients (Dockx et al., 2016; Garcia-Agundez et al., 2019), with an economical advantage, due to quite low cost.

To date there exists multiple commercial exergames proven as feasible and acceptable in PD rehabilitation: *Wii Fit Plus*, *Wii Fit*, *Wii Balance*, *Kinect Adventures*, and *Your Shape: Fitness Evolved* (Barry et al., 2014; Dockx et al., 2016; Garcia-Agundez et al., 2019). Although the variability of training frequency and duration in the pilot studies was very high, they all used big amplitude movements of limbs (superior and/or inferior) as training basis (Garcia-Agundez et al., 2019). Independent studies confirmed that patients can progress and improve their performance in these games, thereby suggesting a possible learning mechanism. These pilot trials also supported an improvement in motor parameters like gait velocity and stride length (Goncalves et al., 2014; Pompeu et al., 2012; Pradhan 2018; Negrini et al., 2017), and of executive functions disability (M. R. Alves et al., 2021; Garcia-Agundez et al., 2019). These games also increased patients' satisfaction in therapy, engagement and intensity of physical exercise (Mirelman et al., 2013; Pompeu et al., 2012, 2014). The effects of exergaming on quality of life are more debateable and variable across studies (Herz et al., 2013; Pompeu et al., 2014). Randomised controlled trials compared the effects of exergaming against the effects of the conventional physical therapy for gait and balance or against no supplementary training, with heterogenous training parameters of duration (4-12 weeks), intensity (2-5 sessions per week), and session duration (20-60 min). Nevertheless, the observed changes confirmed that exergaming can improve clinical measures of balance, motor function, and severity of PD symptoms (UPDRS II) and cognition to the same extent as traditional balance training (Pompeu et al., 2014). The effects of Wii Fit training program were maintained for 60 days after the end of training. However, there was no effect on dual task walking induced by this type of rehabilitation. When compared to the control group without any intervention, patients using commercial exergames tend to show better performance in memory, attention, dual-task, and

simple walking (M. L. M. Alves et al., 2018). Nevertheless, most of these studies were conducted in early to mild stages of PD, therefore the question of adaptability and safety of these games in advanced PD remains. In healthy elderly, the best effects were obtained when standard balance rehabilitation was combined with Wii balance training (Barry et al., 2014; Bateni, 2012). In fact, the specificity of the training plays an important role in motor rehabilitation (Ferrazzoli et al., 2018, 2020). Therefore, using VR as an environment for boosting classical gait and balance rehabilitation techniques seems promising in terms of enhanced sensory stimulation and feedback. Moreover, simulation gives an opportunity to reproduce FOG-triggering situations in safe conditions, as well as bring rehabilitation environment closer to real-life environment.

- **Video games for gait and balance rehabilitation**

As mentioned, it is important that the training focus on what is impacted in patients with FOG, that is: body balance transfer, four limb coordination, trunk rotation, lower limb muscle force, multisensory integration, and dual task during walking (Nuic et al., 2018; Pachoulakis et al., 2018). In consequence, a few studies aimed at creation of VR environments and computer games specifically designed to rehabilitate dynamic postural control (Barry et al., 2014; Mirelman et al., 2011, 2016; Pompeu et al., 2012). In turn, patients showed better progress in terms of gait and postural stability (Pachoulakis et al., 2018).

First study to test the potential of VR in a multimodal training for PD, proposed 6 weeks of treadmill training with a dual task paradigm (Mirelman et al., 2011). While walking on treadmill, patients were asked to take decisions on virtual obstacle avoidance. The difficulty was made progressive with increasing frequency and size of the virtual obstacles, but also by adding distracting variations of lighting and moving objects in the simulated environment (Figure 3-3; Mirelman et al., 2011)).

Patients' movements were recorded and informed the VR system of their progression.

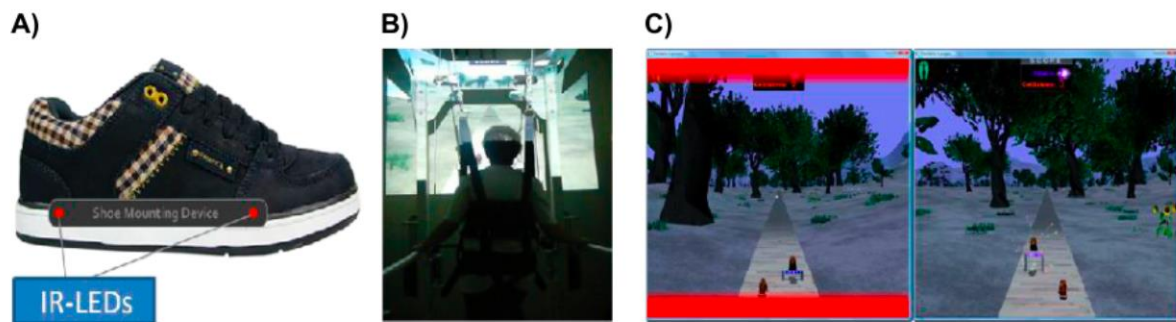


Figure 3-3: Virtual reality (VR) system designed for treadmill gait training,

A. Two light-emitting diodes (LED) were attached to the lateral side of the participant's shoes for the motion capture system to detect movement of the feet. B. A participant walking on a treadmill with a safety harness (without weight support) in front of the virtual environment projection. C. The virtual environment vignettes presenting the negative (red bars) and positive (pink light) feedback, along with red shoes representing patient's steps.

Mirelman et al., 2011

This training induced an increase in endurance, an improvement in gait parameters (velocity, stride length and time). The effects on gait and endurance were maintained at 4-week follow-up. An improvement in motor disability (UPDRS III) and cognition, as well as the PD Questionnaire-39 were reported. When compared to simple treadmill training, the VR-enhanced training showed similar level of gait improvements, with lower dual-task interference effect. It was translated by higher gait speed and stride length in the dual-task condition (Figure 3-4, Mirelman et al., 2011). Patients have shown high adherence to the rehabilitation program and increased training sessions duration.

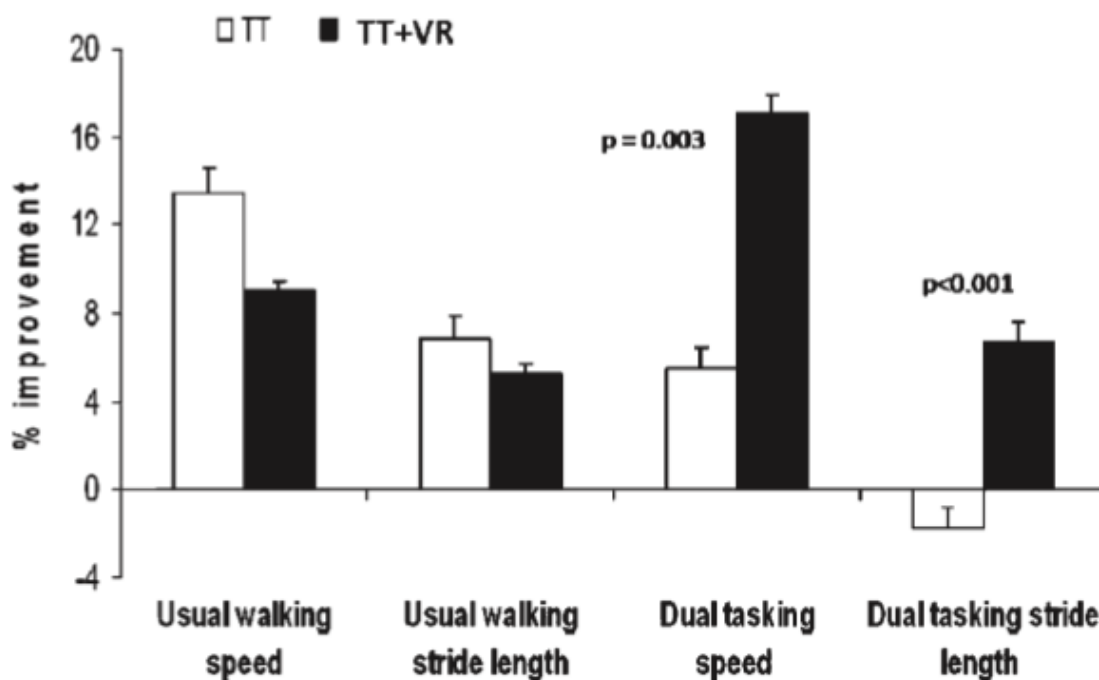


Figure 3-4: Effects of the virtual reality (VR) treadmill (TT) training program on gait speed and stride length in single and dual task conditions.

Mirelman et al., 2011

In a randomised controlled clinical trial across 5 countries (V-TIME project) a non-immersive VR was combined with gait training on a treadmill included older adults with high risk of falls and recent falls history. It has shown that VR training induced a significant reduction in fall rate 6 weeks of intensive training, also for PD patients, when compared to the control group without VR (Figure 3-5 on the left, Mirelman et al., 2016). The difference between VR-enhanced and control groups was still existent 6 months after the end of training, and the most pronounced among PD patients. Within the framework of this project, Pelosin and colleagues have further investigated the effect of the training duration in advanced PD patients (Hoehn-Yahr stage II-III; Pelosin et al., 2022). One group followed VR-enhanced treadmill training for 6 weeks and another one for 12 weeks. Both groups showed improvements in gait parameters in simple and complex (dual task) conditions, without an effect of duration and with retention effect 6 months later. Although, fall rate decreased in both groups, the one training for 12 weeks showed a trend for higher proportion of patients responding to the treatment (75%). A positive effect on fear of falling was equally reported in the 12-week training group only, sustained at the 6-month follow up (Figure 3-5 on the right; Pelosin et al., 2022).

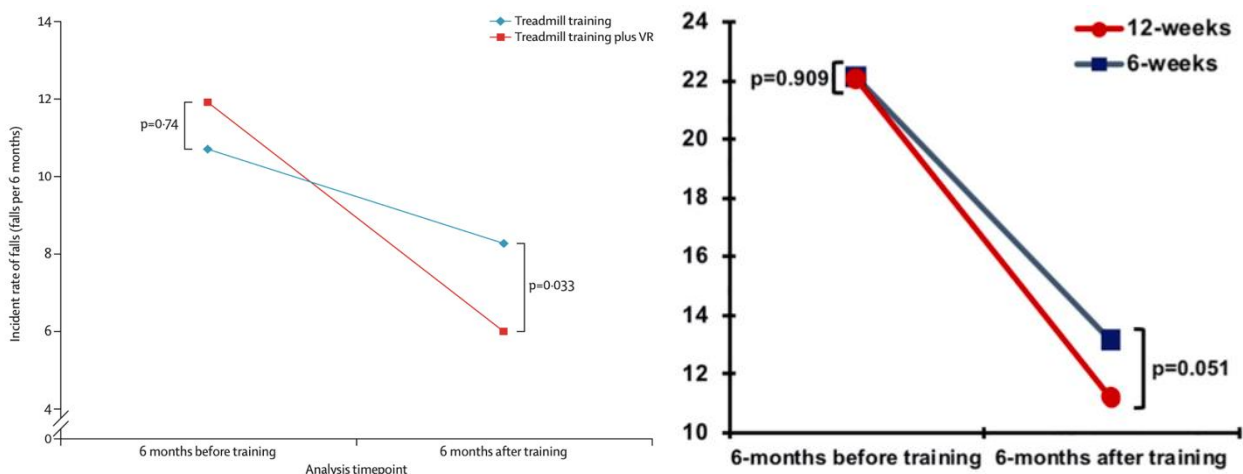


Figure 3-5: Effects of the virtual reality (VR)-enhanced training on fall rate.

Mirelman et al., 2016 & Pelosin et al., 2022

In parallel, executive function improved after the prolonged training only, lasting for a month after the end of the intervention. The combined improvement in cognitive domain would imply better cognitive compensation, and higher confidence in one's abilities to avoid falling. In addition, other studies using VR have shown an increase in number of movements and duration of the training when compared to conventional rehabilitation, hence equally suggesting higher intensity when enhanced with VR (Banina et al., 2019; Ota et al., 2023).

The added value of VR was quickly acknowledged and further studied and exploited. To date, it has been applied to motor, balance, dual task, and aerobic training, with satisfactory effects if the training was intensive and regular enough (M. K. Y. Mak & Wong-Yu, 2019). Among the observed benefits were the improvements in gait velocity, step and stride length, functional gait, functional independence, dual task, cognitive function, and quality of life (Barry et al., 2014; Dockx et al., 2016; Freitag et al., 2019), including the Dynamic Gait Index, Timed-Up-And-Go, 6-minute walking or 10-meter walking tests, and TMT were improved after dual-task VR training (De Melo et al., 2018; Esculier et al., 2012; Espay et al., 2010; Ferraz et al., 2018; Ginis et al., 2016; Mirelman et al., 2011; Pompeu et al., 2014; Strouwen et al., 2017; Yang et al., 2016). When compared to conventional physical therapy, VR-enhanced trainings systematically reported greater improvement in targeted abilities including gait and balance (Feng et al., 2019; Freitag et al., 2019).

To further explore the interest of VR and exergaming to increase the level of motivation while demanding patients to exercise, some authors proposed using customised video games for PD rehabilitation (Galna et al., 2014; Nuic et al., 2018; Pachoulakis et al., 2018; Palacios-Navarro et al., 2015; Summa et al., 2013, 2015). These tailor-made exergames are usually based on the principle of “BIG and FAST” - demanding rapid movements of big amplitude (Farley & Koshland, 2005). The studies targeted arm (Cikajlo et al., 2018) and body movements to reach target (Galna et al., 2014; Nuic et al., 2018; Summa et al., 2013, 2015), as well as lateral leg movements (Nuic et al., 2018; Palacios-Navarro et al., 2015). The observed effects were quite variable, and dependent on the targeted symptom. Cikajlo and colleagues (2018) observed a significant improvement in UPDRS III score, while in pilot studies of Summa and colleagues the observed changes concerned bradykinesia, TUG test and functional mobility (Summa et al., 2013, 2015). Galna and colleagues designed a serious game where patients were to execute hand movements while holding one leg steady on the floor and make large steps to the front, back and sideways with the other leg (Galna et al., 2014). The virtual environment consists of a farmer avatar driving his tractor to pick up the fruits while avoiding different obstacles (Figure 3-6). Patient’s leg movements direct the tractor in the real time, while upper limb movements serve to pick up the fruits. The difficulty is managed going from simple hand movements to

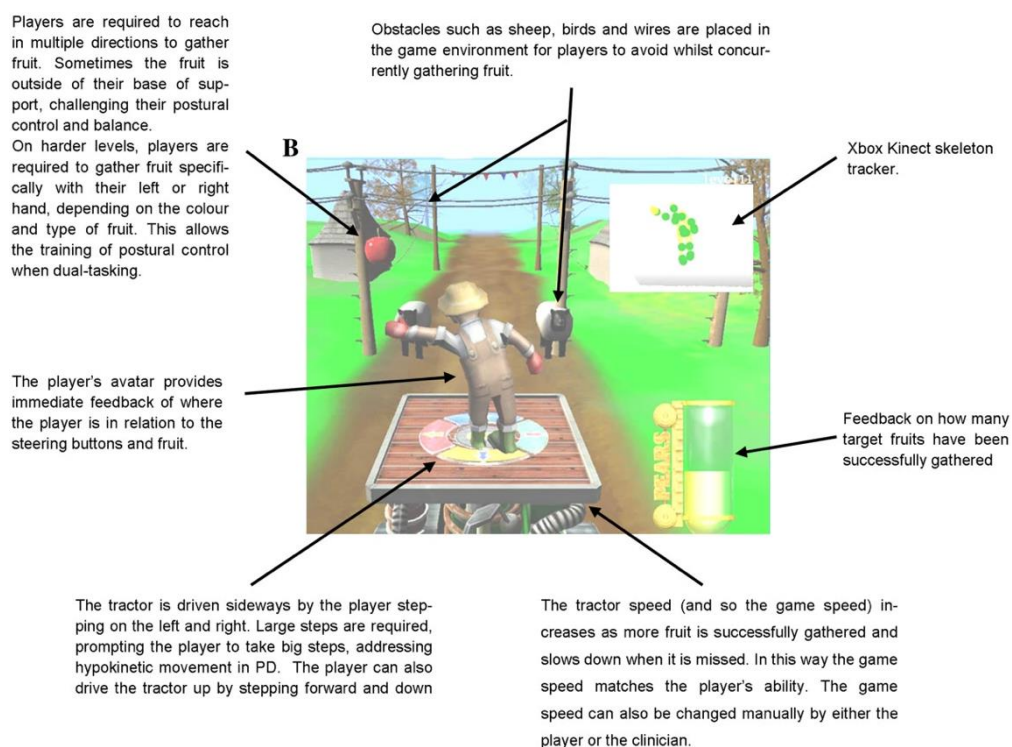


Figure 3-6: Exergame project for gait and balance rehabilitation in PD with FOG.

Galna et al., 2014

complex physical movements combined with cognitive decisions, to finally demand simultaneous hand and foot work.

In their pilot study, 7 out of the 9 patients included, with mild to moderate PD stage, reported that they enjoyed the training and showed good immersivity, nevertheless no clinical measure was evaluated, and no continuation study has been published ever since.

Another pilot study proposed an interactive 3D game platform (built on Unity's 3D game engine) with 2 serious games aimed specifically at motor symptoms of PD patients at mild to moderate stages of the disease (Pachoulakis et al., 2016, 2018). The gestures demanded include purposeful, large-amplitude movements like squats, member extensions, trunk twists and side-leans, and arms stretches. The goal is to improve postural stability, reflexes, and overall functional mobility through two available games: The Baloon Goon and The Slope Creep. First one consists in popping balloons, while the second one is a real cross country ski ride. Cognitive component is assured through in-game decision-making, and the player is informed of his performance through classical to game environment feedback (collected stars and available lives). The feasibility was satisfying, however no clinical measures were reported as to game's efficiency.

These treatments seem efficient in the clinical environment and in presence of a therapist (Freitag et al., 2019). However, to a single individual as well as to the health care system, an intensive training at the rehabilitation centre is highly demanding in terms of time, energy, and very often, money.

B. Home-based rehabilitation with VR/exergaming

Nowadays, few studies investigated the home-based rehabilitation with VR in PD patients using Nintendo Wii (Esculier et al., 2012; Gandolfi et al., 2017; Holmes et al., 2013; Zalecki et al., 2013), Kinect Xbox (Schaeffer et al., 2019; Vallabhajosula et al., 2017), as well as dance (J. Song et al., 2018) and custom-made serious games (Cikajlo et al., 2018; Dauvergne et al., 2018; van der Kolk et al., 2019; Yang et al., 2016; Allen et al., 2017). Control groups either followed classical physiotherapy (Gandolfi et al., 2017; van der Kolk et al., 2019; Yang et al., 2016), or followed their usual clinical agenda (Allen et al., 2017; J. Song et al., 2018) during 6 to 24 weeks, 2 or 3 sessions per week of 15 to 50 minutes. Half of the reported studies are pilots demonstrating good acceptability among patients and promising clinical effects.

Among reported improvements, we note dynamic and static balance (Esculier et al., 2012; Zalecki et al., 2013; Vallabhajosula et al., 2017), APA (Vallabhajosula et al., 2017), and motor handicap score (Zalecki et al., 2013; Cikajlo et al., 2018).

Studies evaluating randomised controlled trials are less positive and uniform. Kolk and colleagues (2019) showed an improvement on the UPDRS motor scale OFF medication after VR-enhanced cycling training when compared to patients doing stretching exercises, who further shows a deterioration. Furthermore, they report an increase in functional mobility. Yet these findings aren't corroborated by other studies (Yang et al., 2016). Gandolfi and colleagues (2017) even exposed that the patient group following a home-based VR balance training, performed worse than the controls following a conventional balance training in the rehabilitation centre. Among other effects researchers reported a decrease in gait component of TUG test (J. Song et al., 2018; van der Kolk et al., 2019; Yang et al., 2016) and an increase in stride length (Schaeffer et al., 2019). An improvement on cognition was also reported by some authors (Allen et al., 2017).

However, this type of rehabilitation presented some weaknesses. Indeed, commercial games may be maladapted to patients' individual state and difficulties. Moreover, patients' autonomy in the installation of the VR devices and adaptation of their living space to the training could also be restricted, with only 26% of patients reported capable to manage the installation of electronics necessary for the training (Cikajlo et al., 2018). PD patients also often fail to find motivation to follow the instructions of the therapists. Despite good training acceptability and feasibility, only 58% of the demanded training duration is executed and 50% of success rate is reached in the training (Dauvergne et al., 2018). It goes in line with need to adapt available VR home-based trainings to make them fully flexible according to patients' needs and capacities. It concerns both the game difficulty and its use. It has also been argued that for safety reasons, the VR system shouldn't depend on holding the remote during the training, for in PD FOG population this represents a high risk of falling (Barry et al., 2014).

The mechanisms underlying the improvement induced by this type of treatment is also not fully understood by now. In the following part I will address the question of potential mechanisms alleviating gait and balance disorders, and potentially alleviating FOG severity.

3.2 Potential mechanisms induced by multimodal rehabilitation with exergaming

3.2.1 Recognised compensation mechanisms in PD so far

Data from pharmacological and neuromodulation studies suggest different levels of compensation accordingly to the advancement of the disease. Fronto-parietal circuits are the first to take the lead, in order to compensate for lost automaticity of motor control. It resembles the early stages of motor learning, when cognitive and attentional control is needed for motor execution. However, as the disease progresses, these networks become inefficient. Thus, more posterior regions try to put in place compensatory mechanisms through visuomotor networks, to guide the attention and the movement. Finally, when the dorsal stream of visuomotor processing is impacted, the compensation relies only on external sensory cueing.

3.2.2 Potential neuroplasticity and new compensatory mechanisms in perspective of video games and exergaming

As presented at the beginning of this chapter, rehabilitation with video games, and particularly the exergaming, usually combines all identified aspects of formerly presented efficient rehabilitation techniques (sensorimotor, cognitive, emotional). Combining all these drivers, would act on dopamine liberation in all available dopaminergic networks (Alexander et al., 1986; Doyon et al., 2009) while stimulating motor learning. It is to say, as the automated motor activity starts to fail, the new motor learning needs to be boosted and coping mechanisms put in place, through intensive and regular training.

Therefore, one might hypothesise that the effects on neuroplasticity observed in other strategies can be reproduced through exergaming. Taken into consideration rare studies using neuroimaging and exergaming protocols, I argue that potential mechanisms underlying this kind of intervention may potentially overlap with those found in trainings using the same components.

Neural mechanisms underlying playing video games have been principally studied in young populations. A simple video game played on a computer reinforces visuo-spatial and visuo-motor capacities, as well as attention and action anticipation (Kühn et al., 2019). An increased GM volume in the prefrontal cortex, hippocampus (Kühn et al., 2013, 2019; Kühn

& Gallinat, 2013), and cerebellum (West et al., 2017), along with a decreased task-based activity in these regions have been reported after video game playing. These findings suggest that an increase in GM volume and a decrease in its activity may be the result of the same optimisation mechanisms. Moreover, Kuhn and colleagues have equally revealed alterations in dorso-striatal (putamen) connectivity following a working-memory training in older healthy adults (Kühn et al., 2013; Kühn & Gallinat, 2013), suggesting that cognitive training through video-games may involve motor structures involved in skill automatization.

Most of the studies presented here-by focused on general PD population with the majority patients being in mild-to-moderate disease stages. Nevertheless, the targeted population was defined as suffering from postural instability and falls. A few studies also addressed population suffering from FOG, thereby demonstrating a difference between the induced changes in these groups of patients. I will attempt to present the observed mechanisms as a possible continuum of the observed effects relative to the severity of FOG.

A. Neuroprotection & neurogenesis (intensive motor activity)

The mechanisms behind intensive and regular motor activity have long been ignored, therefore in order to understand which processes support the observed effects in PD, researchers deployed rodent models who underwent intensive motor training. Firstly, it was exposed that such a training has a neuroprotective function on nigrostriatal pathway, and dopaminergic neurons, through the increase in blood levels of brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF; (Cohen et al., 2003; Tuon et al., 2012, 2015). Moreover, such an increase in BDNF expression, as well as its up-regulation were accompanied with attenuation of the MPTP-induced dopamine loss (Da Silva et al., 2016; Fredriksson et al., 2011). Indeed, the observed neurotrophic activity of dopaminergic neurons (Y. S. Lau et al., 2011) and their increased migration are the result of neurotrophic factors (BDNF and GDNF) in the striatal subventricular area (Tajiri et al., 2010). In addition, researchers further demonstrated that 4 weeks of treadmill exercise before the induction of PD in mice is sufficient to reduce the observed neuronal damage when compared to sedentary mice (Da Silva et al., 2016; T. Wu et al., 2011). However, for this mechanism to take place the motor activity must be intensive (Da Silva et al., 2016; Z. Wang, Guo, Myers, Heintz, Peng, et al., 2015) and there must remain a neuronal network for the neurotrophic proteins to be released and captured by nerve terminal. Once these proteins reach the nucleus through retrograde transmission, they

induce gene reprogramming stimulating the survival of the neuron (Da Silva et al., 2016; Ibáñez & Andressoo, 2016).

Furthermore, the observed results were equally associated with diminished neuroinflammation once the BDNF signalling pathway is activated (Da Silva et al., 2016; S.-Y. Wu et al., 2010). Indeed, long-term physical exercise in a forced treadmill training paradigm seem to increase antioxidant activity, thereby decreasing oxidative stress and hence, the observed neuronal death (Svensson et al., 2015). In line, a reduced mitochondrial dysfunction has equally been observed after a long-term forced treadmill training in mice, along with motor improvements (Y. S. Lau et al., 2011).

Interestingly, the running wheel and endurance exercise in mice have also shown the effects on neurogenesis in hippocampus (During & Cao, 2006; Sah et al., 2017). These studies suggest that restoring motor, limbic and cognitive deficits through intensive training is possible. Along the neurogenesis, a synaptogenesis and axonal sprouting has also been reported (Crowley et al., 2019; Francardo et al., 2017; Shin et al., 2016), which implies a training-induced mechanism of the long-term potentiation (LTP). LTP is known as a marker of neuroplasticity and learning on the cellular level – thereby suggesting that goal-based and intense rehabilitation may stimulate motor learning.

Furthermore, Reynolds and colleagues argue that regular exercise also potentially stimulates other neurotransmitter systems, including serotonergic, noradrenergic, and GABAergic neurons (M. K. Y. Mak & Wong-Yu, 2019; Reynolds et al., 2016)

These findings have been partly corroborated also in humans. Fisher and colleagues have shown an increased density of D2 dopamine receptors in the putamen through PET imaging in PD patients following an 8-week treadmill training (Fisher et al., 2013). This work confirms a possible synaptogenesis in the striatum induced by motor rehabilitation. Furthermore, other studies have equally demonstrated the increase of BDNF levels following an aerobic training (Zoladz et al., 2014) and a multidisciplinary training (Frazzitta et al., 2013). Altogether it suggests that exercise may be an efficient tool for PD no matter the advancement stage. In early stages preserving the dopaminergic integrity against degeneration, and in moderate and advanced disease stages, on decreasing neuroinflammation, therefore slowing down the process at the origin of neuronal death (M. A. Hirsch & Farley, 2009; Zigmond et al., 2009).

Although animal studies suggest that only the intense, regular, and sufficiently long (≥ 4 weeks) exercise seems to have such promising results, study from Zoladz and colleagues showed an increase in basal BDNF levels after a moderate level intensity exercise, which may suggest that production of neurotrophic proteins in humans may follow different mechanisms (Zoladz et al., 2008, 2014). Nevertheless, these results were not confirmed elsewhere, therefore they are to be interpreted carefully.

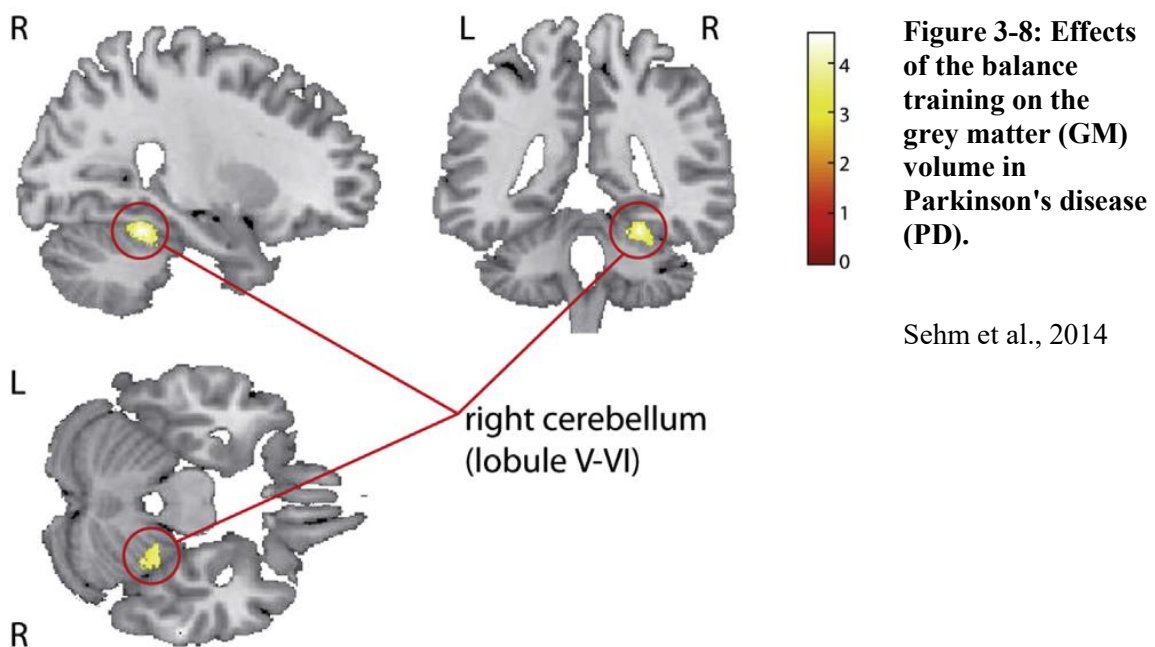
B. Training-induced structural and functional brain changes

- Evidence from animal PD models

Data from the animal studies show significant changes in regional cerebral blood flow-related activity and functional connectivity of PD rats following intensive 4-week aerobic training when compared to PD rats with no intervention (Z. Wang et al., 2013; Z. Wang, Guo, Myers, Heintz, Peng, et al., 2015). The regions with increased activity corresponded to striatum, GP, thalamus, PPN, and rostral secondary motor cortex. Moreover, in the study using a complex aerobic training, Wang and colleagues equally observed changes in functional connectivity at rest (Z. Wang, Guo, Myers, Heintz, Peng, et al., 2015). After replicating a disconnection of the dorsolateral striatum and cerebellar vermis from the motor functional network observed in PD patients, PD rats following a physical training presented a normalisation of the motor functional network. It was characterised by the reintegration of the dorsolateral striatum and cerebellar vermis. Further changes included the emergence of the ventrolateral striatum as functional hub, as well as an increase in FC among motor cortex, motor thalamus, basal ganglia, and cerebellum (Z. Wang, Guo, Myers, Heintz, & Holschneider, 2015; Z. Wang, Guo, Myers, Heintz, Peng, et al., 2015). This work demonstrates that it is possible to restore lost FC thanks to aerobic training. Moreover, the observed emergence of new FC hub could translate the creation of new compensatory circuits.

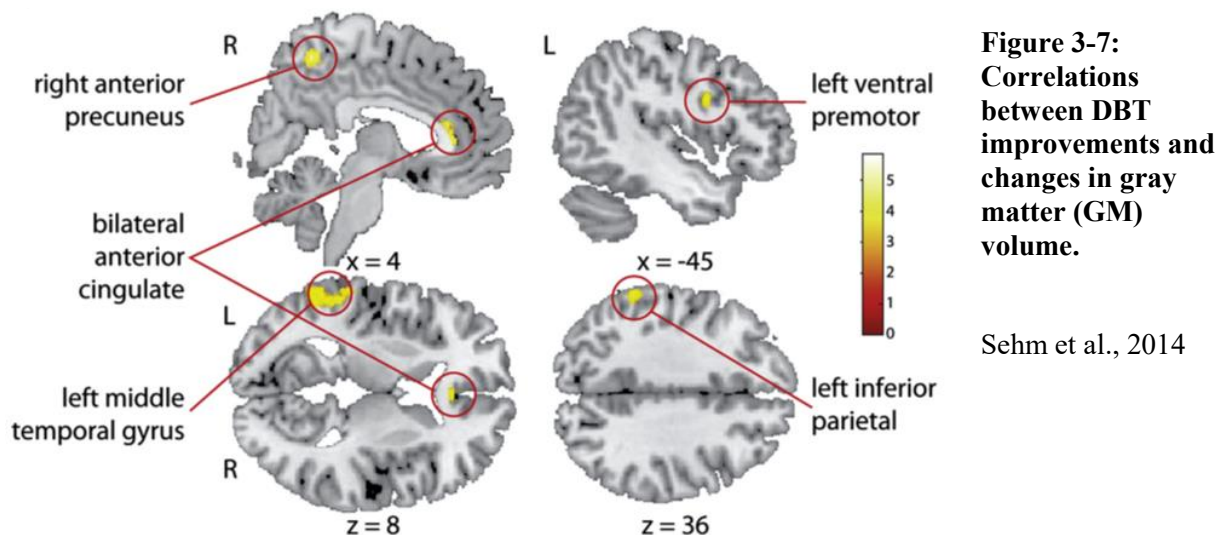
- **GM volume changes in humans**

Furthermore, when the rehabilitation was based on the goal-oriented behaviour, that is a 6-week complex balance training, PD patients have shown a significant linear increase in GM volume in the right cerebellum V-VI when compared to the healthy control group (Figure 3-8; Sehm et al., 2014). Changes in patients' performance were also correlated with GM volume changes in fronto-parietal regions (right precuneus, left inferior parietal, left ventral premotor, and bilateral anterior cingulate cortices) and in middle temporal gyrus (Figure 3-7; Sehm et al., 2014). These regions are related to integration of sensorimotor and proprioceptive information, and necessary for motor planning.



Sehm et al., 2014

- **FC changes (resting state) in PD patients without FOG**



Sehm et al., 2014

Multiple studies were interested in measuring the changes in FC induced by different rehabilitation techniques and were reported in a recent review (Baglio et al., 2021). PD patients following an aerobic training showed an increase in FC between GP and posterior cingulate gyrus (Messa et al., 2019), as well as between primary motor cortex and sensorimotor regions (Messa et al., 2019), and thalamus (Shah et al., 2016). Thalamic FC also increased with posterior temporal cortex (Segura et al., 2020). This type of training equally showed an increase of global FC of basal ganglia circuit (Segura et al., 2020), primary motor cortex and the SMA (Shah et al., 2016), as well as a left anterior cerebellar cortex (Maidan et al., 2017). These data suggest a higher FC of cortico-thalamo-cerebellar circuitry, equivalent as the one observed in animal models. On the other hand, primary motor cortex had decreased FC with prefrontal cortex after the training (Shah et al., 2016), probably in line with better recruitment of automaticity-related networks and diminished need for prefrontal compensation. Decreased FC was also shown in mid-temporal cortices (Maidan et al., 2017).

When VR was added to the treadmill training, researchers further observed a decrease in the recruitment of frontal regions (Brodmann area 10 and right inferior frontal cortex, Maidan et al., 2017), executive control and fronto-striatal circuitry (Droby et al., 2020). On the other hand, increased FC was reported in premotor cortices and in right mid-frontal cortex (Droby et al., 2020). Authors argued that these findings may go in line with reduced need for compensation from cognitive and attentional resources.

A study from Ding and colleagues (2022) has equally shown a training-induced normalisation of the observed effective connectivity patterns towards those observed in healthy controls (Ding et al., 2022). The patients followed a 6-week intensive training on the treadmill and were evaluated in two conditions: simple walking and dual-task walking. During the evaluation the activity of their PFC was measured using the functional Near Infrared Spectroscopy (fNIRS). Their functional connectivity at rest was equally measured before and after the training. The observed effects demonstrated slightly reduced activity of the PFC when two conditions were confounded but not separately. However, the connectivity at rest between the motor cortices, brainstem, and subcortical regions seemed reduced to the level observed in healthy population.

Nevertheless, these studies focused on mild to moderate stages of PD at which the compensation through frontoparietal cortices is still efficient. This would thereby present the effects of training when it is still possible to restore functional networks of motor control.

- **fMRI changes in PD patients with FOG**

King and colleagues proposed a training combining intensive cognitive and motor training for 6 weeks (King et al., 2020). The observed changes showed a decrease in FC at rest between SMA and PPN, known as hyperconnected in FOG. Consequently, these changes were accompanied with a decrease in FOG. In another study, Agosta and colleagues proposed a 4-week motor training accompanied with action observation therapy (AOT) to FOG patients. For the group not following the AOT a simple landscape viewing sessions were proposed as control. Both groups executed 12 sessions of 60 min training (3 sessions per week), where 24 minutes were dedicated to passive video-watching, and 36 to physical therapy. The fMRI was assessed before and after the training period, as well as the clinical assessments, with a supplementary evaluation 4 weeks after the end of the training. fMRI protocol consisted in 3 task-based imaging sequences: 1) a pedalling task (motor execution), 2) watching videos in a first-person perspective simulating FOG-triggering situations (motor imagery), and 3) watching the same videos but in a third-person perspective (action observation task). Researchers observed a decrease in activity of attentional and sensorimotor regions in the control group during motor execution and imagery, following a simple motor rehabilitation. On the other hand, the AOT group showed an increased recruitment of fronto-parietal networks during motor imagery (Agosta et al., 2017). Moreover, the activity of inferior frontal gyrus (IFG) during motor imagery was correlated with a decrease in motor handicap post-training (UPDRS III score). In the meanwhile, the increased recruitment of the right precentral gyrus during motor execution (pedalling paradigm) was correlated with a decrease of UPDRS III score 4 weeks after the end of training period (Agosta et al., 2017).

- **Conclusions on potential general effects of rehabilitation**

Overall, animal and human studies have proved that motor exercise accompanied with cognitive and sensory enhancement leads to the increase of the overall dopamine levels (Ferrazzoli et al., 2020; Fisher et al., 2013; Sacheli et al., 2019). Furthermore, it also affects the vascularisation and the hippocampal neurogenesis (Boldrini et al., 2018). These effects are nonetheless more pronounced in patients with smaller motor severity, pointing out the importance of starting the rehabilitation at the early disease stages. Altogether, more the training is complex and multimodal, more extended brain networks are stimulated and modulated (Saleh et al., 2017). In consequence, the neuroplasticity can be observed in different areas including the sensorimotor integration circuits, premotor areas, prefrontal cortex, and cerebellum (Ding

et al., 2022; Sehm et al., 2014; Silva-Batista et al., 2020). In individuals with FOG, after a multimodal training a decrease in pathological functional connectivity was found, as well as increased recruitment of compensatory networks, formerly lost. Taken into consideration that these compensatory networks are still functional in patients with earlier FOG, it would suggest a step back on the disease evolution.

3.2.3 Potential emerging effects: conclusion and opening

Firstly, one hypothesis would be to argue that adapted multimodal rehabilitation with exergaming might stimulate new motor learning, and thereby recreate the automatisms of gait and balance. As formerly presented, the automatization process relies on the execution-adaptation loops and a high number of repetitions. Studies from the VR field have shown that VR-enhanced training participates in increasing the intensity, and therefore the number of executed movements, thereby probably accelerating the motor learning process (Banina et al., 2019; Ferrazzoli et al., 2020). In fact, these studies have also shown that patients have also increased their speed while keeping high level of performance. Therefore, it would appear that patients have at least reached the associative learning phase and have engaged the consolidation process. However, the possibility for PD patients to reach the automatization level is highly

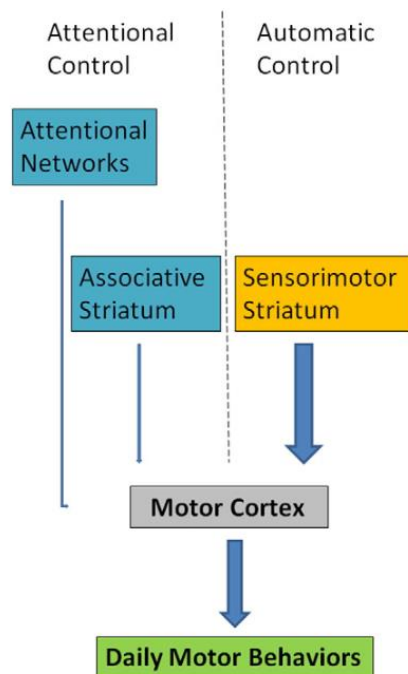


Figure 3-9: Models of attentional and automatic control of daily motor behaviours.

Model of circuits for the execution of daily motor behaviours in attentional control and automatic control conditions.

It shows that once the sensorimotor striatum is impaired, there seems to be no alternative structure to take over the automatic control.

Adapted from Wu, Hallet & Chan, 2015

debated. In fact, the dopamine seems to be irreplaceable for effective reward-based and associative learning (as presented in Chapter 1.1.2). Moreover, Wu, Hallet & Chen (2015) have presented that the dorsal striatum is necessary for automatized movements execution (Figure 3-9), hence for PD patients showing neurodegeneration in this structure it may in fact seem impossible to reach the

autonomous phase of motor skill acquisition but very plausible to perpetuate the consolidation phase of the learning if the training is maintained.

However, learning mechanisms don't limit to the basal ganglia and the striatum. In fact, the cerebellum can be an important actor identified in cortico-cerebellar and striato-cerebellar learning loops, specifically in the error-based learning mechanisms. Nevertheless, as proposed by Fermin and colleagues (Bostan & Strick, 2018; Fermin et al., 2016), it also seems to contribute to every step of automatised skill acquisition (Figure 3-10). In fact, different regions of the cerebellum are involved in exploration/model-free control (limbic posterior cerebellum), the cognitive model-based control (lateral posterior cerebellum) through its communication with the PFC and DLPFC, and in the formerly presented motor adaptation control (anterior cerebellum).

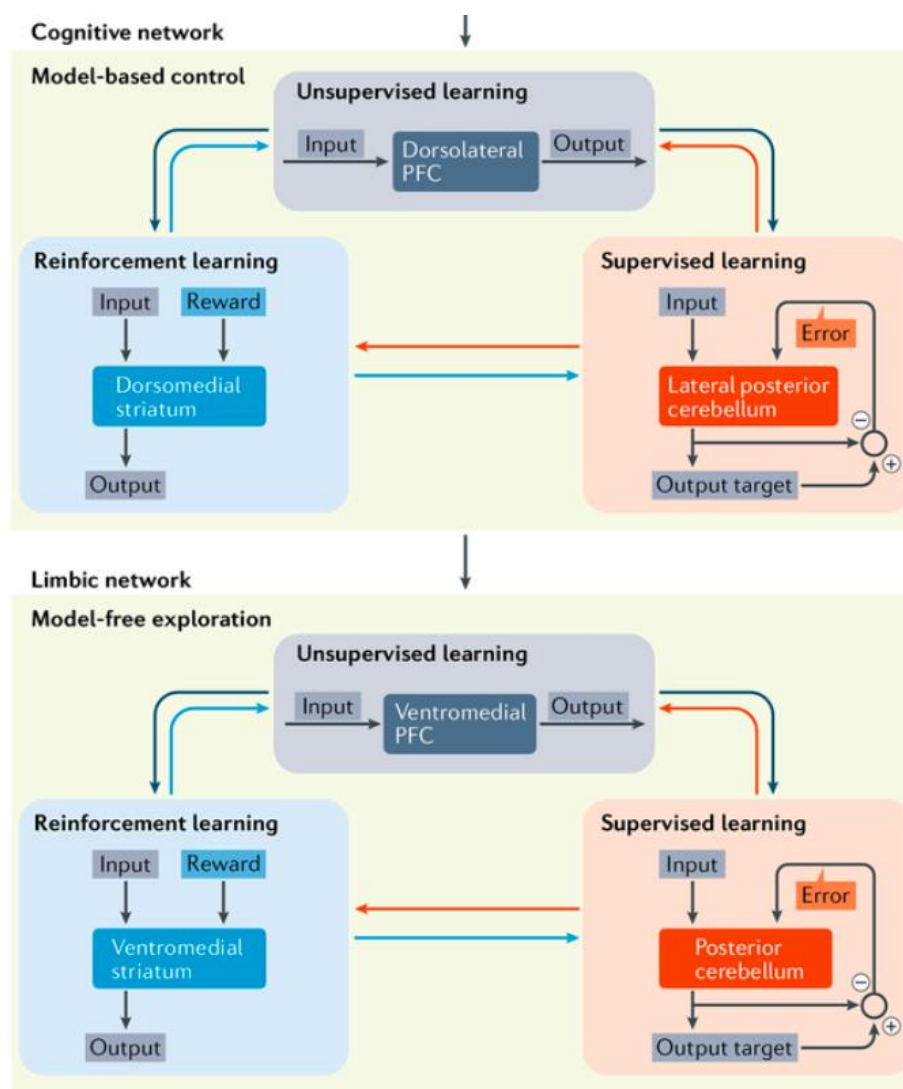


Figure 3-10: Cortico-striatal, cortico-cerebellar & striato-cerebellar loops in motor learning (cognitive and limbic networks).

Bostan & Strick, 2018

On the other hand, some authors argue that the limbic dopamine can be engaged and used in motor learning through positive feedback after the successful movement execution – characteristic to video game training setup. Moreover, this dopaminergic input can also impact the associative learning and fronto-striatal loops, thereby creating stronger bonds between motor choices and stimuli and accelerating decision-making. These new associative automatisms would diminish the cognitive load of motor execution and hence reduce FOG frequency and severity, along with the recruitment of the remaining dopaminergic neurons.

Indeed, clinical studies strongly suggest that motor learning in advanced PD is preserved as long as patients don't suffer from dementia (Mendes et al. 2012; Mirelman et al., 2011), thereby suggesting that the learning mechanisms are principally cognitive. In consequence, it means that preserving functional cognitive functions is necessary for implementing efficient learning. As observed in studies from Mirelman and colleagues (2011), an efficient training of executive functions through repeated decision-making tasks combined with gait may bring beneficial effects on gait and cognition, along with a transfer of learnt skills. Their improvement at follow-up may be the effect of enhanced motor adaptation learning relying on executive functions. Furthermore, we may hypothesise that the use of the immersive dynamic environment further brings a cognitive involvement and resemblances to the real-life conditions. Patients would therefore increase their capacities of external and internal cues integration and their association to the motor program to execute. Once again, some authors suggest that these mechanisms are partly supported by the cerebellum (Boyden et al., 2004; Celnik, 2015; Doya, 2000; Ito, 2000). Therefore, the multimodal rehabilitation with VR could use the cerebellar and fronto-striatal networks to put in place the effective learning.

Secondly, at different disease stages different compensatory mechanisms were reported, becoming obsolete as the disease progresses. Indeed, as observed in mild to moderate stages of FOG severity, PD patients use more cognitive resources and therefore increase the activity of their frontal and prefrontal regions (Bardakan et al., 2022; Ding et al., 2022). However, when FOG becomes more severe, frontal hyperactivity is replaced by the increase in visuomotor regions, which then is replaced by sensory compensation (Bardakan et al., 2022; Lord et al., 2012). Therefore, it would be also possible that the decline of the compensatory networks results from the decreasing energetical resources in the brain, related to the disease. Therefore, from the metabolic point of view, the intensive exercise is known to improve the energetic capacities of the brain (Huang et al., 2005; Thyfault & Bergouignan, 2020). Moreover, recent

studies have shown that the consumption of glucose in the brain equally diminishes and is replaced by the lactate, which is produced during the motor training (Brooks, 2018, 2020). These results may explain the important role of the intensive physical exercise in the multimodal rehabilitation.

Taken together, the mechanisms of motor learning put in place through limbic dopaminergic networks and cerebellar contribution could lead to the associative phase of motor skill acquisition inducing a functional optimisation of its execution. In addition, combined with intensive physical exercise patients could get back at compensatory networks thanks to the supplementary metabolic optimisation, and possible neuroprotection and synaptogenesis.

In general, in studies comparing VR-enhanced rehabilitation with conventional programs, the evidence tends to show that VR induces higher benefits to gait and balance in PD (Lei et al., 2019; B. Wang et al., 2019). Nevertheless, the consistent evidence is missing for the effects of serious exergaming programs, for the samples are small and the studies are only just emerging. It is also important to further explore the neural mechanisms of improvement to better understand the effects induced by different protocols with a possibility to improve them.

In this research program we aim at addressing these missing points in a randomised controlled trial in order to 1) assess the efficacy of customised exergaming to treat gait and balance disorders in advanced forms of PD, and 2) to evaluate related structural and functional changes in the brain via multimodal neuroimaging.

Experimental work

Chapter 4: In the research continuity

4 Context of the research: the pilot study

The first step was to build the tailored exergaming program “*Toap Run*” developed by our team in collaboration with e-Genious. It was tested for acceptability, feasibility, and efficiency to improve gait and balance disorders in PD patients suffering from FOG (Nuic et al., 2018). The game consisted in navigating in 3 distinct environments (garden, mine, river) with an animal avatar following patient’s movements in the real time (Figure 4-1; Nuic et al., 2018).



Figure 4-1: "Toap Run" video game paradigm and environments.

Vignettes from the “*Toap Run*” videogame training. The images show screen shots of one patient during a training session composed of three different scenarios (“*The Garden*”, “*The Mine*” and “*The River*”, from top to bottom).

The schemes of movements to execute in each environment are presented on the side of the images, with the arm extension, lateral step, lunge, squat, trunk rotation with arm movements, and anteroposterior trunk movement.

Nuic et al., 2018

The goal of the game was to earn the maximum of points by collecting golden coins and avoiding the obstacles on the way. As means to do that patients were to execute rapid whole-body movements of large amplitude (Farley & Koshland, 2005). Coin collection was achieved via upper limb extension movements, while obstacle negotiation followed the trunk and lower limb movements.

The movements differed in relation to the training environment and difficulty (Figure 4-1):

- In the garden environment, patients executed lateral steps, accompanied with arm abduction.
- In the mine environment, the avatar was placed on a virtual trolley, as addition to previous movements patients did squats, or lateral lunges combined with torso lateral flexion and arm abduction/squats combined with arm abduction (according to difficulty level).
- In the river environment, the avatar used a virtual surfboard, hence, to navigate it patients had to be in lateral position and execute torso flexion, extension, and rotation, along with the semi-flexion of knees and shoulder abduction.

Game was equally equipped with visual and auditory cues. Rhythmical music indicated game flow speed (slow 20Hz, normal 30 Hz, rapid 40 Hz), while specific auditory cues (metronome beep) marked the imminent contact with an obstacle. Visual cueing included hints for patients for the movements to be executed next and their direction, as well as their timing (before the audio beep). Altogether these cues aimed at helping patients to anticipate and facilitate their interaction with the VR.

The rehabilitation movements were designed by a physiotherapist, and the difficulty was managed through the number and frequency of movements to execute, the duration of the training, the game tempo, the timing of visual cueing, the timing of the auditory cueing in relation to the obstacles (Nuic et al., 2018). Different combinations of these parameters defined 3 difficulty levels but could be further modulated if needed. Each training session combines different environments and therefore different movements with equilibrated duration and with real-time feedback of their performances. Lastly, patients were informed of their performance at the end of each environment-specific component of a training session with a score (percentage of successful movements).

In this pilot trial (Nuic et al., 2018), I was also involved in gait parameters analysis to explore the impact of the exergaming on intra-individual variability of gait initiation and execution measured by the surface of the CoM displacement across evaluated trials per evaluation session. The preliminary results showed a significant change in the intra-individual variability during APA and first gait cycle, suggesting a potential motor learning process and regain of automaticity after exergaming training with “*Toap Run*” in 10 PD patients (Figure 4-2, unpublished).

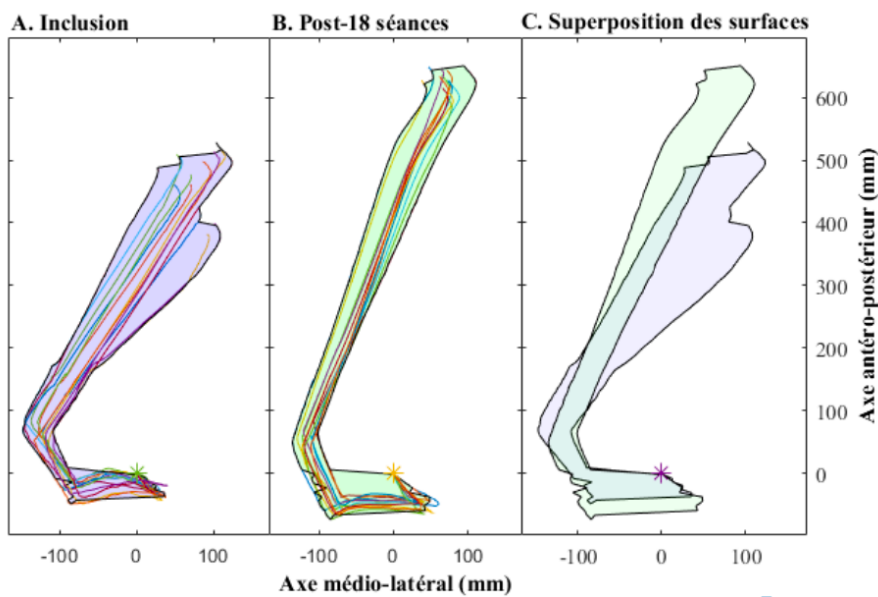


Figure 4-2: Gait variability evolution across the evaluation sessions in the pilot study on "Toap Run" feasibility.

Gait variability as measured by the surface areas at three evaluation time-points before (A.) and after (B.) the training with “*Toap Run*” at the institute.

Nuic, thesis, 2020

Following this pilot study, we now performed a randomised controlled trial PARKGAME II with a bigger sample, being the object of this manuscript. We divided the trial into two studies investigating 1) the clinical efficiency of the home-based rehabilitation with “*Toap Run*”, and 2) the neural underpinnings of the observed effects.

Chapter 5: “Home-based exergaming to treat gait and balance disorders in PD (randomised controlled trial)”

5

5.1 Objectives and overview of the methods

The study was designed to respond to the insufficient evidence for using VR-enriched and custom-made video games for in-home rehabilitation in PD patients with gait and balance disorders. As formerly presented, previous randomised controlled trials addressing home-based motor rehabilitation with VR have shown promising but inconsistent results (3.1.3B). Therefore, given promising results of the institute-based exergaming rehabilitation pilot study using our tailor-made game “*Toap Run*”, the main objective of this project was to assess the effects of this training program in a home-based teleguided condition.


This study was deployed as a multicentre, single-blind, randomized controlled trial. Fifty PD patients suffering from FOG and/or falls were recruited across two centres specialised in PD: the Paris Brain Institute (Paris, France) and the Radboud University Medical Centre (Nijmegen, The Netherlands). They were randomly assigned through the RedCap software either to the active whole body motor rehabilitation with motion capture system (Kinect®), or to the control group using the serious game with the computer keyboard while seated for 18 sessions (2-3 per week). After the 18 sessions of training, all patients could continue with the active motor training at their convenience before being evaluated 3 months later. During the randomised phase, the gaming parameters were progressively increased along the training and adapted individually depending on each patient’s performance from previous sessions.

Home-based exergaming to treat gait and balance disorders in patients with Parkinson's Disease: a phase II randomized controlled trial

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ORIGINAL ARTICLE

Home-based exergaming to treat gait and balance disorders in patients with Parkinson's disease: A phase II randomized controlled trial

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Abstract

Background: Exergaming has been proposed to improve gait and balance disorders in Parkinson's disease (PD) patients. We aimed to assess the efficacy of a home-based, tailored, exergaming training system designed for PD patients with dopa-resistant gait and/or balance disorders in a controlled randomized trial.

Methods: We recruited PD patients with dopa-resistant gait and/or balance disorders. Patients were randomly assigned (1:1 ratio) to receive 18 training sessions at home by playing a tailored exergame with full-body movements using a motion capture system (Active group), or by playing the same game with the computer's keyboard (Control group). The primary endpoint was the between-group difference in the Stand-Walk-Sit Test (SWST) duration change after training. Secondary outcomes included parkinsonian clinical scales, gait recordings, and safety.

Results: Fifty PD patients were enrolled and randomized. After training, no significant difference in SWST change was found between groups (mean change SWST duration [SD] -3.71 [18.06] s after Active versus -0.71 [3.41] s after Control training, $p=0.61$).

Dijana Nuic, Sjors van de Weijer, Nienke M. De Vries, and Marie-Laure Welter contributed equally to this work.

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Some 32% of patients in the Active and 8% in the Control group were considered responders to the training program (e.g., SWST duration change ≥ 2 s, $p=0.03$). The clinical severity of gait and balance disorders also significantly decreased after Active training, with a between-group difference in favor of the Active training ($p=0.0082$). Home-based training induced no serious adverse events.

Conclusions: Home-based training using a tailored exergame can be performed safely by PD patients and could improve gait and balance disorders. Future research is needed to investigate the potential of exergaming.

KEYWORDS

exergaming, falls, gait disorders, Parkinson's disease, rehabilitation

INTRODUCTION

Gait and balance disorders are common and represent the main motor disabilities in Parkinson's disease (PD) [1, 2]. With time, these axial motor signs deteriorate, and freezing of gait (FOG) and falls occur [2, 3]. These signs become unresponsive to dopaminergic agents or deep brain stimulation [1], imposing a significant burden on patients and families and impaired quality of life, and leading to increased morbidity and mortality rates, and healthcare costs [3, 4].

Physiotherapy is a non-pharmacological treatment including different modalities such as progressive resistance training, treadmill training, cueing and cognitive techniques, aerobic exercise, dance, or martial arts [5, 6]. Given the progressive worsening of PD, physiotherapy needs to be maintained over prolonged periods of time [6, 7]. However, long-term compliance represents a major challenge, due for example to the travel burden and the monotonous and generic training content. Virtual reality and exergaming have emerged as novel rehabilitation methods using enriched immersive and non-immersive environments, with comparable results to traditional physiotherapy if combined with exercise [8, 9], with the potential to make training more engaging and motivating, thus providing long-term engagement [10]. Up to now, four randomized clinical trials have tested such training performed in hospitals or at home with the aim of improving PD motor signs. In one study, hospital-based treadmill training combined with virtual reality compared to treadmill training alone led to a greater reduction in the falls rate, with additional benefits on gait and balance performance [11, 12]. Three randomized controlled studies testing home-based commercial or custom-made exergaming training with physical activity training, with online supervision by a physiotherapist for two studies (telerehabilitation), showed a good feasibility, with a possible benefit for gait and balance, but no superiority of exergaming combined training relative to control training [13–15]. Recently, home-based aerobic cycling combined with exergaming and online coaching was tested in de novo PD patients [16]. In this study, no significant aggravation of the PD motor symptoms (Off-dopa) was found after 6 months of aerobic cycling exergaming-combined training, while the control patients deteriorated (non-aerobic physical activity). However, no

significant effect on gait, balance, or On-dopa motor disability was observed in either group [16].

These previous trials suggest that combining exergaming with home-based physical activity, enriched with remote coaching, may potentially attenuate PD motor disability. However, the evidence remains insufficient to recommend in-home exergaming with concurrent physical activity to treat gait and balance disorders in advanced stages of PD [16]. Here, we aimed to evaluate the effects of a tailored home-based exergaming ('Toap Run') [17] training combining virtual reality and physical activity, without supervision, to improve gait and balance disorders in PD, in a randomized controlled trial.

METHODS

Study design and patients

In this prospective, randomized, multicenter, controlled single-blind trial, we recruited PD patients from two hospitals: Brain and Spine Institute (Paris, France) and Radboud University Medical Centre (Nijmegen, The Netherlands). Eligible patients for inclusion were aged between 18 and 80 years, diagnosed with PD according to the UKPD Society Brain Bank, had gait and/or balance disorders unresponsive to levodopa treatment (item 12 of the Movement Disorder Society-Unified Parkinson's Disease Scale (MDS-UPDRS) Part II, gait and balance ON-drug ≥ 1 and/or item 13-FOG ≥ 1) [18]. Additional inclusion criteria included stable dopaminergic medication for at least 1 month prior to study enrolment, absence of medical conditions that could interfere with the research study, had agreed to participate, provided written informed consent, and affiliation to a social security scheme. Exclusion criteria were inability to stand or walk alone (Hoehn and Yahr stage 5), dementia (Mini-Mental State Examination [MMSE] < 24) [19], and the presence of impulse control disorders (item 6, MDS-UPDRS Part I > 2) [18].

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the local ethics committee of both countries and recorded on [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03560089).

Randomization and masking

Patients were randomly assigned to receive either full-body-controlled exergaming training (Active group) or gaming on a computer keyboard (Control group). Randomization was computer-generated and based on random number blocks of four, with 2:2 random ratio, with a location-based stratification factor. Allocation was automatically generated by the RedCap software®. The primary outcome measure, the Stand-Walk-Sit Test (SWST) time, was videotaped and scored by an independent investigator unaware of the patients' group allocation.

Procedures

Patients had an assessment at inclusion (baseline), followed by randomization to the Active training or Control group for 6–9 weeks (Figure 1, single-blind period). During this single-blind period, patients played with the videogame 'Toap Run' [17] designed to treat gait and balance disorders for PD patients, 2–3 times/week for a total of 18 sessions. The first two sessions took place at the institute, and the two following at home with a research assistant. Subsequently, patients played independently at home using a web-based platform (Curapy.com). Participants were allowed to contact the investigator by telephone if needed.

The Active training group played with full-body movements performed upright in front of a RGB-D Kinect® motion sensor (Version 2, Microsoft, USA). The motion sensor was placed below a television screen, positioned approximately 2m in front of the patient. The Control group played seated with a keyboard without any physical efforts. The participants' movements (Active) or keyboard pushes (Control) induced the displacements of a small animal (the avatar) in real time, to gain points by collecting coins and avoiding obstacles (Methods in Appendix S1; Figure 2). For Active training, the required movements consisted of large amplitude and rapid movements of all four limbs, pelvis, and trunk, with lateral, vertical, and forward

displacements of the legs, to reinforce foot lifting and postural control. Visual (schematic representation of movements) and auditory (rhythmic music) cues were used to encourage movements. Patients received real-time and online feedback while playing, in the form of an auditory or visual stimulus. In addition, their performance was graded at the end of each session.

The programme was divided into three phases of six sessions, with predetermined difficulty levels: easy, medium, and difficult (Figure 2). The session duration, number of movements, and success rate were automatically recorded, allowing the investigator to follow and individually tailor the game difficulty. Follow-up assessments were done after the 18th session (W6). At the end of this period, patients can continue (Active) or start (Control) active full-body movement training sessions for a period of 3 months (Figure 3 open-label period), and a final follow-up assessment was performed (Post-M3).

Clinical assessments were done at each visit approximately 1h after intake of the usual morning dopaminergic treatment (On-dopa). For participants included at the Brain Institute, gait parameters were also recorded using a force plate (0.9×1.8m, AMT Inc., LG6-4-1) and a motion capture system (Vicon Nexus, Oxford Metrics, UK; Figure S1) [17].

Outcomes

The primary outcome measure was the between-group difference in the change in duration of the SWST between baseline and after 18 training sessions (W6). The SWST is a functional mobility assessment where patients are asked to stand up from sitting, walk 5m at a comfortable speed, turn around 180°, walk back to the chair, and sit again while turning 180° [20].

Secondary outcomes consisted of the between-group differences for the changes between baseline and after training (W6), on the following scales: the MDS-UPDRS Part I (mental state), Part II (activities of daily living [ADL]), Part III (motor disability) that comprises the axial score (e.g., sum of the items 9-10-11-12

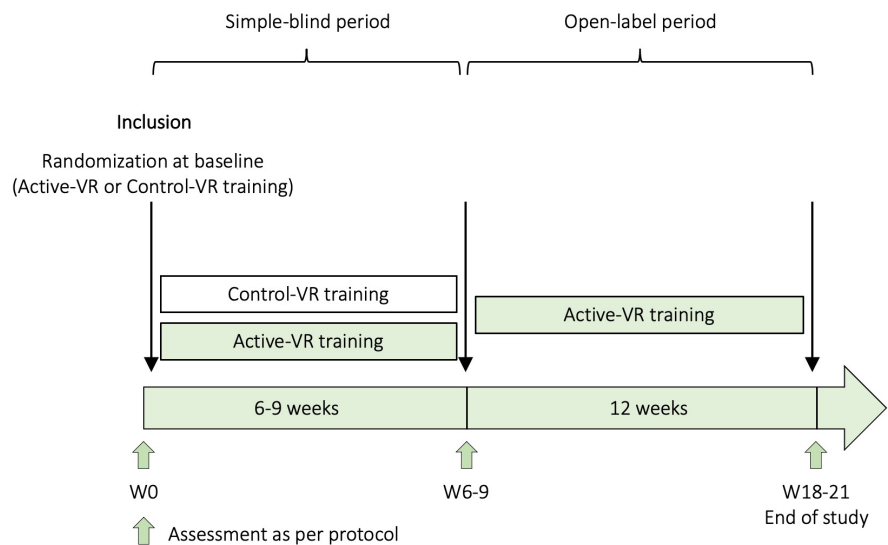


FIGURE 1 Flowchart of the study design.

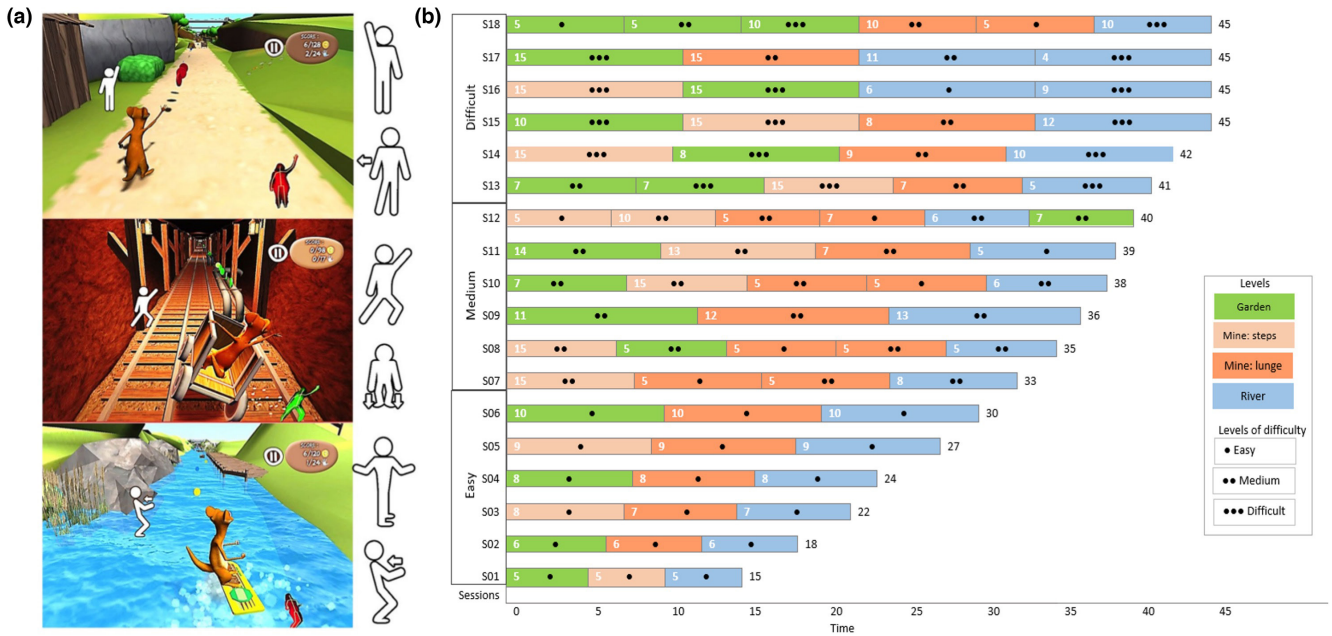


FIGURE 2 'Toap Run' exergaming and training program. (a) Top to Bottom: 'The Garden', 'The Mine', and 'The River'. The movements are schematically represented on the right side of the images, from top to bottom: arm extension, lateral shift, trunk lateral displacement with knee flexion, knee flexion/extension, trunk rotation with arm movements, and anteroposterior trunk movement. (b) The diagram represents the changes in the duration = x-axis-time in minutes (from 15 min for the first session S01 to 45 min for the last session S18) and gaming environments – garden in green, mine with steps in light orange, mine with lunge movements in dark-orange, and river in blue – for the two patient groups. The level of difficulty was also increased with time, from easy (one point) to difficult (three points), for each environment. The duration of training in each environment is shown in white numbers. The level of difficulty was defined according to the frequency of movements to be performed with three different rhythms: easy: 20 beats/min, medium: 30 beats/min, and difficult: 40 beats/min.

and 13: 'arising from chair', 'gait', 'FOG', 'postural stability', and 'posture') and Part IV (dopaminergic-related complications) [18]; the Gait and Balance Scale Part B (GABS-B) [21]; the Tinetti gait and balance scores [22]; the New Freezing of Gait Questionnaire (NFOG-Q) [23]; the Activity-specific Balance Scale (ABC) [24]; the Montreal Cognitive Assessment (MoCA) [25]; the Hospital Anxiety and Depression Scale (HADS) [26]; and the Parkinson's Disease Questionnaire (PDQ-39) [27]. A falls diary was also completed once a week to assess falls frequency. We also assessed the changes in these scales and the SWST duration between baseline and Post-M3.

Adherence endpoints included the between-group differences in the number of sessions, duration, adherence (percentage of sessions performed relative to sessions programmed), and success rate (percentage of movements correctly executed). This was done thanks to the Kinect® system for the Active group and the computer for the Control group. The acceptability, competence, self-efficacy, usability, and difficulty of the exergame training were measured using Likert scales [28] after the first session, weekly, and after the last session.

Additional secondary outcomes for patients at the Brain Institute were the changes in the gait kinetic parameters between baseline and W6, and between baseline and Post-M3 (see Appendix S1). It includes: (1) the anticipatory postural adjustments (APAs), double-stance and single-stance phases duration, (2) the center of foot pressure (CoP) displacements during the APAs, (3) step length, gait

speed, and cadence, and (4) gait asymmetry index, defined as the absolute value of gait cycle duration between left and right limbs. Higher displacements, length, speed and cadence, and lower durations and gait asymmetry index indicate better gait and postural control (Figure S1) [17].

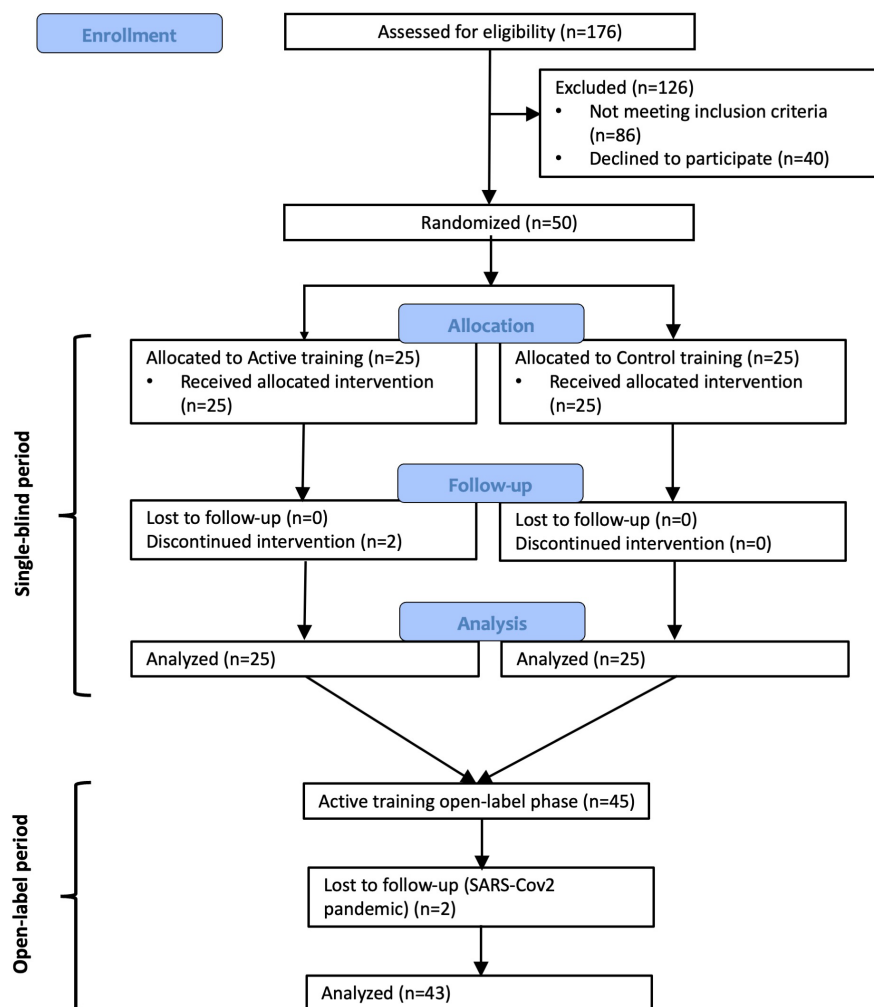
We also assessed the safety, and all adverse events were recorded. Any new symptom was classified as an adverse event and defined as serious if the patient required admission to hospital, if sequelae were present, or the clinician considered the event to be serious.

Statistical analysis

Our study was powered to show an effect of active exergame training on SWST duration after 18 sessions. In line with the published data regarding the estimated duration and effects of rehabilitation programmes on this test in PD patients [5, 29], we expected a decrease of 2 ± 1 s for the Active group and of 1 ± 1 s for the Control group. Assuming these values, a sample of 50 patients will allow a power of 90% ($\alpha = 5$, Mann-Whitney Wilcoxon test). To account for premature dropouts, we planned to include up to 60 patients.

Analyses were done on an intention-to-treat basis in patients who completed the follow-up assessment, regardless of whether they completed the assigned intervention. Missing data for the

FIGURE 3 CONSORT (Consolidated Standards of Reporting Trials) diagram.



primary outcome were imputed and the baseline duration of the SWST was used for a post-training session for missing post-training values (Post-W6). The primary and secondary outcomes were analyzed using nonparametric Mann–Whitney Wilcoxon rank tests. We employed Cliff's delta to assess the effect size of the differences between the two groups. It ranges from -1 to 1 , with 0 indicating stochastic equality between the two groups. A value around $|0.1|$ is considered a small effect, approximately $|0.3|$ a medium effect, and around or exceeding $|0.5|$ a large effect [30].

Additional analyses were done to compare (1) the number of patients with a change in the SWST duration of 2 s or more (considered responders) using Fisher's exact test and (2) the relationship between baseline characteristics, game parameters, and post-training severity of gait and balance disorders to identify potential predictors of good feasibility, adherence, and positive effects, using Pearson correlation tests. Corrected p -values <0.05 were considered significant. All analyses were performed using R statistical software (R Core team [2021]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org/>).

RESULTS

Cohort analysis

Between 18 July 2018 and 11 June 2021, we screened 176 potential participants, 82 did not fulfil the inclusion criteria and 40 refused to participate. Finally, 54 patients were included. Four patients were screen-failures (failing to meet inclusion criteria) and therefore not randomized (Figure 3). Fifty patients (25 in each center) were randomly assigned to either the Active training group ($n=25$) or the Control group ($n=25$). Due to the COVID-19 pandemic, the assessment of the primary outcome could not be conducted at the hospital for three patients (one from the Active and two from the Control groups) and was instead performed via teleconsultation; and we were unable to replace the two patients (Active group) who left the study prematurely at their own request and were not evaluated after the 18th session. Baseline characteristics of both patients' groups are shown in Table 1. We found no significant differences between groups at baseline (Mann–Whitney test, all p -values >0.05 ; Table 1).

TABLE 1 Patient characteristics at baseline and changes in the primary and secondary outcomes after Active or Control training in patients with Parkinson's disease.

	Baseline, mean (SD)		6 weeks, mean (SD)		Within-group change from baseline after 6 weeks, mean ± SD (effect size)		Between-group difference in change from baseline		P-value
	Active group (n = 25)	Control group (n = 25)	Active group (n = 25) ^a	Control group (n = 25)	Active group (n = 25) ^a	Control group (n = 25)	Mean ± SD	Effect size (95% CI)	
Age (years)	68.6 (6.9)	64.8 (8.2)							
Sex (M/F)	14/11	17/8							
Disease duration (years)	11.8 (6.3)	12.0 (5.9)							
LEDD (mg/day)	904 (498)	900 (495)							
Primary outcome									
SWST duration On-dopa (s)	22.5 (24.1)	14.7 (4.8)	18.8 (9.2)	14.0 (3.2)	-3.7 ± 18.1 (0.18)	-0.7 ± 3.4 (0.11)	-3.0 ± 3.83	-0.1 (-0.4_0.3)	0.61
Secondary outcome									
MDS-UPDRS Part I	9.3 (4.2)	9.4 (5.0)	8.5 (3.4)	8.8 (4.9)	-0.9 ± 2.9 (0.20)	-0.5 ± 4.7 (0.01)	-0.35 ± 1.12	-0.2 (-0.5_0.1)	0.41
MDS-UPDRS Part II	14.8 (5.4)	15.2 (5.6)	13.4 (4.5)	15.2 (5.0)	-0.9 ± 4.8 (0.21)	-0.0 ± 3.3 (0.06)	-0.83 ± 1.20	-0.2 (-0.5_0.1)	0.49
MDS-UPDRS Part III	30.2 (14.0)	34.3 (11.2)	26.2 (12.2)	33.7 (11.5)	-3.3 ± 8.6 (0.37)	-1.7 ± 6.9 (0.24)	-1.59 ± 2.26	-0.3 (-0.6_0.1)	0.56
On-dopa									
Axial subscore On-dopa	5.6 (3.5)	4.7 (2.5)	3.8 (2.8)	4.7 (2.1)	-1.5 ± 2.0 (0.70)*	-0.2 ± 1.6 (0.04)	-1.24 ± 0.52\$	-0.6 (-0.8_-0.3)	0.0082
MDS-UPDRS Part IV	4.8 (3.6)	4.7 (2.9)	4.7 (3.7)	4.9 (3.2)	0.0 ± 2.7 (0.03)	0.2 ± 2.3 (0.08)	-0.20 ± 0.73	-0.2 (-0.5_0.1)	0.57
GABS Part B On-dopa	18.9 (7.9)	15.6 (8.7)	14.6 (7.3)	15.5 (7.6)	-2.7 ± 4.3 (0.51)*	-0.7 ± 4.3 (0.22)	-2.03 ± 1.24	-0.4 (-0.7_-0.1)	0.22
Falls rate (item 4 GABS Part A)	1.4 (1.1)	1.0 (0.9)	1.3 (1.3)	0.6 (0.8)	-0.1 ± 0.7 (0.19)	-0.4 ± 1.0 (0.42)	0.19 ± 0.25	0.0 (-0.3_0.3)	0.39
Tinetti gait score	9.6 (1.7)	10.4 (1.7)	10.5 (1.2)	10.7 (1.3)	0.8 ± 1.6 (0.44)*	0.2 ± 1.3 (0.16)	0.58 ± 0.42	0.1 (-0.2_0.4)	0.23
Tinetti balance score	12.6 (2.0)	13.4 (2.0)	13.2 (1.9)	13.6 (1.4)	0.3 ± 1.0 (0.35)	0.2 ± 1.7 (0.05)	0.14 ± 0.40	0.0 (-0.3_0.3)	0.41
NFOG-Q	10.6 (4.2)	9.6 (3.6)	10.3 (4.6)	8.8 (3.5)	-0.1 ± 3.2 (0.07)	-0.8 ± 3.0 (0.19)	0.71 ± 0.89	0.0 (-0.3_0.3)	0.65
ABC Scale	65.6 (19.7)	73.0 (13.6)	63.1 (17.3)	72.3 (14.2)	-2.5 ± 10.1 (0.20)	-0.7 ± 7.9 (0.12)	-1.81 ± 2.63	-0.1 (-0.5_0.2)	0.70
MoCA score	25.8 (2.8)	25.4 (2.8)	26.6 (3.3)	26.4 (2.3)	0.6 ± 2.5 (0.24)	1.3 ± 2.6 (0.50)	-0.71 ± 0.73	-0.3 (-0.6_0.0)	0.47
HADS	9.4 (6.1)	12.3 (5.4)	9.0 (6.4)	10.8 (5.1)	-0.0 ± 3.1 (0.06)	-1.5 ± 2.5 (0.52)*	1.44 ± 0.82\$	0.2 (-0.1_0.6)	0.046
PDQ-39 SI	22.8 (8.2)	24.9 (8.4)	25.5 (10.9)	22.1 (9.4)	2.4 ± 4.8 (0.25)	-2.2 ± 6.7 (0.46)*	4.68 ± 1.67\$	0.3 (-0.1_0.6)	0.014

Note: LEDD = levodopa equivalent daily dosage expressed in milligrams/day. MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale where Part I assesses non-motor aspects of experiences of daily living with scores ranging from 0 to 52, Part II reflects motor aspects of experiences of daily living with scores ranging from 0 to 52, Part III reflects the parkinsonian motor disability with scores ranging from 0 to 132, and Part IV assesses the severity of motor complications with scores ranging from 0 to 24; the axial score is extracted from the UPDRS Part III and is the sum of 'arising from chair', 'gait', 'freezing of gait', 'postural instability', and 'posture' items with scores ranging from 0 to 20. The Gait and Balance Scale (GABS) Part B reflects the severity of the gait and balance disorders with scores ranging from 0 to 46. The falls rate (item 4 of the GABS Part A) ranging from 0 (no falls) to 4 (falls ≥1/day). The New Freezing of Gait Questionnaire (NFOG-Q) with scores ranging from 0 to 24 with higher scores indicating more severe FOG. The Activities-specific Balance Confidence (ABC) scale reflects the feeling of imbalance in various daily life activities, ranging from 0 to 100, and the Tinetti scores for gait and balance reflect gait and balance control with scores ranging from 0 to 12 and 0 to 16, respectively, with higher scores for ABC and Tinetti scores indicating better gait and balance confidence or control. The Montreal Cognitive Assessment score is an education-adjusted scale of cognition with a maximum score of 30. The Hospital Depression and Anxiety Scale (HADS) ranges from 0 to 42 with high scores indicating more severe depressive and anxiety signs. The Parkinson's Disease Questionnaire-39 (PDQ-39) is a quality-of-life scale specific to PD with the summary index ranging from 0 to 100 with higher scores indicating worse quality of life. **p* < 0.05 for within-group changes between baseline and after 6 weeks' training. \$*p* < 0.05 for between-group differences in the change between baseline and after 6 weeks' training.

^aFor the Active group, data were collected from 23 patients for the secondary outcomes due to premature dropout of two patients.

Adherence, game parameters, and success rate

We progressively increased the game duration, number of movements, and movement frequency between the 1st and the 18th session (Figure 2). Both groups adhered and performed well in the training sessions, with a mean adherence, duration, and number of movements that did not differ between groups (Table 2). The movement frequency and game performance were higher in the Control relative to the Active group (Figure 4, Table 2). Patients also reported high perceived levels of acceptability, competence, self-efficacy, and usability, with low difficulty, with no significant difference between groups or over time (Table S1).

Effects of home-based exergaming on Parkinsonian disability and gait and balance disorders

The changes in the SWST duration between baseline and after 18 training sessions (Post-W6) did not differ significantly between groups (Figure 4; Table 1). Some 32% of patients in the Active group ($n=8$) and 8% ($n=2$) in the Control group were considered responders to the exergaming training (e.g., change in the SWST duration ≥ 2 s, $p=0.03$; Figure 4).

At the end of the randomized training period (W6), axial motor signs severity decreased in the Active group, with no significant change in the Control group resulting in a significant between-group mean difference of 1.24 (Table 1). In addition, a significant decrease in the GABS Part B score and increase in the Tinetti gait score were found in the Active group, with no significant change in the Control group, resulting in a non-significant between-group mean difference of 2.03 and 0.58, respectively (Table 1). Due to a significant amount of missing data from the falls diary, we assessed the falls rate using item 4 of the GABS and found no significant change after training (Table 1). For the Control group, we observed a significant decrease in the quality of life (SI-PDQ39) and HADS scores, with a significant between-group mean difference of 4.68 and 1.44, respectively (Table 1). We found no other significant difference between groups (Table 1).

In the Active group, we found a significant negative correlation between the mean success rate during gaming and both the mean post-training SWST duration ($r=-0.42$, $p=0.034$) and age ($r=-0.48$, $p=0.015$), with no other significant correlation (data not shown).

For gait parameters, at W6 relative to baseline, we found significant decreases in APAs and double-stance durations, and asymmetry index, and increases in CoP displacements, step length, gait speed, and cadence in the Active group; and for the Control group significant increases in step length, gait speed, and cadence, with no other significant changes (Table S2).

During the 3-month open-label period, 15 patients performed Active training with at least 8 sessions of at least 10 minutes and 25 patients performed fewer than 10 training sessions. We found no significant change in clinical scores at the end of the open-label

period relative to baseline (data not shown). However, we observed non-significant decreases of 4.6 s in the SWST duration and 5.3 points in the MDS-UPDRS Part III (On-dopa) in PD patients that did Active training during the open-label period, and of 0.1 s and 1.4 points in PD patients that did not.

Safety and tolerability of home-based exergaming

Nine adverse events occurred in eight patients, four in the Active and four in the Control group (Table 3). Three serious adverse events were reported during the open-label period and found to be unrelated to the intervention and consisted of recurrent falls, or hospitalization for antiparkinsonian medication adjustment. Five non-serious adverse events were reported in five patients during the randomization and open-label periods (Table 3).

DISCUSSION

In this randomized controlled trial of 50 PD patients with medically refractory gait and balance disorders, we observed no significant difference in functional mobility (the SWST duration) between Active full-body movement training and Control gaming. However, Active exergaming training did improve clinical gait and balance disorders scores and postural gait kinetics. The Control group showed no changes in motor signs, but improvement in quality of life and anxiety. The exergaming training was well received and tolerated.

The SWST duration was chosen as the primary outcome due to its ease of administration, and the ability to assess video-recorded performances independently. However, it did not significantly change in either group, as recently reported in three recent studies assessing the effects of home-based exergaming training (involving cycling or dancing programs), although improvements in mobility were observed [13, 16, 31]. Institution-based rehabilitation, with or without exergaming or virtual reality, has shown significant decreases in SWST duration with moderate-to-large effects ranging from 0.6 to 2.86 s [5, 32, 33]. This suggests that the intensity of home-based training or the specificity of our exergaming approach may have been insufficient to impact this multifaceted task, which encompasses actions such as rising from a chair, walking, turning, and returning to the starting position. The study duration and targeted patient group may also have contributed to the lack of benefits. Our Active training duration was approximately 100–110 min/week whereas recent findings indicate that a minimum of 150 min/week of home-based training is necessary to achieve balance improvement in PD [34]. However, the number and frequency of training sessions were comparable to other trials [11, 16, 34]. Moreover, our patients already exhibited significant impairments in static balance, encountered difficulties in learning [10], with possible limited application of effective compensation strategies after training [35]. The higher success rate

TABLE 2 Game adherence, duration, and number of movements per session for Active-VR and Control-VR groups during the 6-week randomized period.

Session	Active group						Control group					
	Adherence (%)	Game duration (min)	Number of movements	Movement frequency (Hz)	Success rate (%)	Adherence (%)	Game duration (min)	Number of movements	Movement frequency (Hz)	Success rate (%)		
S01	95.8	10.8 (4.8)	135 (72)	11.8 (2.8)	69.9 (15.7)	100	10.5 (5.8)	138 (83)	12.9 (2.9)	72.0 (20.0)		
S02	95.8	16.1 (5.8)	201 (92)	12.5 (2.5)	76.2 (14.0)	100	17.3 (4.4)	239 (74)	14.1 (3.1)	84.9 (13.3)		
S03	100	18.6 (6.2)	237 (100)	12.6 (2.9)	75.2 (17.2)	100	18.7 (5.3)	284 (103)	15.6 (3.5)	87.6 (12.8)		
S04	95.8	22.3 (5.7)	307 (105)	13.7 (2.5)	81.3 (13.5)	100	21.1 (5.4)	347 (124)	16.5 (4.8)	88.5 (13.7)		
S05	100	23.9 (6.0)	311 (115)	12.8 (3.2)	77.5 (19.6)	100	24.3 (8.1)	406 (199)	16.5 (4.7)	89.0 (13.6)		
S06	95.8	26.1 (6.2)	392 (153)	14.6 (3.6)	79.6 (16.4)	100	26.5 (7.3)	486 (207)	17.8 (5.1)	88.6 (16.9)		
S07	95.8	28.7 (7.1)	460 (187)	15.6 (4.1)	79.3 (17.5)	100	30.7 (7.6)	615 (271)	19.0 (5.5)	88.0 (17.2)		
S08	91.6	28.8 (9.9)	501 (245)	15.9 (5.3)	75.0 (21.3)	100	31.0 (8.3)	655 (258)	20.2 (4.6)	87.8 (16.7)		
S09	87.5	31.8 (6.3)	594 (185)	18.1 (3.8)	82.4 (10.9)	100	32.2 (8.3)	691 (260)	20.9 (4.0)	90.3 (13.1)		
S10	87.5	33.5 (9.0)	630 (238)	17.9 (4.3)	80.1 (13.5)	95.8	33.5 (11.3)	744 (308)	20.9 (6.0)	87.1 (20.6)		
S11	87.5	32.5 (10.2)	654 (268)	19.2 (5.3)	82.3 (13.3)	95.8	33.4 (10.1)	755 (333)	20.9 (5.2)	86.7 (19.3)		
S12	87.5	35.3 (7.9)	711 (259)	19.4 (4.8)	82.0 (13.6)	87.5	35.0 (10.7)	780 (329)	21.3 (5.5)	89.8 (14.5)		
S13	79.1	36.7 (8.6)	809 (314)	21.3 (5.9)	81.4 (12.5)	87.5	34.9 (12.4)	823 (347)	23.4 (5.7)	89.1 (13.3)		
S14	70.8	40.4 (5.4)	902 (288)	21.4 (6.1)	80.4 (16.9)	79.1	36.7 (10.6)	883 (336)	23.5 (6.4)	86.5 (18.2)		
S15	75.0	39.4 (9.6)	915 (330)	21.6 (7.0)	81.1 (21.7)	79.1	36.8 (10.5)	939 (366)	25.3 (5.9)	88.6 (16.9)		
S16	66.6	41.6 (6.3)	980 (268)	23.7 (6.2)	85.0 (12.8)	66.6	35.5 (13.2)	960 (426)	24.9 (5.5)	86.0 (16.1)		
S17	66.6	41.8 (7.5)	991 (303)	22.7 (6.2)	81.4 (20.0)	50	37.4 (11.9)	988 (310)	25.1 (4.9)	86.5 (13.8)		
S18	62.5	41.0 (7.8)	925 (252)	22.9 (5.4)	86.7 (12.0)	45.8	37.5 (16.2)	945 (437)	21.4 (7.2)	81.2 (25.6)		
Mean (SD)	85.6 (12.4)	29.4 (11.5)	554 (345)	17.1 (5.9)	79.4 (16.1)	88.2 (17.6)	28.7 (12.0)	613 (370)	19.5 (6.1)*	86.7 (16.7)*		

Note: Data are mean and standard deviation (SD) for each session. Adherence is the ratio of the effective duration of the session relative to the programmed duration of the same session. This ranges from 0 (no training) to 100% (complete training duration). * $p < 0.05$ between groups.

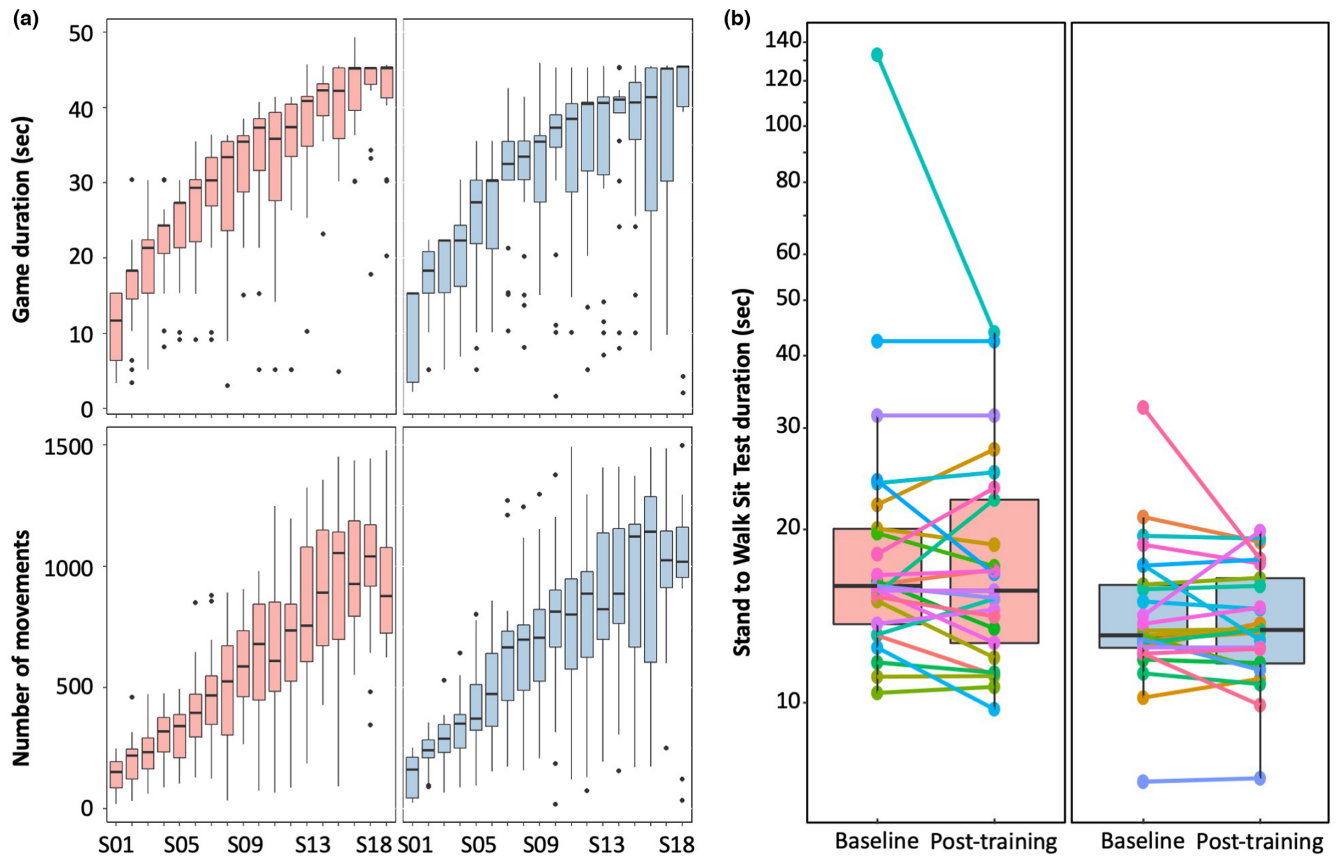


FIGURE 4 Training programmes and Stand-Walk-Sit Test (SWST) durations before and after Active or Control exergaming training at home. (a) Box plots for the duration (upper) and number of movements (bottom) performed during the home-based exergaming training sessions and over time in patients from the Active (pink) and Control (blue) groups, during the 6-week randomized period from the first (S01) to the last training session (S18). (b) Box plots for the SWST duration at baseline and after 6 weeks of training (post-training) in patients from the Active (pink) and Control (blue) groups, with a base-10 logarithmic scale. Each dot represents one individual patient.

TABLE 3 Adverse events.

Adverse events	Active group	Control group
Serious adverse events		
Hip fracture	0	1 (P47)
Wrist fracture	1 (P48)	0
Hospitalization for antiparkinsonian treatment adaptation	1 (P52)	0
Non-serious adverse events		
Epileptic fit	0	1 (P09)
Ankle tendonitis	0	1 (P23)
Hip osteoarthritis with pain	1 (P27)	0
Fall with hand wound	1 (P39)	0
Ankle sprain	0	1 (P44)

Note: Values are number of adverse events.

during training among participants who responded positively, and the persistent decrease in the SWST duration and parkinsonian motor disability observed in patients who engaged in longer training during the 3-month period, suggest that a better ability to engage in the training is a factor for a more efficient compensation after training [35]. Finally, the SWST duration measurement may

have inherent limitations, including high measurement error, and may not be suitable for reliable comparisons at both individual and group levels [36].

Active training showed positive effects on secondary outcomes, indicating potential improvements in gait and balance disorders, that needs to be interpreted cautiously. However, a similar

improvement in gait and balance disorders was also reported after home-based exergaming training with online coaching or when performed within an institution, sometimes combined with conventional rehabilitation methods [11, 12, 14, 32, 37, 38]. This indicates that patients in advanced stages of PD can potentially improve their motor function if the training is appropriately tailored to their needs [39]. Our Active training incorporated full-body movements, postural tasks, visual and auditive cues, and motivational elements with success rates. Although, we did not analyze the impact of separate training routines on these endpoints, our results indicate that the combination of all these motor, cognitive, and emotional components are likely key features to achieving a better effect on gait and balance disorders, that potentially leads to the transfer of acquired skills to other untrained tasks in everyday situations [5, 40]. Control gaming also had mild positive effects on gait parameters, along with anxiety and quality of life improvements. These motor and psychological effects of videogame playing may result from a dopamine striatal release, as reported in the limbic striatum of young healthy adults [40, 41], and recently in patients with PD. [42]

During the optional open-label training period, adherence was limited with approximately one-third of the patients engaged in active training. This suggests that game-based training alone may be not sufficiently attractive to maintain long-term adherence. Combined training with inertial sensors and smartphone device and/or with daily tele-coaching would probably enhance adherence over time [16, 43]. Although our training was individually tailored, the game did not contain automated, performance-based decision-making, which has been suggested to improve the efficiency of gait training [43]. These data indicate that training should be personalized and fine-tuned, using highly interactive programs in PD management [44], and maintained over time, to achieve beneficial results and motor improvement [6, 16, 45]. Patients faced challenges using the software and conducting the training sessions independently, with older individuals exhibiting lower performance, and a potential fear of falling that could result in a voluntary decrease in movement amplitudes to prevent falls. This highlights the importance of user-friendly and interactive systems to enhance patient adherence and motivation over time, particularly for individuals with more severe forms of PD [33, 44].

LIMITATIONS

The present study has some limitations. First, two patients in the Active group prematurely dropped out of the study, and they were not replaced due to the COVID-19 crisis. This may have resulted in underpowering of the results. However, we performed data imputation and the effect size for the primary outcome was found to be small, suggesting that this may have had a minimal impact on the results. Second, both patient groups received intervention programs, which prevented us from examining the effects of active exergaming training compared to no training or usual care programs. Third, the

study design did not allow for a comprehensive assessment of retention effects as all patients were given the option to engage in Active training after the randomized period.

CONCLUSIONS

Home-based, full-body movement, active training using tailored exergaming shows feasibility and potential improvement in gait and balance disorders in advanced PD patients. While our findings do not definitively conclude on the effectiveness of our exergaming approach, they do contribute valuable insights into the development of rehabilitation programs incorporating exergaming to improve patients' adherence and efficacy. Further research is needed to explore the impact of exergaming on disease progression in patients with less severe forms of PD, assess the health-care implications, and gain deeper insights into its effects on brain function.

AUTHOR CONTRIBUTIONS

Project design: ML Welter, N De Vries, D Nuic; Methodology: D Nuic, S Van de Weijer, S Cherif, A Skrzatek, E Zeeboer, C Olivier, J-C Corvol, P Foulon, JZ Pastor, G Mercier, B Lau, BR Bloem, N De Vries, ML Welter; Resources: ML Welter, N De Vries; Writing original draft, review and editing: ML Welter, S Van de Weijer, S Cherif, A Skrzatek, E Zeeboer, C Olivier, JC Corvol, P Foulon, J Meija, G Mercier, B Lau, B R Bloem, N De Vries, ML Welter; Supervision: ML Welter, N De Vries; Project administration: ML Welter, N De Vries; Fund raising: ML Welter, N De Vries, P Foulon.

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CONFLICT OF INTEREST STATEMENT

D.N., S.v.d.W., S.C., A.S., E.Z., C.O., J.-C.C., J.Z.P., G.M., B.L., B.R.B., N.M.d.V., and M.-L.W. declare they have no conflict of interest relative to the research. D.N., A.S., S.v.d.W., C.O., J.Z.P., G.M., S.C., and E.Z. have no conflict of interest to declare. B.L. received research grants from the Brain Institute Foundation and Agence Nationale de la Recherche outside of this work. P.F. is employed by Genius Healthcare France which has no property rights on the data. J.-C.C. received research grants from the Paris Brain Institute, France Parkinson, and Agence Nationale de la Recherche outside of this work; fees for advisory boards for Servier, Biophytis, Biogen, UCB, Prevail Therapeutics, and Alzprotect

outside of this work. B.R.B. serves as the Co-Editor in Chief for the *Journal of Parkinson's Disease*, serves on the editorial board of *Practical Neurology* and *Digital Biomarkers*, has received fees from serving on the scientific advisory board for UCB, Kyowa Kirin, Zambon, and the Critical Path Institute (paid to the Institute), has received fees for speaking at conferences from AbbVie, Biogen, UCB, Zambon, Roche, GE Healthcare, Oruen, Novartis, and Bial (paid to the Institute), and has received research support from the Netherlands Organisation for Health Research and Development, The Michael J. Fox Foundation, UCB, the Stichting Parkinson Fonds, Hersenstichting Nederland, de Stichting Woelse Waard, Stichting Alkemade-Keuls, de Maag Lever Darm Stichting, Parkinson NL, Davis Phinney Foundation, the Parkinson's Foundation, Verily Life Sciences, Horizon 2020, the Topsector Life Sciences and Health, Nothing Impossible, and the Parkinson Vereniging outside the submitted work. N.M.d.V. received research grants from the Netherlands Organisation for Health Research and Development outside of this work. M.L.W. received research grants from the Paris Brain Institute, Agence Nationale de la Recherche, The Michael J. Fox Foundation, and Boston Scientific; and personal fees from Boston Scientific and Medtronic outside of this work.

DATA AVAILABILITY STATEMENT

All relevant data appear within the article. Requests for anonymized data should be sent to M. L. Welter at the Brain Institute, 75013 Paris, France.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Supplementary online content

Nuic et al. Home-based exergaming to treat gait and balance disorders in patients with Parkinson's disease: a phase II randomized controlled trial

Supplementary Methods

Supplementary References

eFigure 1. Gait parameters recordings

eTable 1. Acceptability and usability of the Toap Run game in Active and Control groups

eTable 2. Effects of Active-VR and Control-VR training on gait parameters in 24 PD patients during the randomized period

Supplementary Methods

The ‘Toap Run’ videogame

The movements consist of large amplitude rapid movements of all four limbs, pelvis and trunk, with lateral, vertical and forward displacements of the legs, to reinforce foot lifting and postural control:

- In ‘The Garden’, the patients had to extend their arms to collect coins and perform lateral displacements to avoid laterally placed obstacles,
- In ‘The Mine’, the patients had to collect coins and avoid obstacles with the same movements as in ‘The Garden’, plus knee flexion/extension to avoid high level obstacles and lateral trunk displacements with one leg flexion to move the wagon and collect coins,
- In ‘The River’, the patients had to perform trunk rotation and arm movements to collect coins, and anteroposterior trunk movements to avoid obstacles.

Visual cueing consisted of a schematic representation of the movements required to perform along the trajectory of the avatar. Auditory cueing consisted of rhythmic music that beats in relation to the velocity of the avatar displacement. Three different rhythms were presented: 20, 30 and 40 beats/min. The first session was stereotyped and consisted of a 15 min session with a 20 beat velocity first in the garden and then in the mine, corresponding to a total of 100–150 movements. Game difficulty, i.e. velocity and number of movements to capture the coins and avoid obstacles, was then adjusted manually and individually by the investigator for subsequent rehabilitation sessions, in relation to the patient’s ability. For this purpose, the investigator was instructed to increase the rhythm, number and complexity of movements, i.e. the environment, depending on the performance in the previous session with a view to obtaining a session of at least 40 min duration after the 9th session.

Game parameters

To assess the patient's good adherence to his rehabilitation program, we calculated a ratio between the playing duration programmed for a session and the duration actually achieved by the patient during this session, excluding breaks during the session training. Thanks to the Kinect® system, we were also able to measure the number of movements performed and the performance rate, defined as the percentage of movements correctly performed during the session. This was done for both patient groups.

For all patients, the first four sessions were performed with a physiotherapist, with the first two at the institute, and the following at home.

Gait recordings

For patients at the Salpêtrière Hospital, gait parameters were recorded at each visit using the VICON system with Plug-In-Gait model, with fiducial markers positioned on the arm and leg joints. The patients, barefoot, initiated gait on a force platform (0.9X1.8m, Advanced Mechanical Technology Inc. LG6-4-1) and walked for 5-m at a self-paced speed, making a half-turn and returning to the initial position (n=15-20 trials, Figure S1). The gait initiation and straight forward walking events were manually identified. For gait initiation, the following parameters were calculated:¹ 1) anticipatory postural adjustments (APAs) phase duration, 2) maximum posterior and 3) lateral center of foot (CoP) displacements during the APAs, 4) length, width and velocity of the first step. For straight forward walking, we also measured: 5) mean stride length, 6) width and 7) velocity during a gait cycle, 8) cadence, 9) stride and double-stance durations and 10) gait asymmetry index, defined as the absolute value of gait cycle duration between left and right limbs. For length and velocity, higher values indicate better performances; for durations and gait asymmetry, lower values indicate better performances.

Acceptability and usability questionnaires

We assessed the acceptability and usability of the “Toap Run” game at the end of each first session, weekly, and after the last session during the randomised period using a questionnaire² with:

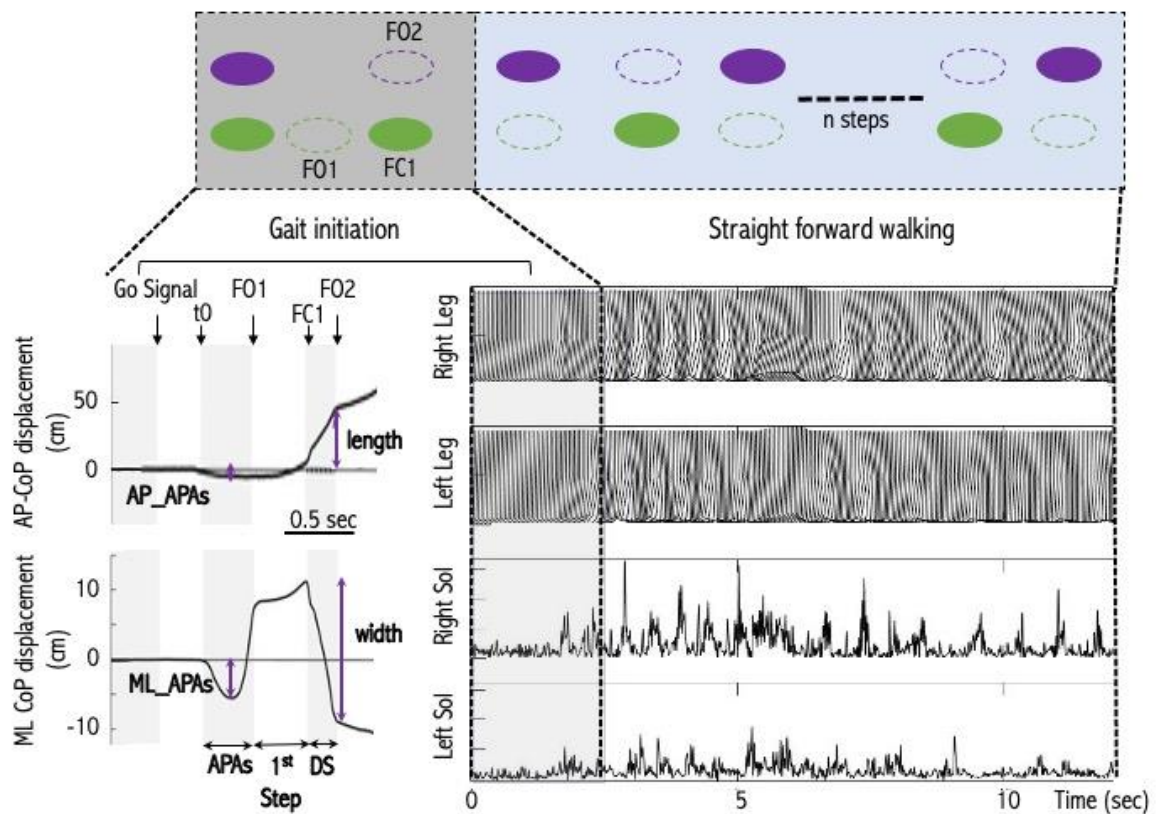
- 4 items on the feelings of self-efficacy toward physical activity measured using a scale to assess the degree of confidence in the ability of participants to practise at least 30 minutes of moderate to intense physical once, twice and three times a week.

- 7 items on the feeling of self-efficacy towards videogames including 4 items on physical activity and 3 items on the confidence of participants in their skill to play video games.
- 3 items on perceived difficulty.
- and 4 items on perceived interest.

For each item, participants rated their confidence on a Likert-type scale ranging from 1 "not at all able / competent / good / difficult / interested" to 7 "very capable / competent / good / difficult / interested." An emotional questionnaire, adapted from the Positive Affect Negative Affect Scale (PANAS)³ was also completed at each visit.

Supplementary References

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eFigure 1. Gait parameter recordings

Top Row: The subject stands motionless on the force plate (Grey square) and initiates gait with their right leg (Gait initiation), and then walks straight forward self-paced. The standardized gait alternation is represented with green and purple filled ellipses when the foot makes floor contact and a dotted outline ellipse during the swing phase of the foot. *Bottom row:* Illustration of the AP and ML CoP displacements during the gait initiation phase (left). Events of the gait initiation task are represented with black arrows and grey and white columns. At bottom right, illustration of both pelvis, knee, and ankle kinematics (upper rows) and soleus EMG signal (lower rows) for right and left legs, during gait initiation and straight-line forward walking, and bilateral simultaneous soleus muscle activity. AP: Anteroposterior; APAs: Anticipatory Postural Adjustments; CoP: Centre of foot Pressure; DS: double-stance phase; FC1: Foot Contact of the starting leg; F01: Foot Off of the starting leg; FOG: Freezing of Gait; ML: Mediolateral; RT: Sol: Soleus; t0: time of the first biomechanical event corresponding to the beginning of the APAs.

eTable 1. Acceptability and usability of the Toap Run game in Active and Control groups

	Baseline		End of the open-label period		Within-group change from baseline after 6 weeks		Between-group difference in change from baseline (mean, estimate, lower_upper 95% CI)	
	Active group (n=25)	Control group (n=25)	Active group (n=25)	Control group (n=25)	Active group (n=25)	Control group (n=25)		P value
Acceptability	8.2 (1.2)	7.5 (1.4)	8.0 (1.5)	7.3 (1.8)	-0.3 (1.4)	0.2 (1.1)	0.5 (0.60; 0.42_0.75)	0.26
Competence	41.9 (7.0)	43.1 (9.0)	40.5 (9.3)	40.1 (11.3)	-1.4 (7.6)	-2.5 (11.0)	1.1 (0.49; 0.32_0.66)	0.94
Self-efficacy	15.6 (2.9)	16.0 (3.1)	15.5 (2.9)	16.3 (3.9)	-0.1 (2.9)	0.5 (4.2)	0.6 (0.58; 0.41_0.73)	0.38
Usability for physical activity	26.3 (5.3)	27.1 (6.6)	25.0 (6.9)	23.9 (7.9)	-1.3 (6.9)	-3.1 (7.6)	1.7 (0.46; 0.30_0.63)	0.66
Difficulty	13.2 (3.5)	13.3 (3.4)	12.9 (4.1)	10.7 (3.6)	-0.0 (3.0)	-2.1 (4.0)	2.1 (0.38; 0.24_0.56)	0.22
System usability scale	76.7 (10.9)	72.4 (15.4)	72.2 (14.7)	70.7 (12.6)	-3.6 (9.8)	2.3 (7.9)	5.9 (0.68; 0.50_0.82)	0.05
Positive emotions	35.4 (6.2)	33.5 (5.2)	34.7 (6.2)	32.4 (6.4)	-1.0 (5.0)	-0.7 (5.2)	0.3 (0.49; 0.33_0.66)	0.98
Negative emotions	13.7 (4.1)	14.5 (3.7)	13.2 (4.4)	14.2 (4.4)	-0.4 (5.2)	0.3 (4.6)	0.6 (0.52; 0.36_0.68)	0.82

eTable 2. Effects of Active and Control exergaming training on gait parameters in 24 PD patients during the randomized period

	Baseline		Post-training		Within-group change from baseline		Between-group difference in change from baseline (mean, estimate, lower_upper 95% CI)	P value
	Active group (n=12)	Control group (n=12)	Active group (n=12)	Control group (n=12)	Active group (n=12)	Control group (n=12)		
Gait initiation								
APA duration (s)	0.63 (0.15)	0.61 (0.12)	0.58 (0.13)	0.61 (0.13)	-0.06 (0.07)*	-0.01 (0.05)	0.05 (0.68; 0.43_0.84)	0.15
AP CoP displacement (mm)	31.5 (12.9)	38.7 (15.1)	37.5 (16.6)	44.4 (12.2)	7.4 (10.1)*	6.6 (9.9)*	1.2 (0.45; 0.25_0.67)	0.71
ML CoP displacement (mm)	36.8 (12.3)	38.1 (14.6)	39.2 (14.7)	40.2 (15.3)	3.0 (8.9)*	1.1 (8.5)	2.0 (0.42; 0.23_0.65)	0.54
First step length (cm)	31.8 (8.8)	36.8 (11.7)	33.8 (8.6)	39.3 (11.4)	2.7 (7.9)*	2.8 (6.2)*	0.1 (0.52; 0.30_0.74)	0.88
First step velocity (m/s)	0.69 (0.18)	0.79 (0.19)	0.75 (0.22)	0.86 (0.24)	0.08 (0.15)*	0.07 (0.16)*	0.01 (0.52; 0.30_0.72)	0.93
Straight forward gait								
Cadence (steps/min)	105.2 (12.9)	112.2 (8.8)	110.3 (12.9)	114.1 (8.3)	5.1 (3.7)*	1.9 (7.1)*	3.2 (0.42; 0.21_0.63)	0.44
Double stance duration (s)	0.20 (0.05)	0.17 (0.03)	0.18 (0.05)	0.17 (0.04)	-0.02 (0.01)*	0.00 (0.03)	0.01 (0.61; 0.38_0.80)	0.37
Stride length (cm)	83.9 (16.2)	93.8 (13.4)	87.6 (16.4)	92.8 (22.8)	3.7 (7.5)*	-1.0 (13.7)	4.8 (0.48; 0.27_0.60)	0.88
Stride velocity (m/s)	0.74 (0.19)	0.87 (0.12)	0.81 (0.20)	0.88 (0.22)	0.07 (0.07)*	0.01 (0.17)	0.06 (0.47; 0.27_0.69)	0.84
Gait asymmetry index	6.7 (6.1)	6.9 (6.0)	5.2 (4.6)	8.4 (8.7)	-1.51 (3.4)*	1.44 (5.9)	2.95 (0.61; 0.31_0.80)	0.37

Data are mean and SD. *p<0.05 for within-group changes between baseline and after 6 weeks. APA= anticipatory postural adjustment; AP= anteroposterior; CoP= centre of foot pressure; ML= mediolateral. Lower APAs, step, double-stance and stride durations, width and gait asymmetry index, and higher length, velocity and cadence, reflect better gait and postural performance.

5.2 Conclusion

Overall, we confirmed the feasibility, the acceptability, and beneficial effects of the “*Toap Run*” exergaming as tool for rehabilitation at distance. The time needed for the SWST in patients wasn’t decreased, as wasn’t the FOG-Q, which suggests that the training was not intensive enough when compared to the institute-based training. Indeed, the program parameters need to be investigated and adapted for higher effects of the home-based training. It is also noteworthy that in both groups we can distinguish responders and non-responders, thereby indicating an inter-individual heterogeneity beyond age, phenotype, or disease duration. This finding further highlights the need for neuroimaging studies to better understand the severity-related neural changes and how different trainings affect the brain in responders, compared to non-responders.

However, the significant benefit was observed on gait and balance disorders severity as supported by decreases in the axial and GABS scores, along with improvements in gait parameters. These objective and subjective measures suggest that patients can potentially benefit from the program to increase their mobility and motor abilities at home. However, as presented in the open-label phase, patients’ adherence, and motivation to continue exergaming training at home by their own was low. This indicates that the tele-coaching from the therapists seems mandatory for improving adherence and, in consequence, the observed benefits (van der Kolk et al., 2019).

This study has also helped separating purely VR-related effects from the VR-enhanced physical therapy. Indeed, considering that the game without the active physical training has increased the quality of life, step length and cadence, while decreasing depression and anxiety scores, it may be reflective of VR-induced changes to the neurotransmitter systems. Given that the game didn’t demand any supplementary decision-making task, no effects on cognitive abilities were observed. This aspect could be addressed further in the new versions of the game.

Chapter 6: “Neural mechanisms underlying effects of the “Toap Run” home-based exergaming rehabilitation program (randomised controlled trial)”

6

6.1 Objectives and overview of the methods

In this sub-study of the PARKGAME II randomised controlled trial we aimed at understanding previously observed effects in terms of induced neural mechanisms by each type of training. First, we wanted to understand neural alterations linked to the severity of the symptoms in our population, and secondly the changes observed after the training. Two principally expected processes were 1) restauration of the lost circuits, either in compensation or novel automatization through motor learning, and 2) neuroplasticity of deleterious compensation networks by creation of the new ones, involving other structures and network complexity.

Among the recruited PD patients with FOG and/or falls, 23 were eligible for MRI, and underwent the neuroimaging protocol during the visits pre- and post-rehabilitation (before the 1st and after the 18th training session). We studied the inter-individual differences in GM volume and in resting state functional connectivity (FC) in relation to the clinical symptom severity, as means to identify neural markers of severity observed in our population. Grey matter volumes were estimated through the Volume Based Morphometry (VBM) performed on the anatomical MRI images, while the FC was assessed with resting state fMRI (rs-fMRI). The differences in these measures pre- and post-rehabilitation were further used to evaluate training-induced changes per group. The secondary objective was to attempt a characterisation of the neural changes typical to the patients showing the highest benefits from the exergaming (the responders). Given the sample size in this study, we focused on the best and the worst cases in terms of clinical gait and balance change in the active group as assessed with GABS.

As formerly presented in the first part of the PARKGAME II study, patients underwent general physical, cognitive, psychiatric, and parkinsonian disability assessments pre- and post-training. However, given the significant results from the previous studies (specifically in the

Active training), we decided to dwell on a restricted number of clinical and neurophysiological measures. In order to better address the specificity of gait/balance disorders severity and of parkinsonian motor signs, the axial subscore and upper limb severity were treated separately from other items of MDS-UPDRS part III - respectively as Axial and UPDRS Sup.

Neuroimage: Reports

Brain modulation after exergaming training in advanced forms of Parkinson's disease: a randomized controlled study --Manuscript Draft--

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	<p>movement training using a tailored exergame induces brain rs-FC changes within the sensorimotor, attentional and cerebellar networks in PD. Further research is needed to comprehensively understand the neurophysiological effects of such training approaches.</p>
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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

ML Welter received research grants from the Paris Brain Institute, Agence Nationale de la Recherche, Fondation de France, France Parkinson Foundation, Boston Scientific and Medtronic.



Professor Marie-Laure Welter
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Salpêtrière Hospital, Paris, France

Paris, August 07, 2023

Dear Professor,
Chief Editor, *NeuroImage: Clinical*

We would like to submit our manuscript entitled: **“Brain modulation after exergaming training in advanced forms of Parkinson’s disease: a randomized controlled study.”** as a Research Article for publication in *NeuroImage:Reports*.

In this study, we investigate the link between gait and balance disorders observed in patients with an advanced Parkinson’s disease and the neurophysiological effects of an innovative rehabilitation program that utilizes a customized exergaming approach targeting gait and balance disorders. To achieve this, we conducted a single-blind randomized trial to assess the feasibility and effectiveness of a home-based exergaming training program involving full-body movements, comparing it to playing with a keyboard computer. The study took place at two centers: Paris Brain Institute (France) and Radboud University Nijmegen (The Netherlands). The clinical results of this study are submitted elsewhere (Nuic et al., 2023). The PD patients recruited at the Paris Brain Institute also underwent anatomical and resting-state functional brain MRI before and after the training, along with gait recordings. We aim to assess the changes in the brain MRI between pre and post-training in both groups. A total of 23 PD patients with severe and dopa-unresponsive gait and balance disorders were included, 11 in the Active group and 12 in the Control group for the MRI study.

Our findings revealed that before training, gait and balance disorders severity correlated with higher resting-state functional connectivity (rs-FC) within the sensorimotor, central executive and cerebellar networks, along with lower rs-FC between these networks and basal ganglia structures. After Active training with full body movements, rs-FC decreased between the sensorimotor, attentional and basal ganglia networks, while it increased between the cerebellar and basal ganglia networks. In contrast, after Control training with keyboard playing, rs-FC decreased in the mesolimbic and visuospatial cerebellar and basal ganglia networks.

This study represents the first examination of the effects of home-based exergaming playing in PD patients with severe gait and balance disorders. We believe that it is an important study, as it not only provides clinical data but also offers insights into the neurophysiological aspects of exergaming’s impact. This knowledge can support the further implementation of such innovative technologies as a means of efficient rehabilitation for these disabled patients, who often face challenges in accessing for effective rehabilitation programs. Furthermore, understanding the key factors contributing to the success of exergaming in this population can have far-reaching implications for improving their overall quality of life.

The authors confirm that this manuscript is an original work, and no related papers from the same study have been published, posted or submitted for publication elsewhere. We take full responsibility for the data, analyses, interpretation, and research conduct, and we have full access to all the data and the right to publish any and all data, separately from any sponsor.

All co-authors have reviewed and approved the contents of the manuscript, and we all agree to the terms of the BioMed Central Copyright and License Agreement.

We sincerely hope that you find the manuscript acceptable for publication in *NeuroImage:Reports*

Please feel free to contact if you require any further information.

Yours sincerely,

Marie-Laure Welter, MD, PhD

Highlights:

- PD gait disorders correlated with higher rs-FC between the SM, attentional and cerebellar networks.
- Full-body movement exergaming induced rs-FC decreases within these networks.
- Videogame playing modified rs-FC within the mesolimbic, cerebellar and BGN networks.

Brain modulation after exergaming training in advanced forms of Parkinson's disease: a randomized controlled study

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Competing interests

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A Skrzatek, D Nuic, S Cherif, C Gallea, B Beranger, E Bardinet have no conflict of interest to declare.

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Authors' contributions

Conceptualization: M-L Welter, C Gallea, E Bardinet; **Investigation:** M-L Welter, A Skrzatek, S Cherif, D Nuic; **Formal Analysis:** A Skrzatek, D Nuic, S Cherif, C Gallea, B Beranger, E Bardinet; **Writing:** original draft: A Skrzatek, E Bardinet, M-L Welter; Review and editing: A Skrzatek, D Nuic, S Cherif, C Gallea, B Beranger, R Bardinet, M-L Welter. **Project administration:** M-L Welter, E Bardinet; **Funding acquisition:** M-L Welter.

Abstract

Introduction Physical activity combined with virtual reality and exergaming have emerged as new techniques to improve engagement and provide clinical benefits for Parkinson's disease (PD) with gait and balance disorders, along with brain changes. Here, we investigate the effects of a home-based exergaming training on brain volumes and resting-state functional-connectivity (rs-FC) in PD patients.

Methods PD patients with dopa-resistant gait and/or balance disorders were randomly assigned (1:1 ratio) to receive 18 training sessions at home by playing a tailored exergame with full body movements (Active group) or with the computer's keyboard (Control group). Clinical scales, gait recordings, and brain MRI were performed before and after the training. We also explored the relationship between baseline MRI and parkinsonian disability, and brain volumes and rs-FC changes after training in both groups.

Results Twenty-three PD patients were enrolled and randomized in the Active (n=11) or Control (n=12) training groups. Before training, gait and balance disorders severity correlated with higher rs-FC between the sensorimotor, central executive and cerebellar networks, and lower rs-FC between these networks and basal ganglia structures. After Active training, rs-FC decreased between the sensorimotor, attentional and basal ganglia networks, while it increased between the cerebellar and basal ganglia networks. In contrast, after Control training, rs-FC decreased in the mesolimbic and visuospatial cerebellar and basal ganglia networks.

Conclusion Full-body movement training using a tailored exergame induces brain rs-FC changes within the sensorimotor, attentional and cerebellar networks in PD. Further research is needed to comprehensively understand the neurophysiological effects of such training approaches.

Key words: Parkinson's disease, Exergaming, brain magnetic resonance imaging, resting-state functional connectivity, gait disorders.

List of abbreviations

ACC = Anterior Cingulate Cortex; AFI = Analysis of Functional NeuroImages; AI = Anterior Insula; APAs = Anticipatory Postural Adjustments; ALFF = Amplitude of Low Frequency Fluctuations; AOT = Action Observation Therapies; BGN = Basal Ganglia Network; CAT-12 = Computational Anatomy Toolbox; CBL = Cerebellar network; CEN = Central Executive Network; CLR = Cerebellar Locomotor Region; CSF = cerebrospinal fluid; DAN = Dorsal Anterior Network; DLPFC = dorsolateral prefrontal cortex; FD = Framewise Displacement; fMRI = functional Magnetic Resonance Imaging; FOG-Q = Freezing-of-gait questionnaire; FSN = Fronto-Striatal Network; GABS-B = Gait and Balance Scale part B; GLM = general linear model; GMV = Grey Matter Volume; M1 = primary motor cortex; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; MLR = Mesencephalic Locomotor Region; MNI = Montreal Neurological Institute; PCA = Principal Component Analysis; PCC = Posterior Cingulate Cortex; PD = Parkinson's disease; PMC = PreMotor Cortex; PPN = Pedunculopontine Nucleus; PSL = Parietal Superior Lobule; rs-FC= resting-state Functional Connectivity; SMA = Supplementary Motor Area; SMN = SensoriMotor Network; STN = Subthalamic Nucleus; SWST = Stand-Walk-Sit Test; VAN = Ventral Anterior Network; VBM = Voxel-Based Morphometry; VOI = Volumes Of Interest; VPFC = ventrolateral prefrontal cortex; WMV = White Matter Volume.

1. Introduction

Gait and balance disorders are common and debilitating symptoms in individuals with Parkinson's disease (PD)(Mirelman et al., 2019; Nutt et al., 2011). These symptoms worsen over time, becoming resistant to conventional medical treatments and deep brain stimulation (Fasano et al., 2015a). Consequently, they contribute to increased mortality, morbidity, and healthcare costs (Bäckström et al., 2018; Kempster et al., 2007; Lau et al., 2019). Rehabilitation programs have shown promising results in improving walking and postural abilities in PD patients, including increased walking speed, step length, and overall quality of life (Conradsson et al., 2015; Jung et al., 2020; Nieuwboer et al., 2007; Radder et al., 2020; Tomlinson et al., 2012). In recent years, the integration of physical activity with virtual reality, combined with task-specific and/or cueing training, utilizing immersive and non-immersive environments, has emerged as a novel approach to enhance motivation and engage patients' motor and cognitive skills (Gallou-Guyot et al., 2022; Laar et al., 2023; Mirelman et al., 2013; Nieuwboer et al., 2001). When combined with exercise, virtual reality and exergaming have shown comparable results to traditional physiotherapy, while also offering potential additional benefits on motor disability, automaticity and gait and balance performance (Canning et al., 2020; Da Silva et al., 2023; Dockx et al., 2016; Ferrazzoli et al., 2018; Laar et al., 2023; Mirelman et al., 2016; Ribas et al., 2017).

The underlying mechanisms through which physical training improves motor disability in PD patients are not yet fully understood. Animal models of PD suggest a potential neuroprotective effect of intensive motor exercise, involving antioxidant activity, reduction of inflammation, and promotion of synaptogenesis (da Silva et al., 2016; Hirsch et al., 2003; Petzinger et al., 2007; Smith and Zigmond, 2003). Neuroimaging studies in PD patients have revealed compensatory mechanisms that involve increased recruitment of

attentional and sensorimotor networks to overcome movement difficulties and promote automaticity (Droby et al., 2020; Maidan et al., 2017; Tessa et al., 2010; Wai et al., 2012). Following training, various significant changes in brain anatomy and functional connectivity have been reported, dependent on the specific training programs employed. High-intensity aerobic training primarily restores the functioning of sensorimotor (primary motor cortex [M1], supplementary motor area [SMA])-cortico-thalamic-striatal pathways, along with possible neuroplastic changes in the nigrostriatal dopaminergic pathway (Ferrazzoli et al., 2020, 2018). Goal-directed exercise training strengthens the functional connectivity of premotor areas and shows increases in gray matter volumes in the cerebellum, premotor cortex, parietal cortex, and temporal gyrus (Baglio et al., 2021; Maidan et al., 2017; Sehm et al., 2014). Lastly, cognitive-challenging exercise mainly modifies the functioning of the fronto-parietal and SMA-pedunculo-pontine (PPN) network and enhances activation of the motor and premotor areas (Agosta et al., 2017; Ding et al., 2022; King et al., 2020). Limited neuroimaging studies suggest that integrating virtual reality into physical activity training promotes further brain changes, such as reduced activation in the right anterior prefrontal and inferior frontal gyrus, and increased activation in the supplementary motor area (SMA) and premotor areas (Canning et al., 2020; Droby et al., 2020; Maidan et al., 2017).

In this study, we aimed to investigate the effects of a customized exergaming videogame designed to target gait and balance disorders in PD patients. The game incorporates auditory and visual cueing, along with real-time feedback, to enhance motor skills (Nuic et al., 2018). To explore the neural mechanisms underlying the impacts of our exergaming training, we conducted a randomized controlled study and examined changes in brain volumes and resting-state functional connectivity before and after the exergaming intervention.

2. Materials and Methods

2.1. Patients

This study was conducted as part of the Parkgame II project, which aimed to evaluate the effectiveness of a home-based tailored exergaming training system for PD patients with dopa-resistant gait and/or balance disorders in a controlled randomized trial. The Parkgame II project was carried out jointly at two hospitals: Brain and Spine Institute (Paris, France) and Radboud University Medical Centre (Nijmegen, The Netherlands). For this sub-study, we enrolled 23 right-handed PD patients included at the Paris Brain Institute (France) that met the following criteria: 1) age between 18 and 80 years, 2) idiopathic PD as defined by UK Parkinson's Disease Society Brain Bank, 3) with gait and/or balance disorders unresponsive to levodopa treatment (item 12 of the Movement Disorder Society-Unified Parkinson's Disease Scale (MDS-UPDRS) part 2, gait and balance >1 and/or item 13, freezing of gait >1, On-dopa). Additional inclusion criteria were stability of dopaminergic medication for at least one month prior to study enrolment, no other medical condition that could interfere with the research study, had agreed to participate, provided written informed consent and affiliation to a social security scheme. Exclusion criteria were inability to stand or walk alone, dementia (Mini Mental State Examination < 24), and the presence of impulse control disorders (item 6 of MDS-UPDRS part I > 2) (Goetz et al., 2008), and contraindication to MRI. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the local ethics committee (CPP Est-III: N° 18.04.04). The study was promoted by the INSERM (RBM, C17-07, 2017-A02531-52) and registered in a public trials registry (Trial Registration: ClinicalTrials.gov NCT03560089).

2.2. Parkinsonian disability, gait and balance assessments

All enrolled participants underwent general physical, cognitive and parkinsonian disability assessments at baseline and after the last training session. All assessments were done ON medication, approximatively two hours after taking their usual dopaminergic treatment in the morning. These assessments were conducted by an independent investigator unaware of the patients' group randomization.

The clinical assessments included: 1) the Stand-Walk-Sit test (SWST) duration, 2) the MDS-UPDRS part 3, including the 'axial' (sum of the items 3.9 'arising from chair, 3.10 'gait', 3.11 'freezing of gait', 3.12 'postural stability' and 3.13 'posture') and the 'upper limb' (sum of the items 3.4 'rigidity' for upper limbs, 3.5 'finger tapping', 3.6 'hand movements', 3.7 'pronation/supination', 3.14-17 'tremor' for upper limbs) subscores ((Goetz et al., 2008); the Gait and Balance Scale part B (GABS-B)(Thomas et al., 2004); the Freezing-of-gait questionnaire (FOG-Q) (Giladi et al., 2009); the Montreal Cognitive Assessment (MoCA)(Dalrymple-Alford et al., 2010).

Gait and balance were assessed using a gait platform allowing us to record gait initiation kinetics parameters, including: 1) the anticipatory postural adjustments (APAs) phase, with duration and anteroposterior and mediolateral centre of foot pressure displacements during the APAs phase, and 2) the first step execution, with the length, velocity of the first step and double stance duration (eFigure 1)(Nuic et al., 2018).

2.3. Training Protocols

After baseline assessment, patients were randomized to either the Active training programme with full-body movements and a Kinect (n=12), or to the Control training programme with a laptop (n=11). Both groups performed 18 training sessions over a 6-9 week period (eMethods, Figure 1, eFigure 2)(Nuic et al., 2018).

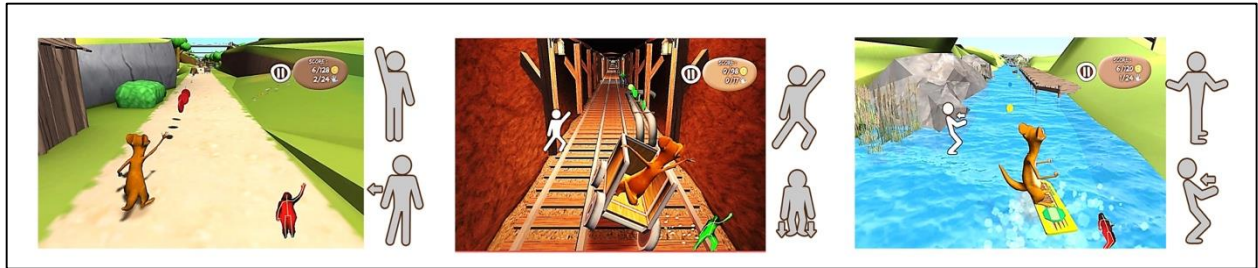


Figure 1. 'Toap Run' exergaming

The 'toap run' exergaming Active training involves full-body movements, performed in front of a RGB-D Kinect® motion sensor positioned approximately 2 meters away from the patient. These movements encompass large amplitude rapid movements of all four limbs, pelvis, and trunk, incorporating lateral, vertical, and forward displacements, which are schematically represented for each environment. As the patient moves, a small animal (the avatar) is simultaneously displaced in real time within three different environments: the garden (left), the mine (middle) and the river (right). The objective is for the avatar to collect coins while avoiding obstacles. In contrast, the Control training patients underwent seated training, interacting by pushing buttons on the keyboard.

2.4. Magnetic Resonance Imaging (MRI) Acquisition

Pre-training MRI datasets were acquired in 23 patients, and post-training MRI data sets in 20 patients, due to COVID crisis in two patients and due to premature study exit in one patient (medical decision).

We acquired anatomical and functional MR images at rest. The MR protocol was carried out using a Siemens Prisma Fit 3Tesla MRI (64-channel head coil, 80 mT/m gradient maximum amplitude) with Magnetization-Prepared Rapid Gradient-Echo sequence (MP-RAGE) T1-weighted sequence (TR = 2400 ms, TE = 2.22 ms, FA = 9, 0.8 iso, 256 slices), followed by blood oxygen level-dependent (BOLD) Multi Echo 3-band T2* for resting state fMRI (TR = 1600 ms, TE = [15.20; 37.17; 59.14 ms], FA = 73, 2.5 iso, 54 slices, 300 volumes), with eyes closed.

2.5. MRI Data Preprocessing

In total, 3 patients were excluded from the MRI analysis due to excessive head motion (n=2) or brain lesions resulting from previous deep brain stimulation (n=1). The remaining 20 patients were assigned to the Active group (n=12) and the Control group (n=8). Finally, MRI data of pre and post-training were obtained in 16 patients for structural MRI and 17 patients for rs-fMRI. These patients were randomized in the Active (n= 8 patients for structural MRI and n= 9 patients for rs-fMRI) and Control (n=8) groups, respectively.

2.5.1. Voxel-based morphometry (VBM)

The Computational Anatomy Toolbox (CAT12) was employed for brain tissues segmentation, and DARTEL algorithm was used to warp the images to the standard Montreal Neurological Institute (MNI) space (Ashburner, 2007; Ashburner and Friston, 2005; Dahnke et al., 2013; Talairach and Tournoux, 1988). Subsequently, brain tissue masks for white matter (WM) and cerebrospinal fluid (CSF) were resliced to a voxel size of 2.5 x 2.5 x 2.5 using FSL (Jenkinson et al., 2012) to match the voxel size of the BOLD images for further functional images processing.

2.5.2. fMRI

Preprocessing of the multi echo BOLD images was conducted using the AFNI pipeline. The images underwent despiking, slice-timing correction and realignment. The optimized combination of these preprocessed images was obtained using the Tedana algorithm (<https://tedana.readthedocs.io/>) (DuPre et al., 2016; Kundu et al., 2017, 2012). Brain masks were extracted using FSL, and the images were co-registered to T1 images using Statistical Parametric Mapping (SPM12, www.fil.ion.ucl.ac.uk/spm/) (Friston et al., 1995; Talairach and Tournoux, 1988). The recombined images were then warped to standard MNI

space using DARTEL and smoothed using a 6 mm full-width at half-maximum (FWHM) Gaussian filter kernel. Motion regressors were combined to other noise regression using the TAPAS : physIO pipeline (<https://www.translationalneuromodeling.org/tapas>) (Frässle et al., 2021) which utilized individual CSF and WM normalized masks. Aberrant volumes with a Framewise Displacement (FD) greater than 1 were identified and excluded, considering that more than 25% of all volumes had $FD > 1$ (Seto et al., 2001). These regressors were used in a General Linear Model (GLM) using SPM12 to denoise the smoothed normalized images.

Region Of Interests (ROIs) were defined in the MNI space using the Wake Forest University (WFU) Pick Atlas for the human brain (V3.0, ANSIR Laboratory). The selection of ROIs was guided by previous studies investigating connectivity in PD patients, with or without gait and balance disorders or FOG, and the association between specific brain regions and gait in both healthy subjects and PD patients (eTable 1). The following functional regions were identified as main ensembles of interest with basal ganglia as a hub, and ROIs associated with cueing strategies, locomotion and action observation therapies (AOT). At the cortical level, the selected ROIs included the primary motor cortex (M1), anterior and posterior supplementary motor area (SMA), dorsolateral and ventrolateral prefrontal cortex (DLPFC, VLPFC); anterior insula (AI), anterior and posterior cingulate cortex (ACC-BA 32, and PCC), superior parietal, inferior temporal cortex, and precuneus. At the subcortical level, the ROIs encompassed the cerebellar locomotor region (CLR), motor areas (lobes VI, VII and VIII), associative areas (Crus I and Crus II) of the cerebellum, basal ganglia (caudate nucleus, subthalamic nucleus, putamen), thalamus, and the mesencephalic locomotor region (MLR) including the pedunculopontine nucleus (PPN) (Figure 2) (Dalla Volta et al., 2015; de Lima-Pardini et al., 2020; Fling et al., 2014; Jahn et al., 2008; Lewis and

Shine, 2016; Marchal et al., 2019; Prodoehl et al., 2015; Shine et al., 2013; Snijders et al., 2011).

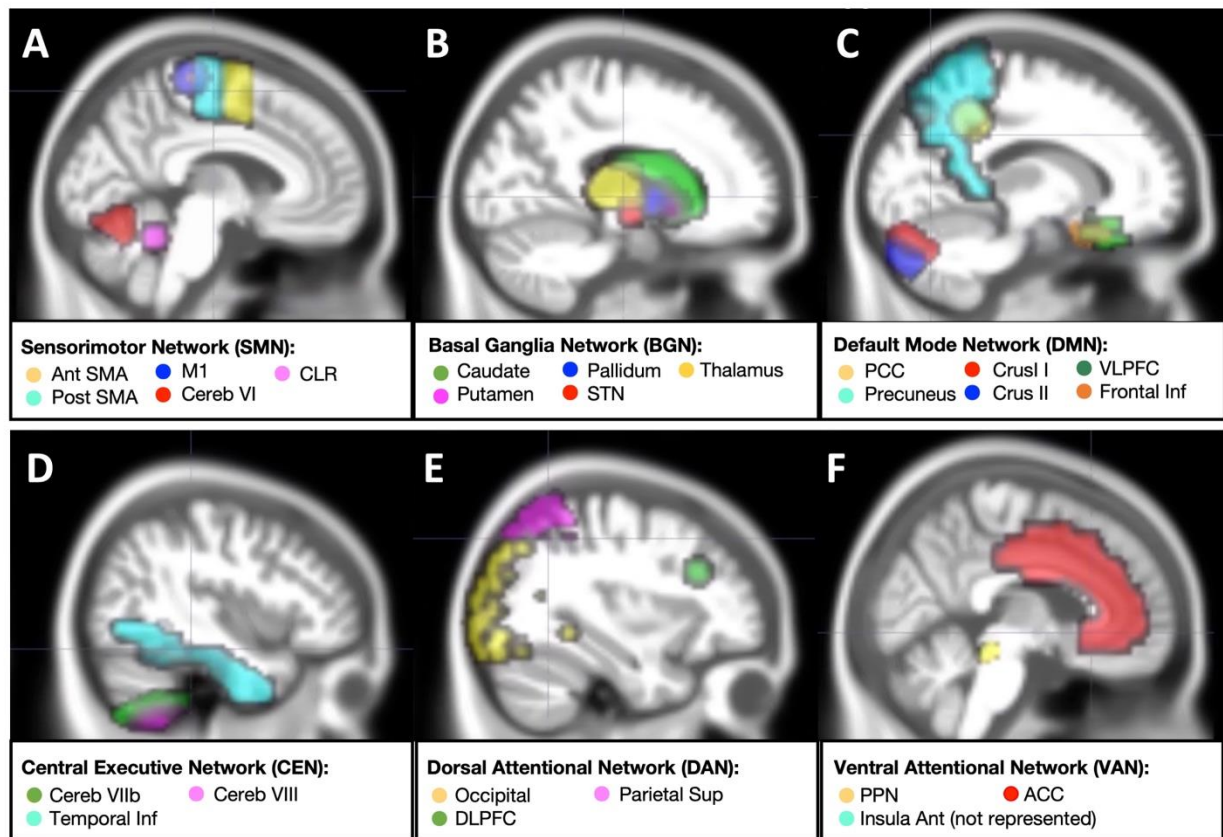


Figure 2. Representation of the brain resting-state networks

The images display the networks examined for rs-FC in PD patients, before and after training. The networks include : A) sensorimotor, B) basal ganglia, C) default mode, D) central executive, E) dorsal attentional and F) ventral attentional networks. In the images, specific regions of interest are labeled: ACC = anterior cingulate cortex; CLR = cerebellar locomotor region; DLPFC = dorsolateral prefrontal cortex; SMA = supplementary motor area; M1 = primary motor cortex; PCC = posterior cingulate cortex; PPN = pedunculo-pontine nucleus; VLPFC = ventrolateral prefrontal cortex.

2.6. MRI Data Analysis

To investigate the changes in grey matter (GM) after training, VBM and an anatomical template were generated from WM, GM, and CSF individual segmentations using DARTEL (Ashburner and Friston, 2005). Individual modulated and warped GM masks were then extracted using the GM template. Total Intracranial Volume (TIV) estimation was conducted using CAT12. Finally, the masks were smoothed with an 8 mm full-width at half-maximum

(FWHM) Gaussian filter in SPM 12, ensuring compatibility with subsequent statistical analysis. The pre-training structural images were subtracted from the post-training image using FSL, resulting in individual delta structural images suitable for regression analysis.

To analyze resting state fMRI, we measured the Amplitude of Low Frequency Fluctuations (ALFF) for each patient per session. ALFF was computed using four binary Fourier pairs with a 90° phase lag at frequencies of 0.01, 0.02, 0.04, and 0.08 Hz (100, 50, 25, and 12.5 s) (Biswal et al., 1995). Classical general linear model (GLM) was employed to calculate the main effect of ALFF, which was then used to extract time-courses of Volumes Of Interest (VOIs). Subsequently, these VOI time-courses were employed as regressors in VOI-specific resting state fMRI GLM, and the positive effect of the VOI contrast was calculated for further statistical analysis.

2.7. Statistical Analysis

To investigate the relationship between parkinsonian disability and gait and balance disorders, GM volumes and resting-state connectivity profiles, we conducted a comprehensive analysis. Initially, a principal component analysis (PCA, RStudio) was performed on the clinical and gait parameters obtained before training. This step helped to address any potential covariability between these parameters. Subsequently, a multiple regression analysis was carried out to establish links between the significant components and GM volumes, with accounting for age and gender as covariates. We employed statistical parametric mapping (SPM) with pTFCE correction, setting the p-value threshold at $p < 0.001$ and a minimum cluster size at $k = 20$.

To assess resting state connectivity, we filtered the connections based on their correlation with clinical parameters per PCA component, using a threshold of $\rho > 0.5$. For

the identification of the most relevant variables and their relationships, we utilized sparse partial least squares (sPLS) regression in MixOmics toolbox (<http://mixomics.org>). Two components were used, and the resulting regression models were further filtered based on correlation scores between the model' axes and the retained descriptors in each dataset. To ensure strong correlations with sufficient patient variability, we set the filter at 0.6 standard deviation of the rho scores. To evaluate the robustness of each model, we performed bootstrapping, and we assessed the specificity of the models through permutation with 1000 repetitions.

To evaluate the effects of the training on GM volumes, we employed a probabilistic threshold-free cluster enhancement (pTFCE) correction with a p-value threshold of $p < 0.001$ and a minimum cluster size of $k = 30$ for VBM data. For the connectivity matrices, tests were conducted for each pair of ROIs with a p-value threshold of $p < 0.01$. Next, we investigated the relationship between the training-induced changes in brain networks and the changes in clinical and gait parameters. To evaluate changes within each group, Wilcoxon signed-rank tests were utilized for in clinical and gait parameters, and paired t-tests were performed individually. Additionally, we applied the Enforced-Convergence Optimization (ECO) algorithm to identify the most significant changes in gait and balance disorders after training (De Vico Fallani et al., 2017). The algorithm helped filter the cases with the lowest and highest behavioral changes, enabling us to pinpoint the strongest individual brain connectivity network shifts associated with the most significant outcomes.

3. Results

3.1. Demographic, clinical characteristics and severity of gait and balance disorders of PD patients

Table 1 presents the demographic and clinical characteristics of the patients enrolled in the MRI study. At baseline both training groups exhibited similar age, disease duration, severity of gait and balance disorders, and gait parameters. However, patients randomized to the Control group displayed more severe non-axial motor signs (Table 1).

Table 1. Demographic and clinical features at baseline.

Patients	Age (yrs) /Sex	Disease duration (yrs)	H-Y Score (ON dopa)	FOG-Q Score	MoCA Score	Clinical GABS-B score (ON dopa)	MDS-UPDRS 3 (ON dopa)	Axial Score (ON dopa)
Active training group								
P001	70/F	15	2	16	29	20	17	2
P002	74/F	18	2	11	28	28	22	4
P007	64/F	7	3	10	29	31	27	7
P008	76/M	10	4	11	26	33	25	7
P025	79/F	10	4	16	24	44	36	10
P027	75/M	19	4	15	26	29	35	10
P039	61/F	14	3	8	26	27	13	4
P040*	71/F	29	4	19	26	48	24	9
P042*	72/M	14	2	11	26	22	19	2
P043	75/M	20	2	7	27	19	20	1
P048	66/M	7	2	9	27	30	15	3
P053*	59/F	14	2	7	21	31	9	2
Mean (SD)	70.1 (6.3)	14.6 (6.4)	2.8 (0.9)	11.7 (3.9)	26.3 (2.2)	30.2 (8.7)	21.8 (8.2)	5.2 (3.4)
Control training group								
P003	72/F	13	3	10	29	19	23	3
P023	68/M	11	2	8	25	19	34	4
P028	68/M	16	4	11	24	32	36	8
P033	72/M	30	3	11	23	26	51	7
P044	56/M	5	2	9	28	14	20	3
P046*	62/F	14	3	5	28	21	37	7
P047	57/F	7	2	6	27	18	31	2
P052	66/F	12	2	14	20	40	34	5
Mean (SD)	65.1 (6.2)	13.5 (7.6)	2.6 (0.7)	9.3 (2.9)	25.5 (3.1)	23.6 (8.6)	33.2 (9.4)	4.9 (2.2)
Mean all (SD)	68.1 (6.6)	14.1 (6.8)	2.8 (0.9)	10.7 (3.7)	25.9 (2.5)	27.6 (9.0)	26.4 (10.2)	5.1 (2.9)

Abbreviations: H-Y, Hoehn and Yahr; FOG-Q: freezing of gait questionnaire; MoCA: Montreal Cognitive Assessment, GABS: clinical gait and balance score (sum of the items 8-25), MDS-UPDRS III: Movement Disorders Society-Unified Parkinson’s Disease Rating Scale part III. * These patients only performed the first MRI at baseline.

Utilizing PCA analysis, we observed the first two components accounted for 54% of the variance in baseline clinical and gait parameters (Figure 3). The first component primarily captured the severity of gait and balance disorders, encompassing scores from axial, GABS and FOG-Q assessment, as well as step length. Higher values on this component indicated higher severity of gait and balance disorders. The second component, on the other hand, represented non-axial motor signs, including MDS-UPDRS III and upper limbs subscores, alongside cognition as assessed by the MoCA score. Higher values on this component indicated higher severity of motor disability.

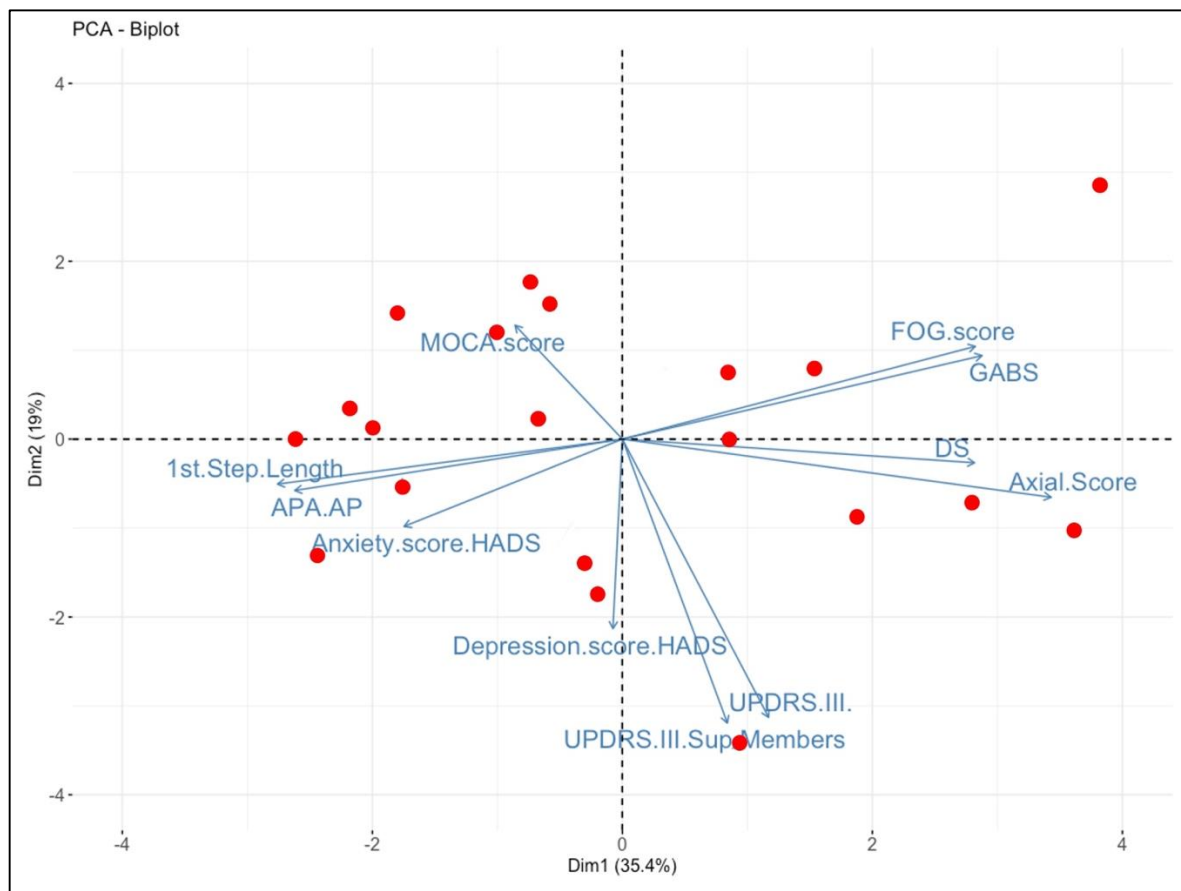


Figure 3. Principal component analysis including clinical and gait data of PD patients at baseline.

The graphs display the results of the principal component analysis for all the clinical and gait recordings data collected from PD patients at inclusion. This analysis effectively distinguished two principal components: the first component primarily comprises clinical and gait recordings data that reflect the severity of gait and balance disorders, and the second component primarily consists of clinical data that indicate the severity of non-axial parkinsonian symptoms, including cognition (MoCA). AP = Antero-Posterior; APA = Anticipatory Postural Adjustment; DS = Double Stance; FOG = Freezing Of Gait; GABS = Gait and Balance Scale; HADS = Hospital Anxiety Depression Score ; UPDRS.III = MDS.UPDRS III = Movement Disorders Society Unified Parkinson's Disease Rating Scale.

3.2. Correlations between parkinsonian disability, gait and balance disorders and brain

MRI at baseline

3.2.1. Voxel-based morphometry (VBM) analysis

In our analysis of baseline VBM data (pre-training), we identified significant correlation between the severity of gait and balance disorders (first principal component) and specific gray matter (GM) volumes. We observed a positive correlation between gait and balance disorders severity and GM volumes in the superior frontal cortex and SMA ($R=0.48$, $p<0.05$, Figure 4). Additionally, In the multiple regression model, Parkinsonian motor signs severity (represented by the second principal component) exhibited a significant negative effect ($p_{TFCE} < 0.001$, $k = 20$) with various brain regions, including the right inferior frontal, superior temporal cortices, temporal pole, left inferior parietal, and precentral cortices, as well as the insular GM volumes (not shown). However, no direct significant Spearman correlation was observed between UPDRS III measures and the GM volumes in these specific regions.

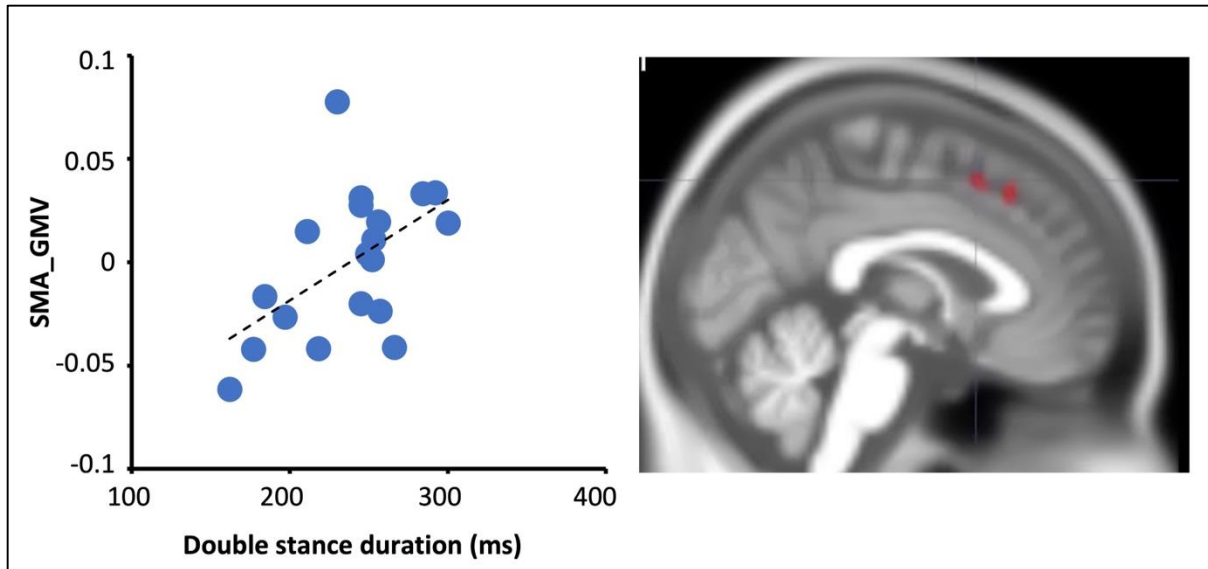


Figure 4. Correlation analysis between grey matter volumes and gait and balance disorders severity.

The left graph represents the linear correlation between the GM volume of the SMA and the double stance time (first component). Right: GM volume positive correlation with measures of the 1st PCA component ($p_{TFCE} < 0.001$; $k = 20$).

3.2.2. Resting-state functional connectivity analysis

Using sPLS regression model with the two principal components, we achieved an adjusted $R^2 = 0.8$ for each component ($p < 0.001$), explaining 69.4% of the remaining variance.

Following final filtering, we identified 21 connections that accounted for inter-individual behavioral variability along the two main component axes (eFigure 3).

Regarding the severity of gait and balance disorders (PC1), we observed high FC connectivity (Figure 5A, positive correlation) between the left temporal inferior cortex and the right primary motor cortex, as well as the left anterior SMA, meaning that more severe gait and balance disorders were associated with higher FC between these brain areas. Additionally, high rs-FC was found between the occipital lobe (BA 17-19) and the right cerebellar lobe VIII and CLR; between the left CLR and the left posterior cingulum and precuneus bilaterally; and between the right PPN and the left cerebellar lobe VII. In contrast, we observed significant correlations between the severity of gait and balance

disorders and low FC connectivity (negative correlation). Specifically, low rs-FC was found between the right subthalamic nucleus (STN) and the bilateral cerebellar lobes VIII; between the left pallidum and the left cerebellar lobe VII and the left anterior SMA. Additionally, low FC was observed between the ventrolateral prefrontal cortex (BA47) and the right cerebellum (lobe VII and Crus II) (Figure 5A).

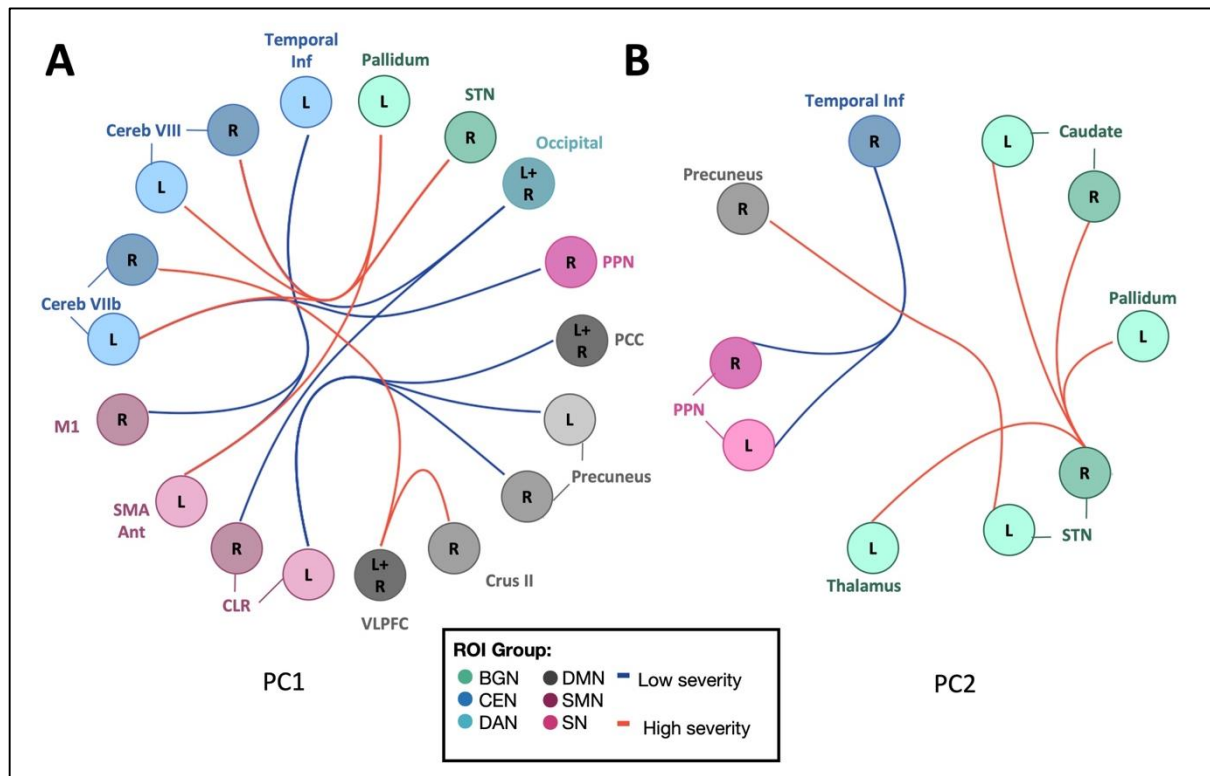


Figure 5. Correlation analysis between brain resting state functional connectivity and clinical and gait recordings principal components.

The graphs illustrate the positive (shown in red) and negative (shown in blue) correlations between rs-FC and the first component, which reflects the severity of gait and balance disorders (A), and the second component, which reflects the severity of non-axial signs (B).

Regarding the severity of non-axial motor signs (PC2), we observed significant correlations with high rs-FC between the right STN and the bilateral caudate nucleus, as well as with the left thalamus and pallidum. Additionally, high rs-FC was observed between the left STN and the right precuneus. Conversely, low rs-FC was found between the bilateral PPN and the right temporal inferior cortex (Figure 5 B).

3.3. Effects of training on gait disorders and brain functional connectivity

3.3.1. Effects of training in the Active group

In the Active group, significant improvements in gait and balance disorders severity were observed after training compared to before training. These improvements included a decrease in the axial and GABS scores ($p < 0.02$), an increase in anteroposterior APAs ($p < 0.05$) and a decrease in the double stance duration ($p = 0.05$) (Table 2).

Table 2. Effects of training of clinical features and gait parameters

	Active group		Control group	
	Before training	After training	Before training	After training
Clinical features				
FOG-Q score	11.7 (3.9)	11.8 (3.9)	9.3 (2.9)	8.9 (3.0)
Axial score	5.2 (3.4)	3.6 (2.7)*	4.9 (2.2)	4.1 (3.1)
GABS score	30.2 (8.7)	23.6 (12.6)*	23.6 (8.6)	21.9 (9.2)
MDS-UPDRS 3 score	21.8 (8.2)	17.5 (9.6)	33.2 (9.4)\$	28.6 (12.8)\$
Gait parameters				
APAs duration (ms)	600 (279)	531 (108)	609 (96)	583 (106)
AP-APAs displacement (mm)	30.5 (12.0)	39.2 (13.8)*	33.9 (4.5)	40.9 (10.6)*
DS duration (ms)	245 (37)	231 (42)*	229 (41)	240 (47)
Step length (cm)	31.5 (10.2)	33.2 (7.7)	32.3 (8.0)	33.7 (8.5)

Values are mean (SD); * $p \leq 0.1$ compared to before training ; \$ $p \leq 0.1$ between groups . AP = anteroposterior; APAs = Anticipatory postural adjustments; DS = double stance; FOG-Q = freezing of gait questionnaire; GABS = gait and balance score; MDS-UPDRS = Movement Disorders Society-Unified Parkinson's Disease Rating Scale.

In this group, VBM volumes analysis did not reveal any significant changes. Notably, we found significant changes in rs-FC after training (not shown). In the Active group, we observed significant changes in the rs-FC after training, that were more pronounced compared to the control group (Figure 6). Specifically, we found a significant reduction in rs-FC between the motor-premotor areas (right M1- left SMA post) and the left temporal

inferior cortex, as well as between the left DLPFC and the bilateral anterior insula, right frontal inferior and VLPFC. Furthermore, we identified reductions in rs-FC between the left parietal superior lobule (PSL) and the right anterior SMA, the posterior cingulate cortex and the right precuneus. Additionally, decreases in rs-FC were found between the left Crus II and the left cerebellar lobe VI, and between the left anterior insula and the left frontal inferior cortex; the left caudate and the PCC (Figure 6A). Conversely, significant increases in rs-FC were observed after the training between the thalamus and the cerebellar area (right crus I and left lobe VIII), as well as between motor cerebellar regions (right CLR with right lobe VI), and between CLR and the two pallidum (Figure 6 A).

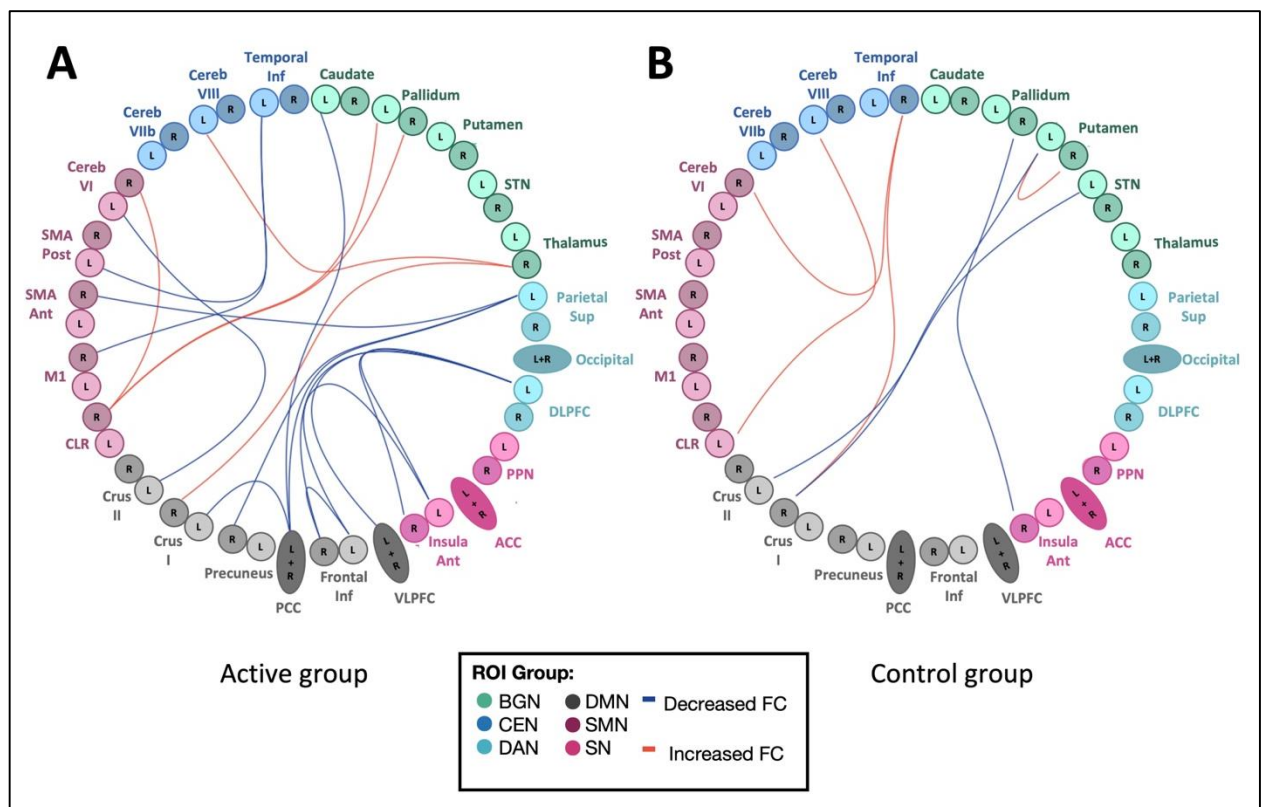


Figure 6. Effects of Active exergaming and Control training on brain resting-state functional connectivity.

The graphs represent the significant changes in rs-FC after Active training (A) and Control training (B). The red lines represent increases in rs-FC, while the blue lines represent decreases in rs-FC after both training methods.

In the Active group, we did not find any significant correlations between changes in brain functional connectivity (FC) and changes in clinical scores or gait parameters.

However, upon visual inspection of individual changes in the brain rs-FC map, we observed distinct patterns between the patient with the best effects of Active "Toap Run" training on the GABS score (P043) and the patient with the worst effects (P025, eFigure 4). In the patient with the best effects, we noted a highest decrease in rs-FC between the cerebellum and the SMA, as well as the premotor cortex (PMC), and between the cerebellum and the precuneus. Conversely, this patient exhibited an increased in rs-FC between the cerebellum and the PPN, thalamus, pallidum, and anterior insula.

3.3.2. Effects of training in the Control group

In the Control group, no significant changes in the severity of gait and balance disorders were observed after training (Table 2). Similarly, VBM analysis did not reveal any significant changes in this group. However, rs-FC significantly decreased after training compared to before computer training between the basal ganglia and cueing circuits. Specifically, this decrease was observed between the left putamen, left STN and cognitive areas of the cerebellum (crus I & II), and as well as between the right pallidum and right anterior insula. Conversely, there was a significant increase in rs-FC between the right putamen and left motor cerebellar areas (Cerebellar locomotor region and lobe VIII), as well as between the right inferior temporal cortex and the left Crus I and lobe 6 of the cerebellum (Figure 6 B).

4. Discussion

In this study, we aimed to investigate the effects of two different training methods on brain rs-FC and motor performance in individuals with PD. The Active group underwent exergaming using full-body movements while the Control group utilized a computer keyboard.

Before training, we observed correlations between gait and balance disorders severity, including freezing of gait, with the rs-FC between the sensorimotor (SMN, including the SMA and parietal lobe), central executive (CEN, including the precuneus) and cerebellum (CBL, including the CLR) networks, and between the PPN and the CBL (lobe VII). These correlations are consistent with previous studies (Fasano et al., 2015b; Fling et al., 2014; Tessitore et al., 2012), suggesting compensatory mechanisms involving increased cortical and cerebellar involvement to overcome loss of automaticity in gait initiation and postural adaptation while walking in more cognitive/complex situations (Bardakan et al., 2022; Canu et al., 2015; Sigurdsson et al., 2022; Yu et al., 2007). Additionally, increased connectivity between the MLR and SMN networks has also been associated with FOG severity (Fling et al., 2014; Lench et al., 2020). We also observed a higher rs-FC between the occipital lobe and the cerebellum. Previous studies reported conversely a decreased rs-FC between the SMN and visual networks in PD patients with FOG, and more particularly in those who later developed FOG (Bardakan et al., 2022), as well as within the dorsal visuomotor processing stream (Canu et al., 2015; Lenka et al., 2016; Yu et al., 2021). We also observed lower rs-FC between the cerebellum and basal ganglia and SMA networks in correlation with gait and balance severity. This suggests that in our patients, where FOG persists continuously, functional reorganization takes place, leading to a disruption in the striatal output and reduced activity within the BGN-cerebellar networks. Despite an increased rs-FC with visual areas, this may result in a less efficient utilization of (visual) cueing strategies. In our patients, we also observed a correlation between the GMV within the frontal and SMA areas with gait and balance disorders severity. Previous studies mainly reported no significant changes or decreased GMV in these areas in PD patients with FOG,

but with no clear correlation with gait and balance disorders severity (Canu et al., 2015; Kostic et al., 2012; Vastik et al., 2017).

Following Active training, we observed specific changes in rs-FC, along with clinical improvement in gait and balance disorders. Decreased rs-FC was observed between the SMN (M1-SMA), CEN (left inferior temporal, prefrontal), dorsal anterior (DAN, including the left superior parietal), ventral anterior (VAN, including the anterior insula), and BGN (left caudate) networks. Conversely, increased rs-FC was observed between the cerebellum (lobe VI and VIII, Crus I, LCR) and basal ganglia (thalamus, pallidum) networks. These changes may reflect a restoration of automaticity in motor control within the SMN and BGN (Maidan et al., 2017), along with reduced involvement of attentional-executive demands in gait control within the DAN and VAN networks. These findings are consistent with recent studies demonstrating rs-FC changes following rehabilitation programs for gait and balance disorders in PD patients. Reduced rs-FC within the posterior mid-cingulate cortex and left precuneus with the BGN, the bilateral thalamus within the CEN, and the bilateral cuneus and left lingual gyrus within the fronto-striatal network (FSN) was reported after treadmill training, with correlations to post-training improvements in gait speed or stride length (Ding et al., 2022; Droby et al., 2020). Combining cognitive enhancement as part of motor rehabilitation has also been shown to reduce rs-FC between the MLR and SMA in PD patients with FOG, correlating with reductions in FOG severity (Fling et al., 2014, 2013). Additionally, the integration of virtual reality including action observation and feedback, as proposed in this study, could also promote better outcomes with higher engagement of the patient and different changes in brain activity. Action observation has been associated with increased activation in the motor and premotor areas (Agosta et al., 2017) and treadmill training combined with VR with increased rs-FC in cortical areas such as the SMA, right

precentral gyrus, and middle frontal gyrus (Droby et al., 2020). In our study, we did not observe additional rs-FC increases in these cortical areas, but rather within the CBL and BGN networks. Notably, increased cerebellar GM volume has been reported after balance training in PD patients (Sehm et al., 2014), and higher activation in the MLR and cerebellar motor region has been found after adapted resistance training with instability in patients with FOG, aligning with clinical improvements (Silva-Batista et al., 2020). These findings suggest that our Active training approach, which also targets balance control and includes learning of motor skills, could improve the functional connectivity between the cerebellum and basal ganglia (Duchesne et al., 2016; Lehericy et al., 2005).

Less changes in rs-FC were found in patients that played with the keyboard (Control group). Resting state FC within the BGN-anterior insula (VAN) network and striato-cerebellar network was modified, with decreased rs-FC between the visual cerebellar areas and the BGN, and increased rs-FC with the right inferior temporal cortex. In both groups, the rs-FC also increased within the visuomotor cerebellar network (CLR and lobe VI). These changes are reminiscent of findings in healthy individuals playing video games, which were associated with decreased activation in visuospatial and attentional networks, potentially reflecting automatization of videogame playing (Lu et al., 2012; Voss et al., 2012). Increased mesolimbic network activity, particularly during winning trials, has also been reported in young healthy individuals (Cole SW Knutson B., 2012; Kätsyri et al., 2013), potentially linked to dopamine release in the limbic striatum (Koepp et al., 1998; Kühn et al., 2014). Similar dopamine release in the limbic striatum has been recently reported in PD patients during videogame playing (Toldo et al., 2021).

Limitations

The present study has some limitations. These limitations include a relatively low sample size for each group, which may limit the generalizability of the findings. Additionally, the small number of patients hindered our ability to examine the relationships between clinical effects and changes in brain activity following training. Another limitation is the baseline group difference in non-axial motor signs, with PD patients in the control group showing more severe symptoms. However, we addressed this disparity by incorporating all variables into our statistical model using multifactor analysis and extracting principal component factors. Furthermore, both groups received intervention programs, preventing us from studying the effects of active exergaming training on brain activity relative to no training. Nonetheless, the observed brain changes exhibited marked differences between the groups after training, suggesting that the observed changes were specific to the program undertaken by the patients.

5. Conclusions

Our study shows that exergaming interventions can lead to distinct changes in rs-FC and gait performance in individuals with PD. These findings contribute to our understanding of the neural mechanisms underlying the benefits of exergaming interventions in PD and highlight the potential benefits of incorporating virtual reality and action observation into training regimens with increased patient's engagement and motivation. Further investigation is warranted to confirm these results in a larger population of PD patients and elucidate the underlying mechanisms contributing to individual variations in clinical outcomes, but also at an earlier stage of the disease to assess the possible neuroprotective effects as reported after intensive rehabilitation programmes.

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Availability of data and materials

All relevant data are within the article. Requests for anonymized data should be sent to M.L. Welter at the Paris Brain Institute, 75013 Paris, France.

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Supplementary online content

Skrzatek et al. Brain modulation after exergaming training in advanced forms of Parkinson's disease: a randomized controlled study

Supplementary Methods

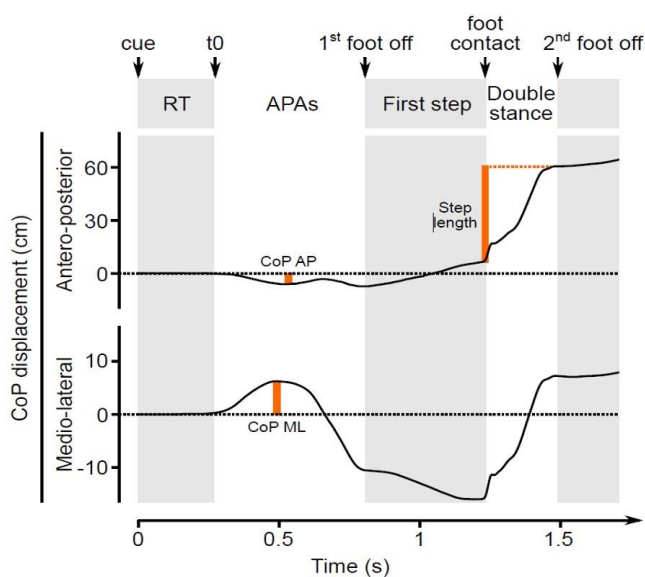
eFigure 1. Gait initiation parameters recordings

eFigure 2. Correlation between clinical and gait parameters and brain resting-state functional connectivity

eFigure 3. Resting-state functional connectivity changes in two individual PD patients with best and worst improvement in gait and balance disorders after Active training.

eTable. Region Of Interests selected for brain resting-state functional connectivity analysis

Supplementary Methods



eFigure 1. Gait initiation parameters

The curves represent from top to bottom, the anteroposterior and mediolateral displacements of the centre of foot pressure (CoP). The mediolateral displacement of the CoP enables the measurement of the lateral displacement of the CoP before foot-off (ML CoP) and the step width. The anteroposterior displacement of the CoP enables the measurement of the posterior displacement of the CoP before the foot-off (CoP AP) and the step length. APAs = anticipatory postural adjustment period; t0: time of the first biomechanical event; RT= reaction time.

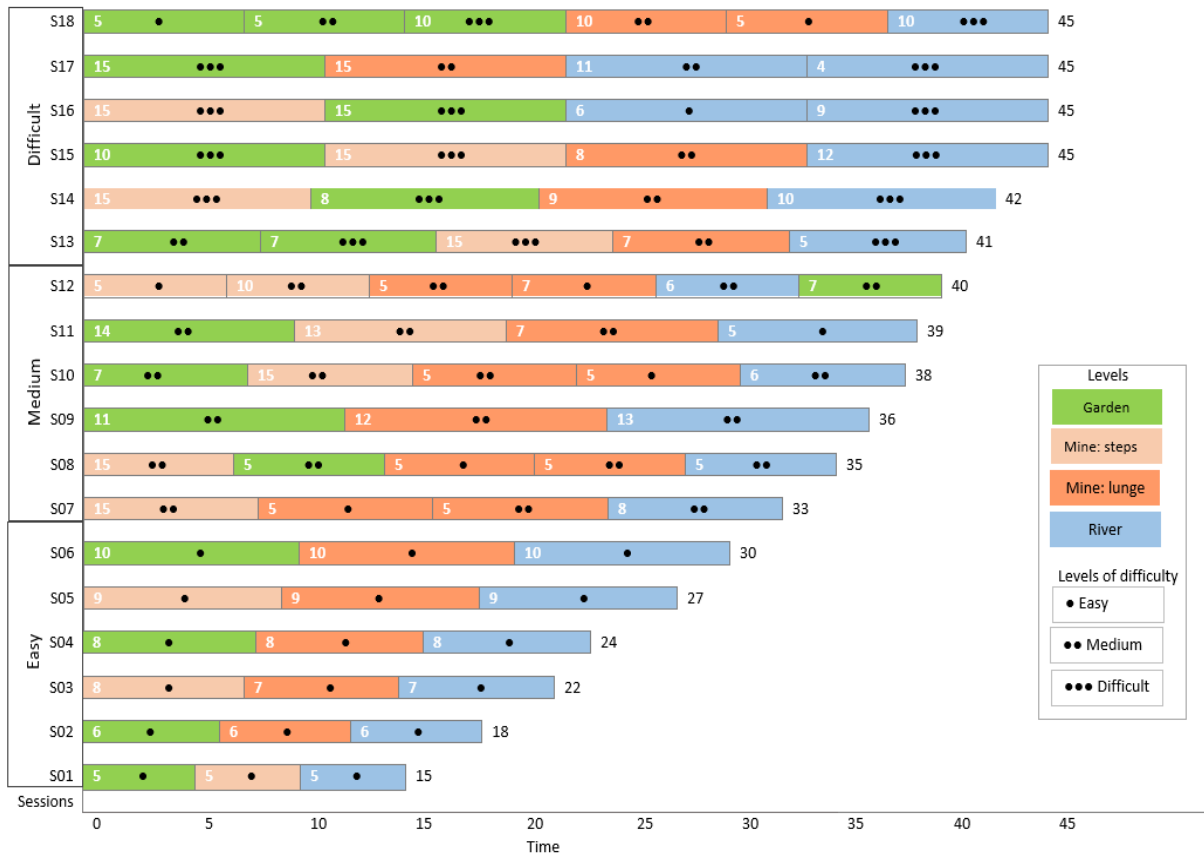
Exergaming training programme

Patients played with the videogame 'Toap Run' designed to treat gait and balance disorders for PD patients, 2-3 times/week for a total of 18 sessions. The first two sessions took place at the institute, and the two following at home with a research assistant. Subsequently, patients played independently at home using a web-based platform (Curapy.com). Participants were allowed to reach the investigator by phone if needed.

The Active training group played with full-body movements performed upright in front of a RGB-D Kinect® motion sensor (Version 2, Microsoft, USA). The motion sensor was placed below a television screen, positioned approximately 2 meters in front of the patient.

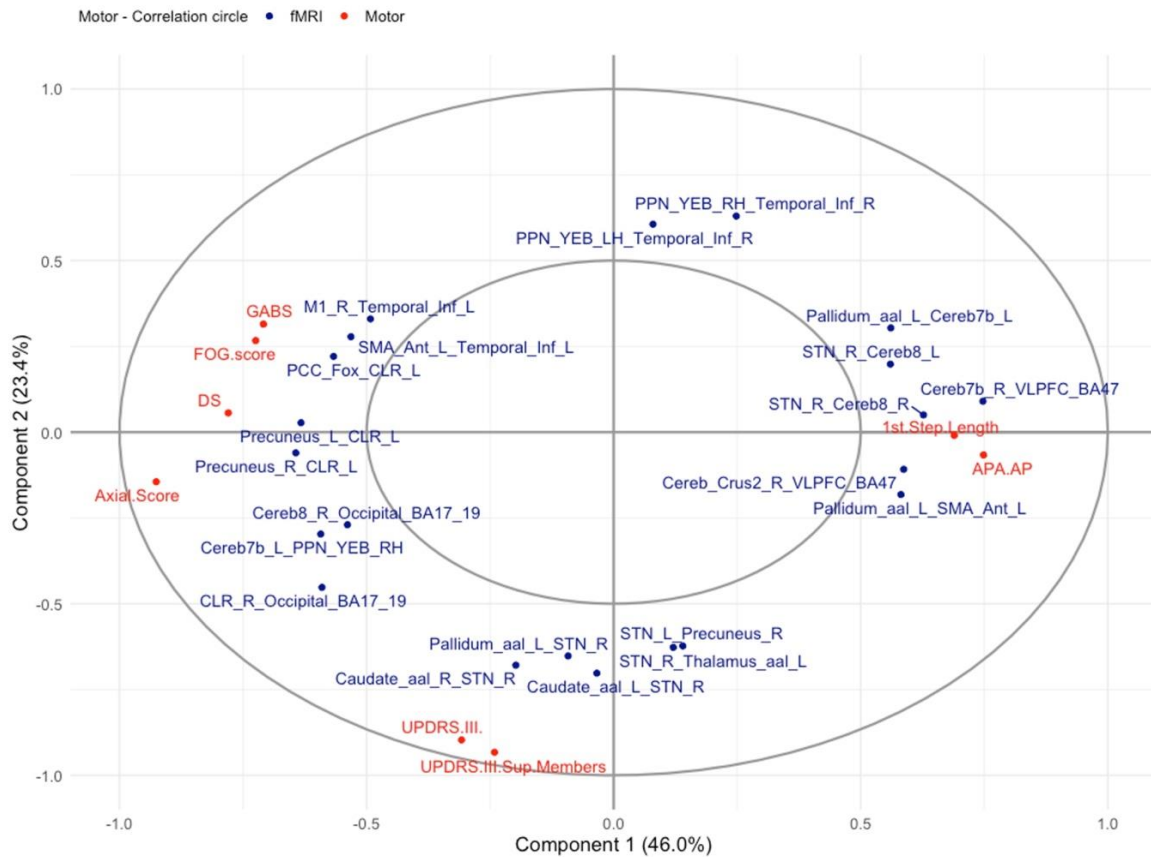
The Control group played seated with a keyboard without any physical efforts.

The participants' movements (Active) or keyboard pushes (Control) induced the displacements of a small animal (the avatar) in real time, to gain points by collecting coins and avoiding obstacles (eFigure 2). For Active training, the required movements consist of large amplitude and rapid movements of all four limbs, pelvis and trunk, with lateral, vertical and forward displacements of the legs, to reinforce foot lifting and postural control. Visual (schematic representation of movements) and auditory (rhythmic music) cues were used to encourage movements. Patients received real-time and on-line feedback while playing, in the form of an auditory or visual stimulus. In addition, their performance was graded at the end of each session. The programme was divided into three phases of six sessions, with predetermined difficulty levels: easy, medium and difficult (eFigure 2).



eFigure 2. Training program

The diagram represents the changes in the duration = X-axis-Time in minutes (from 15 minutes for the first session S01 to 45 minutes for the last session-S18) and gaming environments = garden in green, mine with steps in light orange, mine with lunge movements in dark-orange and river in blue, for the 2 patient groups. The level of difficulty was also increased with time, from easy (one point) to difficult (three points), for each environment. The duration of training in each environment is shown in white numbers. The level of difficulty was defined according to the frequency of movements to be performed with 3 different rhythms: easy: 20 beats/min, medium: 30 beats/min and difficult: 40 beats/min

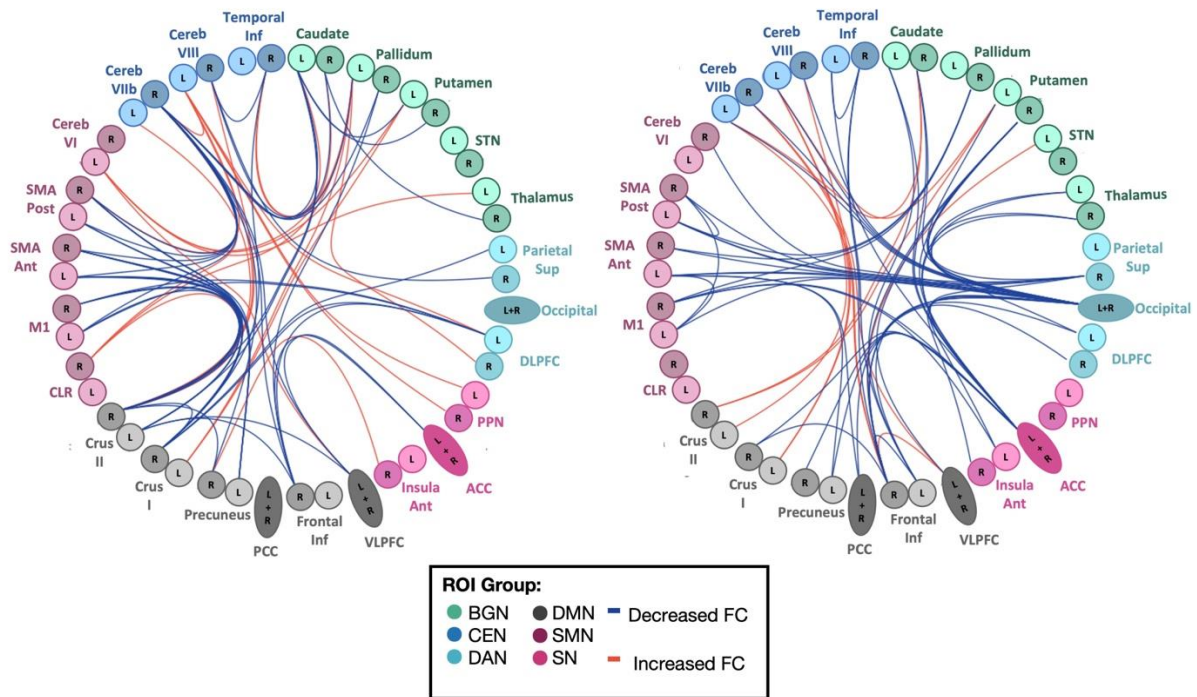


eFigure 3. Correlation between clinical and gait parameters and brain resting-state functional connectivity

The graph represents the significant correlation found between the clinical and gait parameters of the two first components extracted from the PCA analysis and the 21 connections extracted from the rs-FC analysis. These connections were found to explain the inter-individual behavioural variability along the two main axes.

ACTIVE GROUP: Best improvement (P043)

ACTIVE GROUP: Worst improvement (P025)



eFigure 4. Resting-state functional connectivity changes in two individual PD patients with best and worst improvement in gait and balance disorders after Active training.

The graphs represent the rs-FC changes for two individual PD patients after Active training. The left panel shows the results for patient P043, who exhibited the highest decrease in the GABS score, while the right panel displays the data for patient P025, who had the lowest decrease. In the graphs, the red lines indicate an increase in rsFC, while the blue lines represent a decrease in rsFC.

eTable 1. Regions Of Interests selected for brain resting state functional connectivity analysis.

ROI category	ROIs	Resting State Network
(1) Impacted by PD	STN, Putamen, Caudate, Pallidum, Thalamus	Basal Ganglia Network
	ACC	Saliency Network
	Cerebellum (VIIb, VIII)	Central Executive Network
(2) Different in FOG and non-FOG patients	PPN, Anterior Insula	Saliency Network
(3) Stimulated in cueing exercises	PCC, Precuneus, Crus I & II	Default Mode Network
	DLPFC, Superior Parietal Cortex	Dorsal Attention Network
(4) Biomarkers of gait initiation parameters	M1, Anterior & Posterior SMA, Cerebellum (VI), CLR	Sensorimotor Network
(5) Stimulated in motor exercises		
(6) Stimulated in action observation and imagery exercises	VLPFC, Inferior Frontal Cortex	Default Mode Network
	Occipital Cortex (BA 17-19)	Dorsal Attention Network
	Inferior Temporal Cortex	Central Executive Network

6.2 Conclusion

The obtained results in the subgroup of the patients using “*Toap Run*” home-based rehabilitation have shown the disparity between functional and structural alterations related to the postural and gait disturbances and those related to the non-axial motor signs. The link between GM volume increase and the postural instability has already been reported in the literature as the marker of the compensation developed through time. Furthermore, despite small samples we reported training-specific FC changes in both training groups. As expected, the active whole-body training provoked broader changes than the static version of the game. It reached cortico-cerebellar locomotor, visuomotor, attentional and associative networks, as well as the thalamus and the striatum. The effects of the control training concentrated in changes of the basal ganglia and the cerebellar FC. These changes could be related to the dopamine release within the limbic striatum, as reported in young healthy adults (Koepp et al., 1998; Kühn et al., 2013) and recently in patients with PD (Toldo et al., 2021). No significant changes were observed in the GM volume, yet it could be related to the insufficient training intensity and/or duration - previously suggested as reason for no effects on the primary outcome in the first study.

When it comes to our hypotheses, this data suggests that patients in the active training group present an inversion of the severity-related trend in FC, thereby restoring some motor automaticity. Indeed, given that the cortico-cortical hyperconnectivity between motor and associative regions was related to postural disorders severity, the decrease in FC between the sensorimotor network and the inferior temporal cortex after the whole-body exergaming seems to mark the possible improvement of the symptoms. Similarly, the decreases of FC among and between the fronto-parietal regions may also translate the reduced need for cognitive and sensory compensation in these patients. Although, the sample size is too small to draw conclusions on the relations between the behavioural and neural changes, it goes in line with recent studies investigating the effects of the treadmill training on the rs-fMRI (Droby et al., 2020) and the effective connectivity using fNIRS (Ding et al., 2022). The authors demonstrated that the intensive training besides improving gait and executive functions, also results in a decreased fronto-parietal FC. Our protocol aimed at stimulating multiple compensation and motor learning networks, therefore one would suppose the observed effects would go further than the ones already observed in the aerobic training. A confirmation of our results in bigger, non-biased and controlled samples is further necessary to understand the mechanisms

underlying the exergaming in PD patients and how they are related to the observed behavioural changes.

General discussion, Conclusions and Perspectives

In this project, our primary goal was to assess the effectiveness and neural impacts of a personalized home-based rehabilitation training using the exergaming system *"Toap Run"* for addressing severe gait and balance disorders in Parkinson's disease (PD) patients. Building on the promising results of an earlier pilot study conducted at our institute using this game (Nuic et al., 2018), we designed a new controlled trial. However, we were unable to clearly demonstrate the efficacy of the Active training with full-body movement, as there were no changes observed in the Stand-to-Walk-Sit Test (SWST) duration. Nevertheless, some other clinical and gait parameters indicated positive effects on gait and balance performance. Additionally, our imaging data revealed significant changes following Active training, mainly a decrease in functional connectivity between the premotor-motor regions and the temporal inferior and parietal cortices, along with increases in connectivity between the cerebellum and basal ganglia structures.

This research program has allowed us to explore and identify the key components that contribute to effective rehabilitation through exergaming in PD patients with medically refractory gait and balance disorders. Several factors could have influenced the moderate effects of our exergaming program. Firstly, it is essential to note that the PD patients enrolled in our research were in an advanced stage of the disease, which might have hindered their ability to perform training independently with the required intensity and duration. Recent studies suggest a minimum of 150 minutes per week of moderate intensity training for at least 3 months to achieve clinical benefits (Alberts & Rosenfeldt, 2020; Miller Koop et al., 2019; Rosenfeldt et al., 2022). Our study results align with this hypothesis, as PD patients who underwent the Active training during the 3-month open-label period exhibited a non-significant decrease of 4.6 seconds in the SWST duration. However, it's worth mentioning that only one-third of the patients engaged in Active training during this period, indicating possible issues with motivation and adherence among the participants. Age could be a contributing factor, as the patients were relatively older, and they might have faced challenges in using such technology (Laar, 2023). The observed correlation between performance and age in our patients supports this notion. Secondly, executive and/or emotional disorders are frequently reported in the elderly PD population (Diederich et al., 2003; Friedman, 1994; Mendonca et al., 2017). While our assessment using clinical scales (MoCA and HADS) did not reveal major deficits in these areas, these factors have been known to worsen gait and balance disorders

(Galperin et al., 2019) and gait kinetics (Avanzino et al., 2018; Lagravinese et al., 2018). Moreover, they may also affect a subject's ability to engage in exergaming or virtual reality training independently. Some researchers have recently proposed more ecologically oriented tools, such as smartphones or embedded soles, for training, demonstrating good feasibility and adherence in pilot trials (Fujikawa et al., 2022; Putzolu et al., 2023). However, the efficacy of such approaches in treating gait and balance disorders in PD patients has not been fully demonstrated to date.

Another noteworthy aspect of our research is the possibility of efficiently measuring the effects of training on Freezing of Gait (FOG), gait, and balance disorders. FOG, being an episodic phenomenon, manifests less frequently in a hospital setting (Giladi & Nieuwboer, 2008) and is not fully correlated with the severity of bradykinesia (Bartels et al., 2003). Walking abilities in a hospital environment can differ significantly from real-life scenarios, even with the use of gait recordings using complex dual-task gait paradigms (Galperin et al., 2019; Hillel et al., 2019). More complex data analysis, such as machine learning, has recently emerged as a possibility to bridge the gap between gait measures obtained in the lab and real-life mobility (Mirelman et al., 2021). Additionally, various embedded sensors have been developed to record mobility at home for PD patients, showing good feasibility and acceptance (J. L. Adams et al., 2021; Botros et al., 2019; Brognara et al., 2019; Caballol et al., 2023; Goncalves et al., 2021). However, none of these new systems have demonstrated good reliability in detecting FOG and falls in daily life activities. Hence, considering the quality of life (QOL) of our PD patients the use of such devices would provide a more holistic approach to assess the positive impacts of our rehabilitation program using exergaming. In our research program, we measured the PDQ-39 SI score and found no significant changes in the Active group, but an improvement in the Control group. Further examination of the subscores of this scale indicated that this improvement was related to an enhancement in the emotional subscore, which parallels the significant decrease in the HAD score observed in the Control group. FOG has been demonstrated as a key determinant of the quality of life in PD patients (Perez-Lloret et al., 2014), making it a valuable outcome to measure for such treatments. Previous trials and meta-analyses on the effects of physiotherapy also reported a significant improvement in QOL after training, with no obvious additional effects of virtual reality or exergaming implementation (Dockx et al., 2013). QOL is also recognized as a reliable indicator of the

medico-economic impact (World Health Organisation), and exploring the beneficial effects of these new technologies on the public health system, in terms of health costs and caregiver burden, is necessary. This is the aim of our new ongoing trial (PARKGAME_ECO) which assesses the medico-economic impact of our exergaming training in 80 PD patients with gait and balance disorders. This randomized controlled trial includes an Active group of 40 patients who will perform full-body movement training at home using the new version of the exergaming “*Toap Run*”, 2-3 times per week, supervised by a coach/therapist for one session per week, over a one-year period. The Control group will receive their usual care, with no gaming sessions. The main outcome criteria are the incremental cost-utility ratio after 12 months, derived from the EQ5D-3L. Secondary criteria include falls rate, cost-effectiveness ratio, cost-utility ratio, budgetary impacts, as well as usual Parkinsonian clinical scales and gait recordings.

Regarding the neurobiological effects of the "Toap Run" exergaming training, we hypothesized that the use of exergaming could impact the motor, executive, and emotional components of locomotor and balance deficits in PD patients with FOG, by modulating the motor, associative, and limbic cortico-basal ganglia loops (Alexander et al., 1986; Jahanshahi, Obeso, Rothwell, et al., 2015; Koepp et al., 1998; Miller Koop et al., 2019; Teasell et al., 2005), along with reinforcement and motor learning processes. Our imaging data support this assumption, showing significant changes in motor and associative networks in PD patients who underwent Active training, along with decreases in compensatory activities. Interestingly, the Control group patients also exhibited improvements in some gait kinetics parameters and anxiety, confirming the potential relationship between gait performance and emotional status in PD patients. This improvement could be attributed to the release of dopamine from the ventral tegmentum area, known to be preserved even at an advanced stage (Kubis et al., 2000; Marinelli et al., 2017), within the ventral striatum, as recently reported after video game playing (Toldo et al., 2021), and potentially in the hippocampus, both of which being involved in reward processing and linked to the positive feedback delivered during gaming (Marinelli et al., 2017). Such dopamine release may further enhance learning mechanisms and neuroplasticity (Rushworth et al., 2011; Spampinato & Celnik, 2021; Suri & Schultz, 1999; Wood, 2021). However, it is important to note that we did not specifically measure dopamine or other neurotransmitter release induced by training in our study. Further research using more

specific imaging and neurometabolic approaches could shed light on this aspect. Our exergaming approach also includes action observation combined with auditory stimuli, both of which have been shown to improve walking abilities and gait-related disorders in PD patients (Temporiti et al., 2020), and we observed functional changes within the visuomotor cerebellar network in both groups.

Although we were unable to directly link neural changes to the clinical impact of the exergaming training due to the limited number of patients, the significant changes in functional connectivity observed after training indicated brain areas that could be modulated by other non-pharmacological techniques. For example, non-invasive brain stimulation (NIBS) applied over the primary motor cortex, SMA, or DLPFC, or even the cerebellum, have been tested in recent trials to improve FOG, yielding heterogeneous results (Celnik, 2015; Jayaram et al., 2012; M. S. Kim et al., 2015; Y. W. Kim et al., 2019; Liebrand et al., 2020; Mi et al., 2019). Combining exergaming with NIBS performed before training might enhance its positive effects, as recently reported during dual-task walking in older adults (Schneider et al., 2021). Additionally, some propose using brain-computer interfaces to stimulate limb muscles combined with action observation training to enhance the motor benefits (Rossi et al., 2021).

Neuroimaging approaches are crucial for further understanding the neural effects of rehabilitation and identifying patients who will benefit most from these non-pharmacological interventions. It is essential to acknowledge that performing fMRI in patients with a severe form of the disease was highly challenging, resulting in a loss of data in about one-third of patients due to movement artefacts and a large heterogeneity in terms of anatomy. A larger patient cohort would be necessary to achieve keep this data while maintaining a satisfactory level of statistical power. Other teams have proposed the use of less demanding and expensive methods to measure changes in neural activity at rest or while walking. In this context, fNIRS has been shown to be an efficient tool to predict rs-fMRI in patients and is much more robust to movement. The use of fNIRS has been proposed in functional task-based paradigms, such as examining brain activity during gait execution (Ding et al., 2022). Although this technique is limited to cortical regions, previous studies and our results confirm the main changes in sensorimotor cortical areas after training. EEG could also allow to record brain activities with higher temporal and spatial resolution, however at rest - due to movement artefacts during walking.

To conclude, our research program suggests that home-based exergaming could complement conventional rehabilitation methods, particularly with an online synchronous training for some sessions to maintain the intensity, duration, and frequency of the sessions over an extended period, which is crucial for achieving positive effects on walking abilities, FOG, and QOL. Larger studies are needed to determine which patients are best candidates for such training (considering factors like age and disease severity), using adapted outcome criteria, and to assess its potential impact on disease progression, along with its neurobiological effects.

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